Original Research Article

A STUDY OF PREVALENCE OF PHENOTYPIC VARIANTS OF POLYCYSTIC OVARIAN SYNDROME IN REPRODUCTIVE AGE GROUP WOMEN

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A B S T R A C T

Background: Polycystic ovary syndrome (PCOS) is the most frequently encountered endocrine disorder occurring in women of reproductive age. We have divided the women with PCOS into four phenotypes and clinical characteristics among the different phenotypes are compared.

Materials and Methods: The study was a Cross-sectional, Observational study conducted at South Central Railway Hospital, Secunderabad over a period of 18 months from September 2018 to May 2020. A total of 80 women fulfilling the Rotterdam 2003 diagnostic criteria of PCOS attending Gynaecology and Dermatology clinic outpatient departments satisfying inclusion criteria were recruited for the study. Women with PCOS were divided into four phenotypes according to the clinical characteristics and the prevalence of different phenotypes is established.

Results: The most common phenotype in our study is phenotype A (full-blown PCOS) with prevalence of 66.25% (53 patients) which includes all three features: hyperandrogenism, irregular cycles and PCOM on ultrasound, followed by phenotype C 16.25 % (13 patients), phenotype B 11.25 % (9 patients) and phenotype D 6.25% (5 patients). Classic PCOS, Phenotype A represents the most common and severe form of PCOS had significantly higher weight, clinical hyperandrogenism, menstrual irregularities, hirsutism, infertility as compared to rest of the phenotypes. Menstrual irregularities (cycle length >60 days) were significantly more common in phenotype A 42(79.2%) as compared with phenotype B 6 (66.7%) and D 1(20%). Cycle length is normal in Phenotype C. Acne is the second most common manifestation of androgen excess 59 (73.7%).

Conclusion: Phenotype A (Classic PCOS) represents the most common form of PCOS with prevalence of 66.25%. These patients presented with higher modified FG score, more severe clinical hyperandrogenism, more pronounced menstrual dysfunction, infertility suggesting a higher risk of adverse metabolic and cardiovascular outcomes in this phenotypic group as compared to rest of the phenotypes.

Keywords: Polycystic ovary syndrome (PCOS), phenotypes, hyperandrogenism, menstrual irregularities, Rotterdam criteria, phenotype A, classic PCOS.

INTRODUCTION

Polycystic ovary syndrome (PCOS) is the most frequently encountered endocrine disorder occurring in women of reproductive age. It is a multisystem metabolic disorder which has a major impact on quality of life and fertility.[1] Patients present with irregular menses, infertility and clinical signs of hyperandrogenism such as acne, seborrhoea, hirsutism and alopecia along with a polycystic morphology of ovaries on ultrasound.[2] Several studies of diverse populations have estimated its prevalence as 5-10% in women of reproductive age.[3]

The advent of high resolution ultrasound scanning provided a non-invasive technique for the assessment of ovarian size and morphology. In 2003, a further consensus meeting was held in Rotterdam and it was agreed that two of three of the following criteria were sufficient to diagnose the syndrome: Oligo- or anovulation, clinical and/or biochemical signs of hyperandrogenism, and polycystic ovaries.

This revised Rotterdam criteria (2003) also included the ultrasound evidence of PCO as one of the diagnostic criteria.[4] However, some women may be diagnosed with polycystic ovaries at the time of having an ultrasound examination for other reasons, who have none of these symptoms. Once ultrasound became commonly used in the 1980s it was recognized that polycystic ovaries were frequently reported in asymptomatic women and this was one of the reasons that prevalence studies were undertaken.[5]

It is now widely recognized that there is a spectrum of clinical presentations. At one end of the spectrum are the women who ovulate and who have no dermatological manifestations such as acne or hirsutism. At the other end of the spectrum there may be women with menstrual disturbances; oligomenorrhea, increased hair growth, acne, crown pattern baldness, evidence of insulin resistance. The majority of women will present with only one or two of the clinical manifestations. Some women may present with anovulation with no hyperandrogenic manifestations, while others may present with severe androgenic symptoms but remain ovulatory. This created a lot of confusion in the diagnostic approach to PCOS.

So finally in 2012, National institute of health consensus panel proposed the phenotypic approach to classify PCOS.[6]

- Phenotype A (Full blown syndrome PCOS) includes hyperandrogenism, ovulatory dysfunction and polycystic ovaries.
- Phenotype B (Non PCO PCOS) includes hyperandrogenism and ovulatory dysfunction.
- Phenotype C (ovulatory PCOS) includes hyperandrogenism and polycystic ovaries.

- Phenotype D (Non-hyperandrogenic PCOS) includes ovulatory dysfunction and polycystic ovaries.

This study has been done with the aim of establishing the prevalance of these phenotypes. Hence women with PCOS are seen frequently, so this study is planned to evaluate all the reproductive women presenting with features of PCOS and categorise them into different phenotypes and establish the prevalence of different phenotypes.

MATERIALS AND METHODS

It was a Cross sectional, observational, prospective study conducted at department of obstetrics and gynaecology in South Central Railway Hospital, Lallaguda, Secunderabad. A total of 80 women fulfilling the Rotterdam 2003 diagnostic criteria of PCOS attending Gynaecology and Dermatology clinic outpatient departments of the South Central Railway Hospital, Lallaguda, Secunderabad, Telangana from September 2018 to May 2020 were enrolled for the study.

Sample size estimation

On reviewing the past 3 years of medical records in south central railway hospital, it was found that daily attendance of Gynaec clinic at our hospital is 30-40 per day out of which 65% will be reproductive age women.

Prevalence of Polycystic ovarian syndrome is 5 to 10%.

Sample size has been calculated using the Kish Leslie formula

$$Z2 \times p\,(1-p)\,/\,d^2$$

Where Z = standard normal variable of the confidence interval

(1.96 confidence level 95%)

 p = expected prevalence of the disease or proportion.

(5%) – Based on previous studies

d = precision (level of error) (0.05)

Using this formula, the required sample size was found to be 73. Total of 80(eighty) women satisfying the inclusion criteria were enrolled in the study within the time frame of study

Sampling strategy

Random sampling done based on inclusion and exclusion criteria

Inclusion Criteria

All women in reproductive age group (16-45years) attending

Gynaecology and Dermatology outpatient departments fulfilling the Rotterdam 2003 diagnostic criteria of PCOS presenting with any 1 or a combination of the following complaints:

1. irregular menstrual cycles
2. unwanted facial/body hair growth/Acne/seborrhea
3. infertility.

Those willing to participate after taking written informed consent.

Exclusion Criteria

- Pregnant women, lactating women and postmenopausal women.
- Preexisting medical conditions like thyroid disease, hyperprolactinemia and non-classic congenital adrenal hyperplasia.
- Diagnosed case of any androgenic /Insulinemic neoplasm.
- Patients on treatment with hormonal and other drugs influencing PCOS.
- Patients who are not willing to participate in this study.

Approval for the study was taken by the Ethics and Scientific Committee of South Central Railway Hospital, Secunderabad. The scientific aspect of the thesis was evaluated by the scientific committee.

Methodology

Detailed history was taken from all the patients in pre-designed case records. Detailed reproductive and gynaecological history, with emphasis on regularity of menstrual cycle, hyperandrogenic symptoms, family history of irregular menstrual cycles, and treatment history, various clinical manifestations of androgen excess including their duration, evolution and progression was taken. A careful general and systemic examination was done, particularly thyroid, breast, pelvic examination for clinical diagnosis. The physical examination of the enrolled patients included their blood pressure, weight (kg) and height (cm). Body mass index (BMI) was calculated to assess obesity. BMI (kg/m 2) is categorised as (Lean=BMI <18.5, Normal= BMI 18.5- 22.9, Overweight=BMI 23-29.99, obese= BMI 30 and more). FIGO classification was used to characterize menstrual irregularity. 102 The cycle length of 24-38 days was considered normal, and length >38 days were included in the oligomenorrheic group. Amenorrhea was defined as absence of menstruation for 3 consecutive months during the previous year and women having menses only after progesterone withdrawl, as an expression of ovulatory dysfunction.

For the diagnosis of PCO morphology, all women underwent an ultrasonography of abdomen and pelvis during the early follicular phase using Philips ultrasound machine, model IU22 (probe frequency range 5-7 MHz).

The presence of PCO was diagnosed by the presence of 12 or more follicles measuring 2–9 mm in diameter in each ovary and/or increased ovarian volume (>10 cm 3).

History, physical examination, laboratory investigations, imaging studies, clinical manifestations of androgen excess were entered in data sheet, and all the study subjects were divided into four phenotypes according to the clinical characteristics as follows

- Women with clinical hyperandrogenism, menstrual cycle irregularities and polycystic ovarian morphology in ultrasonography is categorised as Phenotype A.
- Women with clinical signs of hyperandrogenism and menstrual disturbances considered as Phenotype B.
- Patients with signs of androgen excess clinically and polycystic ovarian morphology in ultrasonography is categorised as Phenotype C.
- Women with menstrual disturbances and polycystic ovarian morphology in ultrasound is categorised as Phenotype D.

Various clinical parameters of phenotypes of PCOS are compared and the prevalence of different phenotypes is established.

Statistical Analysis

Data was entered in MS excel 2007 and analyzed by using SPSS V22.Normality was checked by using the Kolmogrov smirnov test. Descriptive statistics represented in the form of charts and percentages and Mean with SD. ANOVA (analysis of variance) test was applied based on the nature of the distribution. $P<0.05$ was considered as statistically significant.

RESULTS

Table 1: Age and Marital Status of Study participants

Age in Years	No. of Cases	Percent
16 – 20	12	15.0
21 – 25	27	33.8
26 – 30	30	37.5
31 – 35	7	8.8
36 – 40	4	5.0
Total	80	100.0

The age group of patients ranged from 16-40 years. Maximum number of patients 30(37.5%) belonged to 26-30 years,27(33.8%) 21-25 years age group, followed 16-20 years age group containing 12(15%) patients. 4 (5%) patients were in the age group of 36-40 years. Mean age of PCOS patients is 26.69 years in our study. Among 80 patients enrolled during the present study, 47(58.8%) patients were married and 33(41.3%) were unmarried.30 are married in phenotype A,6 in phenotype B. In phenotype C and D 7,4 women are married respectively.

Table 2: Menstrual pattern and Onset of Menarche in study population

Menstrual pattern	No. of Cases	Percent
Regular	13	16.3
Amenorrhea	13	16.3
Oligomenorrhea	54	67.5
Total	80	100.0

Analysis of menstrual history of 80 patients showed that 13(16.3%) patients had regular menses while 54 (67.5%) patients experienced menstrual disorders in the form of Oligomenorrhea and 13 (16.3%) amenorrhea. Out of 80 PCOS patients, 17(21.3%) women experienced their first cycle before the age of 12 years. 58(72.5%) women had menarche during the age of 12-14 years, while 5(6.3%) women reported their onset of menses after 14 years. Mean age of menarche is 13.56 years.

Table 3: Various Cutaneous Manifestations in PCOS

Cutaneous manifestations	No. of Cases	Percent
Hirsutism	68	85
Acne	59	73.7
Acanthosis nigricans	39	48.8
Striae distensae	43	53.8
Seborrhea	28	35.0
Androgenic Alopecia	29	23.8

The most common cutaneous manifestations was hirsutism which was present in 68(85%) patients. This was followed by acne 59(73.7%), Striae distensae 43(53.8%), Acanthosis nigricans was present in 39(48.8%), Seborrhoea 28(35%), Androgenic alopecia in 19(23.8%),a were present in patients among a total study population of 80.

Table 4: USG finding of PCOS

USG	No. of Cases	Percent
NPCO	9	11.2
PCO	71	88.8
Total	80	100.0

In an ultrasound study, 71(88.8%) patients showed polycystic ovaries, while 9(11.2%) showed normal ovaries.

Table 5: Prevalence of different phenotypic variants of PCOS

Phenotype	No. of Cases	Percent
A	53	66.25
B	9	11.25
C	13	16.25
D	5	6.25

The most common phenotype in our study is Phenotype A with prevalence of 66.25% seen in 53 women, followed by phenotype C 16.25 % (13 patients), phenotype B 11.25 %(9 patients) and phenotype D 6.25% (5 patients).

Table 6: Menstrual irregularities in different phenotypes

Menstrual irregularities	Phenotype							
	A		B		C		D	
	No. of cases	%	No. of cases	%	No. of cases	%	No. of cases	%
24 – 38 days	2	3.8%	0	0.0%	12	92.3%	0	0.0%
38 – 60 days	9	17.0%	3	33.3%	0	0.0%	4	80.0%
> 60 days	42	79.2%	6	66.7%	1	7.7%	1	20.0%

Menstrual irregularities (cycle length >60 days) were significantly more common in phenotype A 42(79.2%) as compared with phenotype B 6 (66.7%) and D 1(20%). Cycle length is normal in Phenotype C.
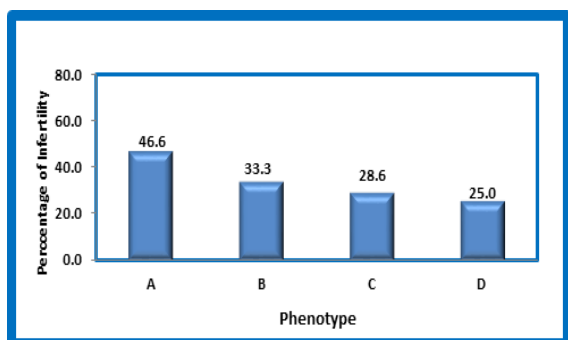
Figure 1: Infertility among married women in different phenotypes

Out of 47 women who were married infertility is seen in 19 (40.42%) women. It is more common in phenotype A, out of 30 married women14(46.6%) had primary infertility most commonly seen in overweight or obese patients and 5 members gave history of conception with ovulation induction. In phenotype B,6 women are married 2(33.3%) had infertility, phenotype C (ovulatory PCOS) among 7 married female 2(28.57%) had infertility may be due to other factors. In Phenotype D 1(25%) women infertility is seen out of 4 married women.

Table 7: Comparison of severity of Acne in different phenotypes of PCOS

Acne grade	Phenotype							
	A		B		C		D	
	Count	%	Count	%	Count	%	Count	%
I	8	50%	4	25%	3	18.75%	1	6.25%
II	20	64.5%	4	12.9%	7	22.6%	0	0.0%
III	8	88.9%	1	11.1%	0	0.0%	0	0.0%
IV	2	66.6%	0	0.0%	1	33.3%	0	0.0%
Total	38	66.25%	9	11.25%	11	16.25%	1	6.25%

In our study phenotype A acne is seen in 38(71.7%), phenotype B 9(100%), phenotype C 10(76.9%), phenotype D 1(20%).Acne is most prevalent in phenotype C in our study. Most of the women presented with grade 2 severity. In our study is seen most commonly 21(39.6%) in phenotype A, 3(33.3%),4(30.76%) phenotype B, C respectively, absent in phenotype. Most frequently distributed over face, scalp.

Table 8: Statistical evaluation among different phenotypic variants of PCOS

Variables	Phenotype								P-value
	A (n=53)		B (n=9)		C (n=13)		D (n=5)		
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	
Age	26.57	4.82	23.89	3.33	26.85	5.34	20.80	2.17	0.032*
AOM	12.72	1.21	11.78	1.20	12.77	1.17	13.40	1.14	0.082
BMI	27.53	5.24	23.43	4.04	24.28	2.10	21.00	22.72	0.001*
Waist circumference	35.63	4.56	33.41	5.21	32.69	5.11	33.56	4.69	0.16
Waist-hip ratio	0.88	0.07	0.86	0.08	0.82	0.09	0.87	0.08	0.09
SBP	119.23	8.63	116.84	7.69	118.31	6.75	115.89	6.34	0.73
DBP	77.52	6.42	74.38	6.71	76.49	5.96	75.61	7.53	0.55
m-FG score	14.2	2.13	12.6	1.12	9.08	1.74	3.2	0.98	0.000*

Mean age of PCOS in Phenotype A is 26.57 years. In our study mean age of PCOS in phenotype D (20.8) is less compared to phenotype A this is statistically significant (p value <0.05). Mean age of menarche in Phenotype A is 12.72 years ,11.78 years in Phenotype B, 12.77 years, 13.40 years in Phenotype C, D respectively. Mean age of menarche in Phenotype D is more compared to other phenotypes this is statistically significant (p value <0.05). Mean modified Ferriman Gallwey score in Phenotype A is 14.2 which is higher compared to Phenotype D (3.2) this is statistically significant (p value <0.05). Mean BMI in Phenotype A is 27.53. Phenotype B is 23.43, 24.28 and 21.0 in Phenotype C and D repectively. Mean Waist hip ratio of phenotype A is 0.88, 0.86, 0.82, 0.87 in phenotype B,C,D respectively, higher in phenotype A however there is no significant differences noted in the waist circumference, waist-hip ratio (P > 0.05) in different phenotypes. Blood pressure among all phenotypes was similar.

DISCUSSIONS

In this study the age group of patients ranged from 16 to 45 years. The youngest and oldest patients recorded were 16 and 40 years old respectively. In our study 30 (37.5%) patients belonged to 26-30 years, 27 (33.8%) belong 21-25 years, 12 (15%),7 (8.8%),4 (5%), belong to 16-20 years, 31-35years,36-40 years respectively. Mean age of total PCOS patients included in the study is 26.69 yrs. Mean age of PCOS in Phenotype A is 26.57 years,23.89,26.85, 20.80 years in Phenotype B,C,D respectively

Koivunen et al. examined a total of 189 healthy volunteers aged 20-45 years. They observed substantial decrease in incidence of PCO with advancing age. The prevalence was found to be

7.8% in women older than 35 years, compared to 21.6% in women younger than this age.[7] The decrease in incidence is probably due to spontaneous decrease in androgen secretion after the age of 35 years in normal and in PCOS women.[8]

In our study out of 80 patients were enrolled, 47(58.8%) women were married and were 33(41.3%) unmarried. In research done by NICHD revealed that most women did not find out that they had PCOS until they have been evaluated for infertility. Similar results were observed in 27-34 years age group by March et al. The study indicated that 68-69% women did not have a pre-existing diagnosis of PCOS.[9]

In a study done on 1741 patients by Balen et al., approximately 30% of patients had regular menses, 50% oligomenorrhoea, and 20% amenorrhoea.10 In a study of 1079 PCOS patients Goldzieher found that 51% patients were amenorrhoeic while 29% were oligomenorrhoeic. The remaining 20% had regular menstrual periods.[11]

Out of 80 PCOS women enrolled, 17(21.3%) women experienced their first cycle before the age of 12 years. 58(72.5%) women started their periods during the age of 12-14 years, while 5(6.3%) women reported their onset of menses after 14 years. Mean age of menarche in Phenotype A is 12.72 years ,11.78 years in Phenotype B, 12.77 years, 13.40 years in Phenotype C,D respectively .Keen et al observed mean age of menarche was 13.8 ± 0.9 years.[12]

In our study USG revealed PCO pattern in 71(88.8%), while 9(11.2%) women in Phenotype B showed normal ovaries on USG. In a study by Botsis et al., PCO were detected by transvaginal ultrasound in 75% of women with clinical diagnosis of PCOS,[13] 25% women with PCOS did not have characteristic finding on ultrasound. Survey of literature data reveal frequencies that resemble closely with our results.

The most common phenotype in our study is phenotype A (full-blown PCOS) with prevalence of 66.25% (53 patients) which includes all three features: hyperandrogenism, irregular cycles and PCOM on ultrasound, followed by phenotype C 16.25 % (13 patients), phenotype B 11.25 % (9 patients) and phenotype D 6.25% (5 patients). Most published studies reported phenotype A to be the most prevalent which is similar to our study.[14,15]

Sharma et al. retrospectively analyzed a complete data of 50 hirsute patients aged between 13 and 17 years. Using Rotterdam criteria 34% of these women were diagnosed with PCOS. Fifty percent patients were aged 20-30 years. A high incidence of acne (64%) was reported in these patients.[16,17]

Our study has few limitations

The sample size of the present study is only 80 and as the study is conducted at a tertiary care hospital where majority of the patients attend the clinic on referral for their persisting/severe problems there is a possibility of bias. Another limitation of the study is that all the study subjects are either Railway employees or their family members who belong to middle class socio-economic status. Therefore, further studies need to be conducted on a larger population.

CONCLUSION

The age of the patients varied from 16-45 years. The youngest and oldest patients recorded were 16 and 40 years old respectively. Our data showed that 30 (37.5%) patients belonged to 26-30 years. Mean age of PCOS patients is 26.69 years. Mean age of PCOS in Phenotype A is 26.57 years,23.89,26.85, 20.80 years in Phenotype B, C, D respectively. Mean age of phenotype in our study is statistically significant (p value <0.05). Irregular menstrual cycles were found to be more common in patients with PCOS. Our study revealed that patients had menstrual cycle irregularities like 54 (67.5%) oligomenorrhoea and 13 (16.3%) amenorrhea. Menstrual irregularities (cycle length >60 days) were significantly more common in phenotype A 42(79.2%) as compared with phenotype B 6 (66.7%) and D 1(20%). Cycle length is normal in Phenotype C.

Phenotypic distribution of PCOS is highly convenient for clinical practice, gives us some idea about the differences in the clinical profile of various phenotypes and identify those women who are at the highest risk for metabolic dysfunction.

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