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Analysis of the phenotypic variants of polycystic ovarian syndrome in women of reproductive age group

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ABSTRACT

Aims: To identify the different phenotypic variant of PCOS in women of reproductive age group and to assess the hormonal and metabolic profile of women with PCOS.

Methods: This Prospective descriptive study was conducted in the Department of Obstetrics and Gynecology, BPKIHS, Dharan for a period of one year from July 2020 to June 2021. All Women presenting to Gynecology OPD with complaints of menstrual irregularity and clinical features of hyperandrogenism were assessed and evaluated for polycystic ovarian syndrome. BMI was calculated. Hormonal Profile (serum LH, FSH and testosterone) and metabolic parameters (fasting blood sugar and lipid profile) were studied; and then further categorized into different phenotypic variants. All data were stored in Microsoft excel format and analyzed using SPSS version 11.5. using descriptive statistics.

Results: Total of 80 cases of PCOS were enrolled during the study period. The most common phenotypic variant was Type B (60%) followed by Type D (30%). The mean BMI was $22.4 \pm 4.2 \text{ kg/m}^2$. All PCOS cases presented with menstrual irregularity as the primary complaint.

Conclusions: Anovulatory PCOS was the most common phenotypic variant in our study population. This study did not find obese PCOS hence emphasizing the need of evaluation in lean women with or without hyperandrogenism presenting with menstrual irregularities.

Keywords: hyperandrogenism, oligomenorrhoea, phenotype, PCOS

INTRODUCTION

The polycystic ovary syndrome (PCOS) is an endocrine metabolic disorder affecting 4-10% of women of reproductive age.¹ Patients with PCOS has a varied clinical manifestation which includes menstrual irregularity, infertility, obesity, hyperandrogenic features (acne, hirsutism), endometrial hyperplasia and features of insulin

resistance and deranged metabolic parameters manifesting as hyperglycemia and dyslipidemia. Mainly the three societies took an initial lead to define and classify PCOS. In 2003, the European Society for Human Reproduction and Embryology and the American Society for Reproductive Medicine redefined PCOS as the presence of 2 or more features: (1) oligo- or chronic anovulation, (2) biochemical and/or clinical hyperandrogenism, and (3) ultrasonographic evidence of PCO.^{2,3} PCOS is a diagnosis of exclusion after eliminating other causes of androgen excess.

The introduction of Rotterdam criteria led to a substantial increase in the number of patients diagnosed with PCOS as well as broadened the heterogeneity of PCOS phenotypes as compared with the NIH definition.⁴ In 2006, the Androgen Excess and PCOS Society (AE-PCOS) criteria considered that the diagnosis of PCOS should be based on clinical or biochemical hyperandrogenism in combination with oligoanovulation or polycystic ovaries.⁵ This criteria eliminated the nonhyperandrogenic phenotypic variant of PCOS. A phenotypic approach to classifying PCOS avoided the drawbacks of currently existing criteria, which may be interpreted as “lumping” all phenotypes together, while providing a simple diagnostic instrument and avoiding the need to decide between multiple different PCOS definitions.⁶

NIH consensus panel 2012 described PCOS according to the different phenotypic variant:⁶

- Type A: hyperandrogenism, chronic anovulation and polycystic ovaries (H+O+P)
- Type B: hyperandrogenism and chronic anovulation but normal ovaries (H+O)

- Type C: Hyperandrogenism and polycystic ovaries but ovulatory cycles (H+P)
- Type D: chronic anovulation and polycystic ovaries (O+P) but no clinical or biochemical hyperandrogenism.

The development of PCOS may start from intrauterine life involving the programming of endocrine axis, namely the hypothalamic-pituitary-ovarian and adrenal axis as well as the pathways of carbohydrate metabolism.⁷ An increasing body of evidence suggested that Hyperandrogenism seemed to be the strongest determinant of the PCOS pathophysiology and a key predictor of the associated metabolic dysfunction.⁸ The severity of the disorder may vary from milder form to the most severe form spanning from adolescence through the entire reproductive life as the pathophysiology depends entirely on hyperandrogenism, obesity, insulin resistance and metabolic alterations.

This study aims to identify the different phenotypic variant of PCOS in women of reproductive age group presenting to a tertiary care centre and to assess the hormonal and metabolic profile of women with PCOS.

METHODS

This Prospective descriptive study was conducted in the department of Obstetrics and Gynecology, BPKIHS, Dharan for a period of one year from July 2020 to June 2021. Patients were recruited by convenient sampling technique. All Women presenting to Gynecology OPD with complaints of menstrual irregularity and clinical features of hyperandrogenism were assessed and evaluated for Polycystic ovarian syndrome. Detailed history and physical examination was done to rule out other features of amenorrhoea and hyperandrogenism. Women with other endocrinological disorder

like thyroid disorders and hyperprolactinemia were excluded from the study. They were assessed for their menstrual pattern. Oligo- or Frank amenorrhea was defined as a history of menstrual cycles of >38 days.⁹ Routine transvaginal sonography of the pelvis was done for all the patients. The Rotterdam 2003 consensus indicated that polycystic ovaries can be established when at least one ovary demonstrates an ovarian volume of greater than 10 cm³ (milliliters) or 12 or more follicles measuring 2–9 mm in diameter.^{2,3}

Height and weight were taken and body mass index (BMI) was calculated. They were assessed for their menstrual pattern and clinical features of hyperandrogenism which included acne, excessive hair growth (hirsutism) and androgenic alopecia. Hirsutism defined as excessive growth of terminal hair in women in a male-like pattern, is the most commonly used clinical diagnostic criterion of hyperandrogenism.¹⁰ Excessive hair growth was assessed by standard scoring system i.e., Ferriman Gallway Score. Clinical hyperandrogenism was defined as modified Ferriman Gallway score ≥ 8 .¹¹ Hormonal Profile including luteinizing hormone (LH), follicle stimulating hormone (FSH) and testosterone level and metabolic parameters like fasting blood sugar and lipid Profile was done for all the patients following 3-5 days of spontaneous menses or withdrawal bleeding. The test was done using autoanalyzer by CLIA method. They were further categorized into different phenotypic variants. Written informed consent was taken and the study was started after obtaining ethical clearance from the Institutional Ethical Review Committee. All data was stored in Microsoft excel format and analysed using SPSS version 11.5. For descriptive analysis mean (\pm SD), frequency

and percentage were calculated to describe the characteristics of variables. Categorical variables were analyzed using Chi-square test. p-value less than 0.05 was considered significant.

RESULTS

Eighty cases of PCOS were enrolled in the study. The mean age of the patients was 26.5 \pm 5years, the mean BMI was in the normal range (22.4 \pm 3.2) and the menstrual cycle length was 102.1 \pm 52.54 days.

The most common presentation was menstrual irregularity (95%). Type B phenotypic variant of PCOS was the most common phenotype (60%) followed by Type D (30%). [Table-1]

Table-1: Phenotypic variants (N=80)

Phenotypic variants	n	(%)
Type A (H+O+P)	4	5
Type B (H+O)	48	60
Type C (H+P)	4	5
Type D (O+P)	24	30

Acne was the commonest presentation in women with clinical hyperandrogenism with acne. Twelve patients had overlapping features and most common combination was acne and hirsutism [Table-2]

Table-2: Clinical Hyperandrogenism (N=80)

Symptoms	(n)	(%)
Acne	44	55
Hirsutism	28	35
Hair loss	20	25

LH/ FSH ratio of more than 2 was seen in 50% of PCOS cases (Type B > Type D). The metabolic parameters were in the normal range. [Table-3]

Table-3: Hormonal and Metabolic Profile

Biochemical Parameters	Mean \pm SD
LH (mIU/ml)	9.15 \pm 3.20
FSH (mIU/ml)	4.45 \pm 1.79
Testosterone (ng/dl)	0.72 \pm 0.36
Fasting blood glucose (mg)	96.55 \pm 5.56
Triglyceride level (mg/dl)	120.8 \pm 40.76

DISCUSSION

The phenotypic approach of categorizing PCOS has a number of practical applications. It would be helpful to identify those women with PCOS who are at the highest risk for metabolic dysfunction— those with “classic” PCOS phenotypes (phenotypes A and B).⁵ In this study the different PCOS phenotypes and their hormonal and metabolic profile was evaluated. Eighty PCOS cases were enrolled in the study. Irregular menstrual cycle was the most common presentation in our study. Sobti *s* et al reported menstrual irregularity in 83% of the study cohort. Menstrual irregularities (cycle length >60 days) were significantly more common in phenotype A as compared to phenotype D (80.18% vs 50%, $P = 0.000$).¹² A study by Ramanand et al in Maharashtra reported oligomenorrhoea in 65% PCOS cases and recommended oligomenorrhoea as a highly predictive surrogate marker of PCOS.¹³

It was reported that over an 8-year period, the conversion rate to type 2 diabetes among oligomenorrhoeic women was approximately two-fold greater than that for eumenorrhoeic women, regardless of whether the oligomenorrhoeic women were obese or lean, indicating that oligomenorrhoea was an independent predictor of type 2 diabetes.¹⁴

It was found that PCOS phenotype B was the most common phenotypic variant (60%) followed by Type C. This is in contrast to the study done by Sobti S et al where the most prevalent phenotype was Type A (45.5%) followed by Type D (23.4%).¹² Saxena et al reported phenotype C as most common. Their study subjects were infertile women presenting in a tertiary care centre.¹⁵ In another study by Sachdeva et al it was found that Phenotype A was most common with 67.7% followed by Phenotype C with 17.7%.¹⁶ Phenotypic variant may vary

according to the study population as different genetic component, racial, ethnicity and environmental factors are thought to contribute to this diversity. Type A is considered to be the full-blown and most severe phenotypic variant whereas ovulatory PCOS (Type C) are regarded as the mild form of classic PCOS. The different phenotype may present with some similarity but differences among them should also be taken into account considering their clinical, endocrinal and metabolic parameters.

The mean BMI in our population was $22.4 \pm 3.2 \text{ kg/m}^2$. This is in contrast to the study by Kar et al where 62.5 % of women with PCOS were found to be overweight.¹⁷ Ramanand et al reported 75 % of the women to be obese in their study.¹³

This study also emphasizes the need to evaluate lean women for PCOS presenting with menstrual irregularities. The importance of obesity in the pathophysiology of PCOS is evidenced by the efficacy of weight reduction to improve metabolic alterations, to decrease hyperandrogenism, to increase ovulatory menstrual cycles, and to improve fertility.¹⁸ Hence lifestyle modification should be addressed as a first line of treatment in women with PCOS.

Acne was the most common clinical presentation among all hyperandrogenic features which was assessed for clinical hyperandrogenism accounting for 55% of all cases whereas in the study done by Sobti S et al the most common hyperandrogenic feature was excessive hair growth 43.3% (39 out of 90) followed by acne (31.1%).¹² Our study showed 95% of the PCOS had hyperandrogenic features that is consistent with most other studies.

The increased LH:FSH ratio seen in PCOS is due to dysregulated gonadotropin secretion as signaled by single nucleotide polymorphism. LH is the ligand for LH

receptor on the ovarian theca cells responsible for ovarian androgen production. This gonadotropin imbalance favors an exaggerated intraovarian androgen environment under the influence of LH and impaired folliculogenesis resulting in anovulation due to a relative FSH deficiency.¹⁹ The study by Gluszak et al observed significantly higher 17-OHP, LH, and LH-FSH ratio in phenotype A ($p < 0.03$).²⁰

Our study did not find any women with deranged metabolic profile as shown in Table 4. Another study found that among women diagnosed with type 2 diabetes, 58% had normal fasting glucose levels and were identified based on elevated 2h glucose levels by an oral glucose tolerance test.²¹

Sobti et al reported that hyperandrogenic phenotypes (phenotypes A, B and C) had a two- to six-fold higher (20-56%) prevalence of metabolic syndrome compared to phenotype D (9%), suggesting that the nonhyperandrogenic phenotype has a mild metabolic profile.¹² Patients with PCOS should be monitored for diabetes if they have a BMI greater than 30 kg/m² (or greater than 25 kg/m² for Asian patients) or have a family history of diabetes, acanthosis nigricans, or features of hyperandrogenism with anovulation.²² The serum testosterone level was also in the normal range in our study which is supported by the study conducted by Ramanand et al in which serum testosterone in most patients were normal or low.¹³

CONCLUSIONS

Anovulatory PCOS (Type B) was the most common phenotypic variant in our study population. The second most common was the nonandrogenic PCOS (Type D). Our study did not find obese PCOS hence emphasizing the need for evaluation in lean

women with or without hyperandrogenic features presenting with menstrual irregularities.

RECOMMENDATION: The classification of different phenotypes according to NIH consensus panel 2012 has given more insight on the commonest phenotypic variant of PCOS prevalent in a given subset of population. This classification tool can be used both in clinical and epidemiological setting which has further broadened our perspective for specific management options. The above findings need to be further verified by doing larger study on community setting. Detailed workup for metabolic syndrome can add more information to the varied presentation of PCOS in our population.

LIMITATION: The study was done under clinical setting. The sample size could have been larger to include more women with PCOS and this was further hindered by restriction of movement imposed by covid 19. More extensive laboratory test to rule out androgen excess was not done. Glucose tolerance test rather than fasting blood glucose would have provided more information on diabetes or impaired glucose status.

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