ORIGINAL ARTICLE

Assessment of metabolic risk among the Rotterdam's polycystic ovary syndrome phenotypes in Bangalore

Chandrika Anand[1], Rakhi Singh[2], Narayana S[3]*

[1]Department of Gynecology and Obstetrics, Saraswathi Speciality Clinic, PCOS Center, Nagarabhavi, Bangalore-560072 (Karnataka) India, [2]Department of Gynecology and Obstetrics, Abalone Clinic, Maternity and Fertility center, Noida-201301 (Uttar Pradesh) India, [3]Department of Biochemistry, Padmashree Institute of Medical Laboratory Technology, Kengeri, Bangalore-560060 (Karnataka) India

Abstract

Background: Polycystic Ovary Syndrome (PCOS) is characterized by a variety of complex manifestations with an unclear underlying cause. This condition is consistently linked to an increased cardio-metabolic risk. It is essential to evaluate this risk at the phenotype level to identify the most vulnerable subgroup within the PCOS population. *Aim and Objectives:* To phenotype the PCOS patients as per the standard Rotterdam's criteria and to assess the metabolic syndrome markers in those phenotypes. *Material and Methods:* A total of seven hundred participants (n=700) were assessed and categorized based on the Rotterdam criteria. Clinical, radiological, and biochemical assessments were conducted and analyzed statistically. Chi-square and two-way ANOVA tests were conducted using SPSS version 19 statistical software. The results indicated that phenotype A was the most prevalent, comprising 83.2% (583) of the cases, followed by phenotype C at 8% (56), phenotype D at 5.55% (39), and phenotype B at 3.1% (22). Notably, phenotype B, while being the least prevalent, exhibited the highest metabolic risk. This phenotype was significantly associated with increased levels of hirsutism, postprandial hyperinsulinemia, impaired glucose tolerance, and hormonal imbalances. Additionally, although not statistically significant, there was a higher occurrence of family history of metabolic syndrome, elevated waist circumference (greater than 35 inches), obesity, stress, and dyslipidemia associated with this phenotype. *Conclusion:* The highest metabolic risk was observed in phenotype B, which was characterized by a combination of hyperandrogenism and irregular menstruation in the absence of polycystic ovaries.

Keywords: Polycystic Ovary Syndrome, Phenotypes, Metabolic syndrome, Hyperandrogenism, Irregular menstruation

Introduction

Polycystic Ovary Syndrome (PCOS) is a predominant reproductive endocrine disorder characterized by hyperandrogenism, irregular menstrual cycles, and the presence of ovarian cysts. The clinical manifestation may vary among different age groups. It is crucial to note that this condition is the primary contributor to female infertility, representing 80% of all cases [1]. The global prevalence of PCOS ranges from 4% to 20% [2], while in India, it is around 10% [3]. The actual prevalence rate may be even greater, as 70% of the women affected remain undiagnosed [4]. The symptoms of PCOS should not be taken flippantly, as it may result in metabolic complications such as type II diabetes mellitus, hypertension, dyslipidemia and it can also increase the risk of developing endometrial cancer. Unhealthy dietary choices and lack of physical activity and play a substantial role in the onset of

this syndrome [5-6]. The exact root cause of this disorder remains elusive, despite extensive research over the years. At present, there is no definitive treatment available for this condition butit can be managed effectively. Early diagnosis is crucial prior to the implementation of management strategies. Nevertheless, numerous criteria are utilized to identify these patients, among which the Rotterdam criteria [7] is the most commonly adopted.

According to this, the diagnosis requires the presence of at least two of the following characteristics: hyperandrogenism, oligo/amenorrhea, and/or cystic ovaries.

Based on this criteria the patients can be further classified into four distinct phenotypes: A: presence of all the three characteristics; B: a combination of hyperandrogenism and oligo/amenorrhea; C: hyperandrogenism accompanied by ovarian cysts; and D: oligo/amenorrhea along with ovarian cysts.

Research concerning metabolic complications at the phenotype level are scarce. Therefore, it is essential to explore the prevalence of PCOS phenotypes in south India and to determine which subgroup presents the greatest metabolic risk in this area.

Material and Methods

The study was conducted at Saraswathi Speciality Clinic, Dr. Chandrika Anand's PCOS center in Nagarabhavi, Bangalore, and was a cross-sectional, observational study. It received ethical approval from the Padmashree Institutional Ethics Committee (PICE) with reference number PIEC/EXT/05/2024. The study included patients who attended the center for diagnosis and treatment and met the specified Rotterdam criteria, while individuals with other endocrine disorders, such as thyroid or adrenal abnormalities, were excluded from participation.

The clinical data of seven hundred patients (n = 700) who sought diagnosis and treatment at the center from 1 September 2018 to 31 March 2024 were thoroughly analyzed. The sample size was determined using nMaster statistical software, achieving a power of 80% and a 5% α error [8]. Clinical parameters, including hirsutism, acne, alopecia, acanthosis nigricans, and skin tags, were assessed according to established scoring criteria [9-12].

Concurrently, anthropometric measurements such as age, height, weight, Body Mass Index (BMI), blood pressure, abdominal circumference, menstrual history, family history of metabolic syndromes, and stress levels were evaluated using validated questionnaires. Subsequently, investigations were recommended to the patients to confirm the diagnosis of PCOS and assess its severity. The investigation panel comprised an ultrasound scan of the pelvic region and laboratory tests, including Fasting Blood Sugar (FBS), Postprandial Blood Sugar (PPBS), postprandial insulin levels, Follicle-Stimulating Hormone (FSH), Luteinizing Hormone (LH), prolactin, testosterone, Oral Glucose Tolerance Test (OGCT), and lipid profile. Not all patients underwent the complete set of investigations; rather, the panel was tailored to each individual based on physical examination findings and the gynecologist's recommendations. The tests were conducted in a National Accreditation Board for Testing and Calibration Laboratories (NABL) accredited diagnostic laboratory, employing standard assay methods and instruments. All results were meticulously recorded and maintained in the medical records section, subsequently tabulated and subjected to statistical analysis.

Patients were classified into four distinct phenotypes according to the Rotterdam criteria, as

described earlier [7]. The findings from all investigations were organized under each phenotype and analyzed using appropriate statistical methods. The data were expressed as mean ± Standard Deviation (SD). For the analysis, correlation (r), chi-square, and Analysis of Variance (ANOVA) tests were employed. The statistical analysis was conducted using the Statistical Package for the Social Sciences (SPSS) software version 19, with a significance level set at $p < 0.05$.

Results

In the current study, phenotype A was found to be the most prevalent and accounted for 83% of prevalence (583 patients), followed by C (8%, 56 patients), D (5.55%, 39 patients) and B (3.1%, 22 patients) (Table1). The mean age of all the participants was around 25 ± 5 years and obesity (BMI: > 27.5, Asia-specific criteria) was observed to be common in the phenotypes associated with hyperandrogenism i.e. A, B and C phenotypes (Table 2). Concerning the biochemical characterization- postprandial insulin resistance was significantly higher in B phenotype and there were no significant inter-phenotypic differences observed with respect to other biochemical parameters such as blood glucose levels in fasting and postprandial state, lipid profile, and hormone profile-FSH, LH, prolactin, and total testosterone.

Interestingly it was found that the mean PHQ9 score, an indicator of psychiatric stress was significantly higher in B phenotype (Table 2). Considering the clinical manifestation of hyperandrogenism in PCOS patients: hirsutism and alopecia were significantly prevalent in the B (91%) and A (76%) groups respectively (Table 3). Acanthosis nigricans was present in almost all the patients accounting for 95-100% of prevalence rate. Skin tags were observed only in A and C phenotypes with a prevalence of 4.4% and 5.3% respectively (Table 3). Phenotype B had the highest no of obese patients accounting for 77.3% of the population, followed by A (69%), C (64.2%), and D (56.4%) but the difference was not statistically significant. Amongst all the biochemical parameters impaired glucose tolerance, hyperinsulinemia and hormonal imbalance i.e. higher levels of LH were significantly higher inpatients with B phenotype and accounted for 50%, 70% and 33% respectively (Table 3). Correlating the grading of clinical manifestations with biochemical parameters of all the patients, a significant positive correlation was observed between BMI with acanthosis nigricans ($r = 0.3$, $p < 0.05$) and insulin ($r = 0.37$, $p < 0.05$). Testosterone levels were positively correlated ($r = 0.32$, $p < 0.05$) with LH, and insulin hormones. There was a negative correlation between prolactin and testosterone ($r = 0.3$, $p < 0.05$) (Table 4).

Table 1: PCOS phenotypes as per the Rotterdam's criteria

Phenotypes	Symptoms	N=700
A	Hyperandrogenism, oligo/amenorrhea, and polycystic ovaries	583 (83.20%)
B	Hyperandrogenism and oligo/amenorrhea.	22 (3.1%)
C	Hyperandrogenism and polycystic ovaries	56 (8%)
D	Oligo/amenorrhea andpolycystic ovaries	39 (5.55%)

Table 2: Mean values of biochemical parameters

Variables	Overall	A	B	C	D	*p*
Age (years)	25 ± 5	25 ± 5	24 ± 5	26 ± 4.6	25 ± 5.1	0.69
BMI (Kg/m^2)	27.7 ± 5.6	28 ± 6	28 ± 5	28 ± 5	27 ± 5	0.9
Systolic blood pressure (mmHg)	118 ± 13	118 ± 13	124±11.5	117 ± 9.3	115 ± 12	0.1
Diastolic blood pressure (mmHg)	80 ± 11	78 ± 10	81 ± 18.5	78 ± 13	74 ± 13	0.1
Stress (PHQ9, Score)	8 ± 6	8 ± 6	11 ± 6	8 ± 6	5 ± 4	0.01*
FBS (mg/dL)	97 ± 17	97 ± 18	100 ± 9	96 ± 14	103 ± 17	0.5
PPBS (mg/dL)	105 ± 32	106 ± 33	107 ± 15	96 ± 22	110 ± 30	0.5
OGCT (mg/dL)	119 ± 33	120 ± 33	127 ± 38	100 ± 28	128 ± 38	0.2
Total Cholesterol (mg/dL)	170 ± 38.4	175 ± 35	171 ± 17	159 ± 25	154 ± 31	0.2
Triacylglycerol (mg/dL)	137.5 ± 71	146 ± 63	94 ± 35	145 ± 55	69 ± 28	0.1
HDL (mg/dL)	39.7 ± 7.7	41 ± 10	37 ± 5	43 ± 18	44 ± 6	0.8
LDL (mg/dL)	114.6 ± 29.6	117 ± 30	120 ± 14	95 ± 26	103 ± 32	0.06
Total Testosterone (ng/dL)	41.6 ± 21	41 ± 24	34 ± 22	36 ± 17	31 ± 10	0.1
FSH (mIU/mL)	5.3 ± 1.8	5.5 ± 2.7	5 ± 2	6 ± 2	7 ± 4	0.9
LH (mIU/mL)	13.1 ± 7.8	13 ± 8	13 ± 5	9.2 ± 4.8	10 ± 4	0.5
Prolactin (ng/mL)	19 ± 10	18 ± 10	21 ± 13	25 ± 20	21 ± 12	0.4
Post prandial insulin (µIU/mL)	124 ± 108	129±107	144 ± 86	76 ± 46	60 ± 47	0.01*

BMI: Body mass index, FBS: Fasting blood sugar, PPBS: Postprandial blood sugar, OGCT: Oral glucose tolerance test, HDL: High-density lipoprotein, LDL: Low-density lipoprotein, FSH: Follicle stimulation hormone, LH: Luteinizing hormone

Table 3: Clinical and biochemical characters in various phenotypes

Parameters	Overall (n=700) (%)	A (n=583) (%)	B (n=22) (%)	C (n=56) (%)	D (n=39) (%)	*p*
Clinical characterization						
Hirsutism	560 (80)	500 (85.7)	20 (91)	40 (71.4)	0	0.02*
Acne	441 (63)	396 (68)	12 (54)	33 (59)	0	0.056
Alopecia	487 (69)	442 (76)	12 (54)	33 (59)	0	0.045*
Acanthosis nigricans	682 (97)	567 (97)	22 (100)	56 (100)	37 (95)	0.46
Skin tags	29 (4)	26 (4.4)	0	3 (5.3)	0	0.93
Obesity	477 (68.1)	402 (69)	17 (77.3)	36 (64.2)	22 (56.4)	0.27
Stress (PHQ9)	437 (62)	361 (62)	18 (82)	38 (68)	20 (51)	0.095
Blood pressure (n=514)	40 (8)	36 (8.4)	1 (6.2)	1 (2.6)	2 (6)	0.60
Abdominal circumference (n=700)	354 (50.5)	291 (49.9)	14 (63.6)	33 (58.9)	22 (56.4)	0.32
Family history of metabolic syndrome (n=700)	380 (54.2)	321 (55)	14 (63.6)	28 (50)	17 (43.5)	0.37
Biochemical characterization						
FBS(n=232)	12 (5)	9 (5)	0	2 (3.5)	1 (8.3)	0.56
PPBS(n=225)	3 (1)	3 (2)	0	0	0	0.10
Impaired glucose tolerance (n=248)	52 (21)	44 (21)	5 (50)	1 (6)	2 (28)	0. 048*
Dyslipidemia (n=148)	71 (48)	61 (50)	4 (57)	5 (36)	1 (25)	0.56
Testosterone (n=330)	110 (33)	104 (36)	2 (15.3)	4 (20)	0	0.086
Post prandial insulin (n=431)	192 (44)	163 (45)	12 (70)	12 (39)	5 (25)	0.041*
FSH (n=323)	33 (10)	28 (10)	3 (20)	1 (6)	1 (6)	0.584
LH (n=126)	37 (29)	33 (31)	2 (33)	1 (12.5)	1 (25)	0. 048*
Prolactin (n=453)	66 (15)	51 (13)	4 (25)	7 (27)	4 (19)	0.13

Cut off values: Obesity (BMI:> 25 Kg/m^2), PHQ9 (>15), Blood pressure (>140/90 mmHg), Abdominal circumference (>35 inches), FBS (>120 mg/dL), PPBS (>200 mg/dL), Impaired glucose tolerance (OGCT:>140 mg/dL), Dyslipidemia (HDL:<40mg/dL), Testosterone (>48 ng/dL), Post prandial insulin (>100 µIU/L), FSH (<3 mIU/mL), LH (>15 mIU/mL), Prolactin (>30 ng/mL)

Table 4: Correlation (r) of clinical and biochemical parameters

	BMI	HS	Acne	AN	AL	PRL	FSH	LH	INS	T	PHQ
BMI	1										
HS	0.12	1									
Acne	0.015	0.237	1								
AN	**0.346***	0.076	0.236	1							
AL	0.265	0.241	0.118	0.134	1						
PRL	-0.097	-0.02	-0.12	-0.07	-0.05	1					
FSH	-0.02	-0.03	-0.07	0.006	0.15	0.17	1				
LH	-0.105	0.093	-0.02	-0.16	0.06	0.04	**0.3***	1			
INS	**0.37***	0.033	-0.002	0.216	-0.04	-0.16	-0.25	-0.14	1		
T	0.232	0.126	-0.02	-0.01	0.25	**-0.3***	-0.08	**0.327***	**0.326***	1	
PHQ	0.173	0.177	-0.05	0.073	0.14	-0.15	-0.01	-0.05	-0.024	0.04	1

Statistically significant correlation values ($p<0.05$), denoted by (*)
BMI: Body mass index, HS: Hirsutism, AN: Acanthosis nigricans, AL: Alopecia, PRL: Prolactin, FSH: Follicle stimulation hormone, LH: Luteinizing hormone, INS: Insulin, T: Testosterone, PHQ: Patient health questionnaire

Discussion

The highest prevalence of A phenotype (83.2%) observed in our study was supported by various studies conducted across the globe- Garima *et al*., India (67.7%, n=164) [13], Gluszak *et al*., Poland (60.2%) [14], Sezcan *et al*., Turkey (50%)[15], Tavares A, Brazil (54.1%) [16] and Daria *et al*., Gorgia (50%) [17]. Comparatively, south Indian population had the highest prevalence of the A phenotype. On the other hand, we reported the least amount of androgens in the D phenotype and this was supported by Garima *et al*. [13]. In addition to this, we found that acne, alopecia and hypertension were predominant in A type. Observations of Garima *et al*. and Anupama *et al*., [13, 18] also suggested the same. In the current study, B type was found to be wild, which consisted of significantly higher number of patients with hirsutism, post-prandial hyper-insulinemia, impaired glucose tolerance, and hormonal imbalance. In addition to this, obesity, stress, and dyslipidemia were also more common in this type, but it was not statistically significant. Our observation was supported by Enes *et al*., [19], Tripathy *et al*. [20] and Soares [21] who also found a higher prevalence of metabolic syndrome in both A and B phenotypes.

Contradicting the above findings, Subarna *et al*. [22] revealed that invariably all four phenotypes were at metabolic risk. Considering the correlations, our data suggested that higher BMI was associated with increased severity of acanthosis nigricans and elevated insulin levels, indicating a potential link between obesity and insulin resistance. The positive correlation between testosterone and LH, along with insulin, highlights a possible interplay between these hormones in metabolic processes. Conversely, the negative correlation between prolactin and testosterone suggests an inverse relationship, which may have implications for hormonal balance and associated conditions. Our findings align with those of Emin [23] and Gloria [24], who established a link between acanthosis nigricans, obesity, and insulin resistance. The research conducted by Kahn *et al*. [25] and Cory *et al*. [26] indicates a positive correlation between acanthosis nigricans and BMI; however, they assert that no significant relationship exists between acanthosis nigricans and insulin resistance. Manlini *et al*. noted that as insulin levels rise, there is a corresponding increase in both LH and testosterone levels [27]. Our study corroborates this by demonstrating a significant positive correlation between testosterone and insulin. Christine *et al*. performed an intricate study monitoring insulin and free testosterone levels in obese adolescent girls over a 24-hour period at various intervals, yet they did not find a statistically significant correlation between the two hormones [28].

Furthermore, Kamrul *et al*. and Mitrasinovic *et al*. identified a negative correlation between testosterone and prolactin, as well as the association of FSH and LH in PCOS [29-30]. Our study supports these findings.The strength of our study was the sample size-700 PCOS patients (n=700) were examined and most of the routine physical and chemical profiling were evaluated. This is one of the first-generation studies on the South Indian population. Limitations of the study include- out of 700 patients only 22 were fit into B group and this was the least number amongst all the other phenotypes. The community approach is the best method to sample the population because most of the PCOS cases remain undiagnosed due to a lack of awareness and are not reported to the medical facilities. Our study included only the walk-in patients, most of them were urban residents. The absolute and phenotypic prevalence of this condition in rural zones is still elusive.

Conclusion

Different phenotypes exhibited variations in both clinical and biochemical characteristics. The full-blown PCOS - Phenotype A emerged as the most common, representing 83.2% of cases. B phenotype was the least prevalent (3.1%) and most virulent group, with significantly higher prevalence of hirsutism, postprandial hyperinsulinemia, and hormonal imbalance. In addition to this, obesity, family history of metabolic syndrome, stress and dyslipidemia were also high in this phenotype but the difference was not statistically significant. In conclusion, our study suggests that the combination of hyperandrogenism and oligo/amenorrhea (B-phenotype) is crucial in PCOS and this phenotype is associated with an increased risk of metabolic complications like type II diabetes and cardiovascular disease.

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***Author for Correspondence:**

Dr. Narayana S, Department of Biochemistry, Padmashree Institute of Medical Laboratory Technology, Kengeri, Bangalore-560060 (Karnataka) India
Email: narayan.s201991@gmail.com
Cell: 8951617506

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