Evaluation of metabolic, hormonal and clinical parameters in different phenotypes of polycystic ovary syndrome: an observational study from a tertiary care centre in Eastern India

Abstract

Aim and Objective: To evaluate the metabolic, hormonal and clinical profiles of adolescents and young women of polycystic ovary syndrome (PCOS).

Materials and Methods: An Observational cross-sectional study was carried out in the department of Endocrinology and metabolism, Medical College, Kolkata. We included 120 patients of PCOS, diagnosed according to Rotterdam criteria 2003, in the age group of 16 to 40 years.

Results: All phenotypes of PCOS had higher BMI with respect to controls (P<0.05). Among hyperandrogenemic phenotypes, hirsutism was more common in anovulatory classic phenotypes A (92%) and B (87.5%) than ovulatory phenotype C (14.2%). However, all phenotypes had significantly higher testosterone level than control. Normo-androgenemic phenotype D had mean testosterone significantly higher (p<0.001) than control. LH and LH/FSH ratio was highest in classical phenotype A followed by phenotype B than newer phenotypes C and D, all being significantly higher than controls. Total cholesterol was significantly higher in phenotype A (172.6± 28.48mg/dl) than control (150.2± 18.3mg/dl). Phenotype A, C and D had significantly lower (p<0.05) HDL cholesterol and higher (P>0.05) triglyceride than control. Phenotype B had HLD and triglyceride similar to control. LDL was high in phenotype A compared to control (p<0.001). Mean FPG was higher in phenotype A and D being 91.17±10.51 and 92.1±14.51 respectively, which were significantly higher (p<0.05) than control. Insulin resistance by HOMA-IR in phenotype A, B, C, D and control are 3.98 ± 2.26, 2.73±1.79, 2.34 ±0.89, 3.35±0.98 and 1.29±0.98 respectively. Prevalence of metabolic syndrome was highest in phenotype A (52.83%). All phenotypes had higher prevalence of metabolic syndrome than controls.

Conclusion: Phenotype A represents the most common and severe form of PCOS. This group presented with higher modified FG score, more severe biochemical hyperandrogenemic and increased levels of LH and LH/FSH ratio than rest of the sub-groups. Metabolic aberrations were greatest for phenotype A with abdominal obesity, elevated insulin and insulin resistance, higher prevalence of impaired glucose tolerance, atherogenic dyslipidemia.

Introduction

Polycystic ovary syndrome (PCOS) is most common endocrine abnormality in women of reproductive age. Several studies of diverse populations have estimated its prevalence at 6%-10%.1,2 They described a constellation of amenorrhea, oligomenorrhea, obesity and hirsutism in presence of polycystic ovary.3 The disorder has since been known as PCOS, although considerable changes in its definition and path physiology have occurred. The endocrine abnormalities in PCOS include hyperandrogenism of ovarian and/or adrenal origin, which vary in clinical presentation, leading to arrested follicular development and consequently anovulation and polycystic ovarian morphology. The majority of women with PCOS have increased luteinizing hormone (LH) secretion further worsening the hyperandrogenemic. Metabolic characteristics of PCOS include central adiposity and hyperinsulinemia with consequential insulin resistance further exacerbating hyperandrogenism. Endocrine and metabolic abnormalities seen in PCOS may vary among affected women, thus creating a heterogeneous biochemical and clinical phenotype producing difficulties in establishing a diagnosis. Most patients with PCOS have metabolic abnormalities such as insulin resistance with compensatory hyperinsulinemia, obesity, and dyslipidemia. All of these metabolic features may play a role in the development of glucose intolerance or type 2 diabetes mellitus and hypertension, thereby increasing risk of cardiovascular diseases.4 However, it is important to note that an attempt to generalize data obtained from any single ethnic group should be approached with caution. Although a true prevalence study would survey a community, our tertiary care centre represents a reference centre for women with all types of menstrual irregularities and clinical signs of androgen excess, hence this study could be a representative sample of the Eastern Indian population. As a result, the aim of this study was to report the relative prevalence of all four Rotterdam PCOS phenotypes in a tertiary care setting and compare all phenotypes for clinical, hormonal, and metabolic differences.
Materials and methods

Observational, cross-sectional single centred study performed in adolescent girls and young women of reproductive age group between 16 to 40 years attending the department of Endocrinology, diagnosed to have PCOS by Rotterdam criteria 2003. A total of 120 patients were recruited consecutively for the study. 32 healthy age matched women with normal menstrual cycles and without clinical or biochemical evidence of hyperandrogenism were recruited as controls. These patients were divided in to four phenotypes based on Rotterdam criteria 2003.

I. Classic PCOS (H+O+P); phenotype A
II. Classic PCOS but normal ovaries (H+O); phenotype B
III. Ovulatory PCOS (H+P) phenotype C
IV. Norm androgenic PCOS (O+P) phenotype D

Then various clinical metabolic and hormonal profiles are studied in these populations.

A pre-specified proforma was used for obtaining demographic and clinical features. Clinical evaluation of each patient comprised of a thorough menstrual, obstetrics, personal, past, family history followed by complete physical examination. Hirsutism was assessed by Ferriman–Galway (FG) score≥8 or elevated serum total testosterone (TT):≥60ng/dl. Pelvic Ultrasonography was performed to assess ovarian morphology including size, echogenicity, stromal thickness, number and distribution of the cyst typical of PCOM and ovarian volume of each ovary. History of depression was assessed by validated Patient Health Questionnaire 2 (PHQ-2). Physical examination included anthropometric data namely weight, height, BMI, waist circumference, hip circumference. Presence and distribution of acne (Grade 1 to 4) and acanthosis nigricans (grade 1 to 4) were assessed.

Statistical methods

In the statistical analysis of our study, Continuous variables were presented as mean for parametric data and median if the data is non-parametric or skewed. Student t test was applied for calculation of statistical significance whenever the data followed normative distribution. Mann-Whitney test was applied whenever data followed non normative distribution. A categorical variable was expressed as frequencies and percentages. Nominal categorical data between the groups was compared using Chi-square test or Fisher’s exact test as appropriate. Analysis of variance (ANOVA) or kruskal-wallis test with multiple comparisons. Correlation coefficient was assessed by Pearson’s correlation test depending on the distribution of data. Multivariate logistic regression analysis was carried out to identify the predictors of outcome (for binary variables) P<0.05 was taken to indicate a statistically significant difference. Minitab version 17 was used for computation of statistics.

Observations and results

CLINICAL PROFILE: Clinical profile of all phenotypes of PCOS and controls is given in Table 1. Most prevalent phenotype in our study was phenotype A (44.16%) followed by Phenotype D (25%), phenotype C(17.5%) and phenotype B(13.3%). Waist circumference was higher in Phenotype A and D with mean WC of 88.08±8.68 and 88.97±7.23 cm respectively than phenotype B and C. Hirsutism was more common in anovulatory classic phenotypes A(92%) and B (87.5%) than ovulatory phenotype C (14.2%) among hyperandrogenic phenotypes. Phenotype A had more severe hirsutism among all phenotypes (FG score 12.96±3.69) which was significantly higher than ovulatory phenotype C. FG score of phenotype D was similar to control. Blood pressure among all phenotypes was similar to control except systolic BP of phenotype B which was significantly higher compared to other phenotypes and control. Depression was significantly higher among hyperandrogenemic PCOS phenotypes (35.85% in A, 31.25% in B and 66.67% in C) than norm androgenic phenotype D (6.67% with P<0.05). Snoring and features of sleep apnea were higher among all phenotypes compared to control. Forty percent of phenotype D demonstrated snoring with higher BMI and WC than other phenotypes.

### Table 1 Clinical profile of all phenotypes of PCOS and controls

| Variables                  | Phenotype A (P+H+O) N=53 | Phenotype B (H+O) N=16 | Phenotype C (H+P) N=21 | Phenotype D (P+O) N=30 | Control N=32 |
|----------------------------|--------------------------|------------------------|------------------------|------------------------|--------------|
| Number of Individuals (%)  | 44.16%                   | 13.33%                 | 17.50%                 | 25%                    |              |
| Age in years               | 23.08 ± 3.93             | 25.5 ± 4.47            | 25.62 ± 6.09           | 24.1 ± 5.62            | 24.78 ± 5.62 |
| BMI(Kg/m2)                 | 26.51 ± 4                | 27.42 ± 6.14           | 25.08 ± 4.12           | 26.69 ± 2.57           | 22.16 ± 2.57 |
| Infertility in married     | 17 (32.08%)              | 8 (50%)                | 16(76.19%)             | 18 (60%)              | 5 (15.63%)   |
| m FG Score                 | 12.96 ± 3.69             | 11.38 ± 4.03           | 4.3 ± 3.83             | 2.66 ± 1.48            | 2.47 ± 1.48  |
| Hirsutism(mFG>8)           | 49 (92.45%)              | 14 (87.5%)             | 3 (14.29%)             | 0 (0%)                 | 0 (0%)       |
| Anxiety                    | 22 (41.51%)              | 10 (62.5%)             | 13 (61.9%)             | 12 (40%)              | 2 (6.25%)    |
| Depression-PHQ2 score>3   | 19 (35.85%)              | 5 (31.25%)             | 14 (66.67%)            | 2 (6.67%)              | 4 (12.5%)    |
| Snoring                    | 6 (11.32%)               | 3 (18.75%)             | 2 (9.52%)              | 12 (40%)               | 0 (0%)       |
| Acanthosis                 | 39 (73.58 %)             | 6 (37.5 %)             | 14 (66.67 %)           | 16 (53.33 %)           | 8 (25 %)     |
| SBP                        | 114.68 ± 8.7             | 123.25±13.68           | 109.9±5.95             | 117.93±11.47           | 114.06±11.47 |
| DBP                        | 78.26 ± 8.15             | 78.88 ± 8.2            | 71.43±4.34             | 74.48 ± 9.21           | 75.13 ± 9.21 |

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Endocrine profile

Endocrine profile of all phenotypes of PCOS and controls is given in Table 2. Mean Testosterone level was highest in women with PCOS phenotype A, intermediate in phenotype B and C and lowest in women with phenotype D. All phenotypes had significantly higher testosterone level than control. Normoandrogenic phenotype D had mean testosterone significantly higher (p<0.001) than control. Similar trend was noted with adrenal androgen DHEAS. LH and LH/FSH ratio was highest in classical phenotype A followed by phenotype B than newer phenotype C and D, all which were significantly higher than controls.

Table 2 Endocrine profile of all phenotypes of PCOS and controls

| Variables | Phenotype A (P+H+O) N=53 | Phenotype B (H+O) N=16 | Phenotype C (H+P) N=21 | Phenotype D (P+O) N=30 | Control N=32 |
|-----------|--------------------------|-------------------------|------------------------|-------------------------|-------------|
| Testosterone | 79.05 ± 42.54 | 58.58 ± 23.51 | 44.5 ± 12.42 | 36.98 ± 10.83 | 26.93 ± 10.83 |
| DHEAS | 254.53 ± 89.63 | 229.67 ± 73.38 | 200.33 ± 39.91 | 207.83 ± 39.16 | 156.06 ± 39.16 |
| LH | 7.85 ± 3.88 | 6.7 ± 1.76 | 6.52 ± 1.06 | 4.53 ± 1.51 | 3.49 ± 1.51 |
| FSH | 5.99 ± 3.17 | 5.03 ± 1.75 | 6.31 ± 1.11 | 4.02 ± 1.84 | 4.78 ± 1.84 |
| LH/FSH | 1.74 ± 0.83 | 1.55 ± 0.5 | 1.4 ± 0.82 | 1.06 ± 0.2 | 0.59 ± 0.2 |
| I17OHP | 1.28 ± 0.59 | 1.36 ± 0.7 | 0.94 ± 0.25 | 0.94 ± 0.4 | 1.18 ± 0.4 |
| TSH | 3.5 ± 4.29 | 2.11 ± 0.56 | 1.9 ± 1.13 | 2.04 ± 1.08 | 2.13 ± 1.08 |
| Prolactin | 12.58 ± 4.89 | 16.41 ± 5.79 | 15.35 ± 4.69 | 8.95 ± 4.02 | 12.94 ± 4.02 |

Metabolic profile

Lipid profile of all phenotypes of PCOS and controls is given in Table 3. Total cholesterol was significantly higher in phenotype A (172.62±28.48mg/dl) than control (150.22±18.3mg.dl). Rest of the phenotypes did not differ from control. Phenotype A, C and D had significantly lower (p<0.05) HDL cholesterol and higher (p<0.05) triglyceride than control. Phenotype B had HDL and triglyceride similar to control. LDL was high in phenotype A compared to control (p<0.001).

Table 3 Lipid profile of all phenotypes of PCOS and controls

| Variables | Phenotype A (P+H+O) N=53 | Phenotype B (H+O) N=16 | Phenotype C (H+P) N=21 | Phenotype D (P+O) N=30 | Control N=32 |
|-----------|--------------------------|-------------------------|------------------------|-------------------------|-------------|
| TC | 172.64 ± 28.48 | 160.56 ± 33.43 | 154 ± 22.7 | 145.28±18.3 | 150.22±18.3 |
| HDL | 40.57 ± 5.38 | 42.5 ± 7.26 | 39.62 ± 6.24 | 35.51±6.29 | 46.31±6.29 |
| LDL | 102.57 ± 22.81 | 92.25 ± 27.07 | 90.6 ± 7.58 | 87.07±17.07 | 83.09±17.07 |
| TG | 139.09 ± 33.27 | 131.44 ± 41.18 | 155.48±38.78 | 122.55±34.33 | 105.69±34.33 |

Insulin resistance

Profile of insulin resistance of all phenotypes of PCOS and controls is given in Table 4. Mean FPG was highest in phenotype A and D were 91.17±10.51 and 92.1±14.51 respectively, which were significantly higher (p<0.05) than control. FPG of phenotype B and C did not differ from control. Average post 75 gm glucose plasma glucose as control. Insulin resistance by HOMA-IR in phenotype A, B, C, D and control are 3.98±2.26, 2.73±1.79, 2.34±0.89, 3.35±0.98 and 1.29±0.98 respectively. Insulin resistance was significantly higher in all phenotypes compared to control. Phenotype A and D exhibited severe IR than other two phenotypes. Insulin sensitivity by QUICKI index was lowest in Phenotype A compared to all other phenotypes. HOMA B was significantly lower in all PCOS phenotypes compared to control.

Table 4 Profile of insulin resistance of all phenotypes of PCOS and controls

| Variables | Phenotype A (P+H+O) N=53 | Phenotype B (H+O) N=16 | Phenotype C (H+P) N=21 | Phenotype D (P+O) N=30 | Control N=32 |
|-----------|--------------------------|-------------------------|------------------------|-------------------------|-------------|
| FPG in mg/dl | 91.17±10.51 | 88.23±13.98 | 88.81±10.58 | 92.1±14.51 | 83.72±14.51 |
| 2 hr post 75 Gm Glucose (mg/dl) | 123.68±22.94 | 114.06±26.77 | 107.57±7.19 | 108.59±14.48 | 103.69±14.48 |
| Fasting insulin µU/ml | 17.3±8.61 | 12.17±6.46 | 11.14±3.41 | 12.27±3.24 | 6.12±3.24 |
| HOMAIR | 3.98±2.26 | 2.73±1.79 | 2.34±0.89 | 3.35±0.98 | 1.29±0.98 |
| QUICKI | 0.31±0.03 | 0.34±0.03 | 0.34±0.02 | 0.34±0.02 | 0.37±0.02 |
| HOMA B | 401.41±180.37 | 286.24±131.05 | 287.73±91.52 | 302.12±876.44 | 1477.25±876.44 |

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**Metabolic syndrome**

Prevalence of metabolic syndrome in different phenotypes and control groups is given in Figure 1. There were 28, 6, 8, 7, 4 subjects with metabolic syndrome in PCOS phenotype A, B, C, D and control respectively. Metabolic syndrome was highest in phenotype A (52.83%). All phenotypes had higher prevalence of metabolic syndrome than control subjects.

![Figure 1 Prevalence of metabolic syndrome in different phenotypes and control groups.](image)

**Discussion**

Present study evaluated clinical, hormonal and metabolic profile of 120 PCOS patients. The Rotterdam criteria for women with PCOS resulted in four phenotypes. The most common phenotype in our study was phenotype A (H+O+P; 44.16%), followed by phenotype D (O+P; 25%), phenotype C (H+P; 17.5%) and phenotype B (H+O; 13.33%). Most published studies reported phenotype A to be the most prevalent which is similar to our study. The phenotype is included in all three-consensus criteria and certainly represents the basis of PCOS diagnosis. The prevalence of the other three phenotypes differs between published studies across the world. Prevalence of Phenotype A in studies from Croatian, Turkish, Bulgarian, and American population were 56.7, 44.09, 53.6, and 60% respectively. Distribution of phenotypes, A, B, C, D from studies of Asian countries like Iran was 32.1, 46.8, 14.8, and 6.3%, and Chinese was 33.2, 15.2, 17.5, 34.1% respectively. Study by S. Kar et al. from India found distribution of phenotype A, B, C, D to be 65.6, 11.2, 0.9, and 22.2% respectively. Pike et al. found most common phenotype to be D(P+O) in a north Indian population. Beena Joshi from Western India found phenotype D (52.6%) to be the most prevalent phenotype. This difference in prevalence of different phenotypes was probably due to complex genetic, ethnic, cultural differences across different geographic areas of Indian subcontinent. This also depends on the study population recruited by different specialities like Gynaecology, Endocrinology and dermatology, who are involved in management of this heterogeneous disorder.

BMI was significantly higher in PCOS and had more truncal obesity than controls. This finding was similar to study by Welt et al. In present study obesity was present in 57%. Thathpudi et al. used similar cut off by Asia specific definition (BMI>25) for defining obesity found higher prevalence of obesity (70%). Phenotype A had significantly higher BMI compared to other phenotypes.

Fasting serum insulin and HOMA-IR is significantly higher in PCOS than controls. 66% of PCOS patients had Insulin Resistance (cut off of 2.5). Previous study by Aziz have shown similar prevalence (64%) of IR in US population. In an Indian study the prevalence of IR was 50.52% when cut off of HOMA IR was 2.5. All PCOS subgroups had higher HOMA IR compared to control, similar to the findings of Chae SJ et al. The present study showed higher level of insulin and HOMA scores in the phenotype A (P+H+O) followed by Normo-androgenemic phenotype D which was more than other two hyperandrogenemic sub groups. Our finding is in disagreement with general opinion that norm androgenic phenotype D is metabolically similar to control. Conflicting reports are reported with respect to metabolic derangement in this controversial sub group. In our study IR was positively correlated with central obesity (r=0.489), BMI (r=0.311) and hyperandrogenemic (r= 0.262). Strongest correlation was with truncal obesity. Both phenotype A and D had higher central obesity than other phenotypes.

Both fasting plasma glucose and 2hr OGT (75gm anhydrous glucose) was more in PCOS than control. Prevalence of IGT was 30% and diabetes was 9.1% which is consistent with study by Ehrmann et al (IGT in 35% and Type 2 DM in 10%). abnormal glucose tolerance and diabetes was more prevalent in phenotype A and D and was consistent with higher truncal obesity and insulin resistance in these two groups.

In our study mean total cholesterol, LDL, triglyceride was higher and HDL was lower in PCOS group compared to Control. These Phenotype A, C and D had higher triglyceride and low HDL compared to control which is characteristic of metabolic syndrome expected in PCOS. Mean LDLc was highest in phenotype A (102.mg/dl± 22.81) than other sub groups and control (83.09±17.07) conferring additional cardiovascular risk. Phenotype A represents more severe cardiovascular risk prone subgroup with respect to lipid profile. This finding was similar to study by Teharani et al. who reported phenotype A to have more adverse lipid profile but other phenotypes in their study did not differ from control.

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Overall prevalence of metabolic syndrome (MS) in our PCOS population was 40.8%. Studies have reported varied prevalence of metabolic syndrome like 47.3% in the U.S.\textsuperscript{14-15} 25.6% in southeast China, 23.8% in Sweden,\textsuperscript{16} 19.9% in Greece,\textsuperscript{17} 12.5% in Turkey,\textsuperscript{18} and 1.6% in the Czech Republic.\textsuperscript{19} The prevalence of metabolic syndrome (MS) ranges from 33% to 45% in Brazilian women with PCOS.\textsuperscript{20,21} Studies from India have reported MS in 35–46.2%.\textsuperscript{22,23} Prevalence of metabolic syndrome in current study was 52.83% in phenotype A (P+H+O) followed by 38.1% in Phenotype C (H+P), 37.5% in B(H+O) and 23.3% in D.

Prevalence of hirsutism was higher in PCOS than control. Among hyperandrogenemic sub-groups’ classic phenotype A (92%) and phenotype B (87%) had higher prevalence of hirsutism than ovulatory phenotype C. Similar trend was seen with severity of hirsutism. Modified FG score was significantly higher in Phenotype A and B than ovulatory phenotype C. This is consistent with various studies.\textsuperscript{24-25} The testosterone levels were elevated in all three groups with hyperandrogenism (A, B, C), when compared to the Group D without the signs of hyperandrogenism. It was highest with phenotype a when compared with a particular group with hyperandrogenism. Our data confirms the report by Dewailly et al.\textsuperscript{26} that patients with non hyper androgenic PCOS (phenotype D) had in fact slightly but significantly higher mean androgen levels than controls.(36.98 ±10.83 ng/dl Vs 26 . 93±10.83ng/dl) although by definition, all individual values were within the normal range.

**Limitations of the study**

Our study population had the potential for bias since participants were recruited based on self-reported concerns over PCOS not from population survey. It would be expected that those with the most concerns over PCOS would be selected for evaluation (i.e. overt PCOS). Secondly our study was not designed to assess the prevalence of PCOS phenotypes in general population rather it was planned for looking at the prevalence of PCOS phenotypes in women who were concerned with the symptoms suggestive of PCOS. Thirdly our PCOS and control populations were not matched for adiposity. The cross-sectional design of our study only allowed for the report of associations among metabolic disturbances and PCOS phenotypes. Therefore future longitudinal and prospective study may address potential causal mechanisms for phenotypic variation in PCOS in our country.

**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 counselled about their present and long-term risks. Classic PCOS, Phenotype A represents the most common and severe form of PCOS. These patients presented as group with hirsutism with higher modified FG score, more severe biochemical hyperandrogenism, increased levels of LH and LH/FSH ratio, than rest of the sub groups. Metabolic aberrations were greatest for phenotype A with abdominal obesity, elevated insulin and insulin resistance, higher prevalence of impaired glucose tolerance, atherogenic dyslipidemia and metabolic syndrome. In our setting, these patients represented almost 45% of all PCOS patients.

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None.

**Conflict of interest**

The author declares that there is no conflict interest.

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