The Egyptian Journal of Hospital Medicine (April 2022) Vol. 87, Page 1436-1441

Polycystic Ovary Syndrome Phenotypes among Infertile Women in Zagazig University Hospitals

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ABSTRACT

Background: Little studies have been performed to study the different Polycystic Ovary Syndrome (PCOS) phenotypes among infertile women.

Objective: Evaluation the phenotypes of polycystic ovary syndrome among infertile women in Zagazig University Hospitals.

Patients and methods: This study was conducted, as cross-sectional study on 48 infertile women attending Cytogenetic Unit and Ultrasound Unit at Zagazig University Hospital, who were diagnosed with PCOS. They were evaluated by ultrasonography. They were assigned into four phenotypes; A, B, C, and D, on basis of Rotterdam criteria.

Results: The primary infertility was more common among phenotype A, while secondary infertility was more common among phenotypes B and D but without statistical significance difference. There was no statistically significant difference between different types of PCO in prolactin, FSH, free testosterone and cortisol but there was a statistically significant increase in LH among type D in comparison to other types, there was a statistically significant increase in total testosterone among type A in comparison to other types and there was a statistically significant decrease in 17 α - OHP among type D in comparison to other types. There was a statistically significant increase in antral follicle count on right side among type A in comparison to other types and there was a statistically significant increase in antral follicle count on left side among type A and D in comparison to other types.

Conclusion: The study suggests that phenotypic group A is the most prevalent phenotype of PCOS.

Keywords: Infertility, Phenotypes, Polycystic Ovary Syndrome.

INTRODUCTION

As a metabolic and reproductive endocrinopathy, polycystic ovarian syndrome (PCOS) is quite common. It is common for young women with PCOS to suffer from infertility, menstrual irregularities, and persistent anovulation due to their condition. PCOS-afflicted women have a 10-fold increased risk of infertility, which affects up to 40% of the population [(1)]. Fertility is reduced because of the endocrine, metabolic, and gynecological problems associated with PCOS, which affect the ovary's ability to function [(2)].

As a result, the frequency of PCOS can vary greatly from place to place and population to population. A person's race and ethnicity play a role in whether or not they are diagnosed with PCOS. According to the Rotterdam criteria, PCOS and PCO have a global prevalence of 5-10% and 17-22%, respectively. There are few research in Africa on the prevalence of PCOS, with estimates ranging from 16 percent to 32 percent from various institutions [(3)]. Polycystic ovaries (PCO) are characterized by antral follicles that have been unable to mature. PCOS is thought to be the root cause of anovulatory infertility in as many as 75% of women with the condition. A quarter of women with PCO go on to develop PCOS symptoms, making it the most common form of PCOS [(4,5)].

PCOS is associated with insulin resistance and obesity, but neither of these symptoms is listed in the diagnostic criteria, thus they should be employed for this reason [(6)]. Diagnosing polycystic ovarian syndrome is a difficult task. Adolescents with polycystic ovaries (PCOS) should be diagnosed using updated Rotterdam criteria that include both hyperandrogenism (HA) and oligo-anovulation (OA), according to a 2018 international PCOS guideline [(7)].

The clinical manifestations of PCOS include infertility, hyperandrogenism, oligo ovulation or anovulation, and other metabolic problems. There was a statistically significant difference between the infertile women with PCOS and the infertile women who had normal ovaries in terms of the frequency of menstruation, oligomenorrhea, hirsutism and serum testosterone levels [(8)].

So finally, in 2012, National Institutes of Health (NIH) consensus panel proposed the phenotypic approach to classify PCOS [(9)] into: (1) Phenotype A (full-blown syndrome PCOS: PCO+OD+ HA) involving polycystic ovaries (PCO), ovulatory dysfunction (OD), in addition to HA (biochemical or clinical), (2) Phenotype B (non-PCO PCOS: OD+HA) involves ovulatory dysfunction (OD) and HA. (3) Phenotype C (ovulatory PCOS: PCO+ HA) involves PCO and HA. (4) Phenotype D (non-hyperandrogenic PCOS: PCO+OD) involves PCO and OD.

These four phenotypes are still to be established as a broad range of the same illness, which is known as PCOS. PCOS phenotypes have not been studied thoroughly enough [(10)].

Aim of the work was to evaluation of polycystic ovary syndrome phenotypes in Zagazig University Hospitals among infertile women.

PATIENTS AND METHODS

Received: 17/10/2021
Accepted: 15/12/2021

The present study was conducted at Cytogenetic Unit and Ultrasound Unit at Zagazig University Hospital, as a cross sectional study involving 48 infertile women, who were diagnosed with PCOS.

Study participants comprised those who met these criteria: (1) Infertile patients with PCOS. (2) Age from 18 –37 years. (3) At least two of the following three criteria must be met for a patient to be diagnosed with PCOS: (i) Oligo and/or anovulation. (ii) Biochemical and/ or clinical hyperandrogenism. (iii) Polycystic ovaries as shown on ultrasound: >12 cysts measuring 2-9 mm in diameter in one or two ovaries, and ovarian volume 10 ml (ovarian volume was measured on the basis of the elliptical formula (length × width × thickness × 0.5).

Patients with the following characteristics were excluded: Hyperprolactinemia, thyroid dysfunction, Cushing syndrome, congenital adrenal hyperplasia, androgen producing neoplasm, women with diabetes mellitus or hypertensive patients, and patients with liver and cardiac diseases.

All cases were applied to full history with detailed menstrual history, and general examination (abdominal examination, laboratory investigation, and ultrasonography).

- Body mass index **(BMI) =** (bodyweight in kilograms)/ (height in meters)^2.

According to WHO classification (BMI) **[11].**

- Waist to hip ratio (WHR) was obtained by dividing waist circumference (WC) by hip circumference (HC) using the same units of measurement (cm) for both.
- Hip circumference was measured using a non-elastic tape that is held horizontally without being restricted at the point that results in the maximum diameter over the buttock.
- Waist circumference, any bulky cloths were removed, it was measured around the abdomen above level of woman's umbilicus using flexible tape measure which is not elastic and not stretched during measurements.
- Acne defined as presence of acne on most days for 3 years or more.
- Hair distribution evaluation scalp hair for presence of alopecia or excessive hair fall, body hair distribution to detect male pattern hair growth **[12].**
- **According to Ferriman Gallways** scoring system hirsutism was diagnosed as score 8 or more over 7 body parts (arms, thighs, confront, stomach area, back, upper lip and mid-section) was considered normal and more than 8 was considered hirsutism **[12].**
- Breast examination for galactorrhea this done by physical examination by expressing some of the fluid from the nipple by gentle compression of the area around the nipple.
- Neck examination for thyroid masses or enlargement.
- Examination of abdomen and pelvis for inspection of hair distribution and palpation of pelvic and abdominal masses.

Investigations:

Ultrasound:

A transvaginal ultrasound scan was performed for sexually active women. Technique of trans-vaginal ultrasound: using high-resolution (Voluson 730 HD 2 with a 4-7MHz, USA), each patient was advised to empty bladder before examination, between cycle day 2-7 in menstruating females. In case of amenorrhea withdrawal bleeding was induced then ultrasound was done between days 2-7 of withdrawal bleeding. The transducer was wrapped in gel and inserted into a latex condom that had been greased with gel before being inserted into a woman's lithotomy position. Transducer was introduced into posterior vaginal fornix and scanning was done. Ultrasonic scanning of pelvic organs was done including uterus (size, shape, and endometrial thickness), cervical outlines and measurement of cervical canal length, ovaries size and shape and pelvic mass. After identification of the ovaries, the volume of the ovary was measured in three planes. Ultrasound picture of polycystic ovary was diagnosed by presence of 12 ≥ follicles measuring 2-9 mm in diameter, peripherally distributed throughout the entire ovary or ovarian volume more than 10 cm^3.

Estimation of biochemical and hormonal parameters:

Fasting blood glucose level, lipid profile, serum level of prolactin, serum level of follicle stimulating hormone (FSH), serum level of luteinizing hormone (LH), serum level of testosterone (free and total), dehydroepiandrosterone sulfate (DHEA-S), 17 alpha hydroxyprogesterone (17 α –OHP), and serum cortisol.

Blood samples were obtained in minimal invasive procedures under complete aseptic condition on day 2-7 of the cycle in menstruating females. In case of amenorrhea withdrawal, bleeding was induced and blood sample was taken 2-5 days of withdrawal bleeding. Withdrawal bleeding was done by oral progesterone pills (typically medroxyprogesterone, provera, 10 mg oral daily for 10 days). After stopping the pills, the patient would be expected to have a withdrawal bleeding.

Enzyme linked immunosorbent assay was used for all of the tests on the serum hormones (ELISA System).

Classification of study participants:

Women with PCOS were assigned into four phenotypes on basis of Rotterdam criteria, phenotype A androgen excess (HA), ovulatory dysfunction (OA) and polycystic ovarian morphology (PCO), phenotype B (HA+OA), phenotype C (HA+PCO) and phenotype D (OA+PCO) **[9].**

Androgen excess (HA) was defined in terms of biochemical HA or clinical signs of HA.
Oligo-anovulation (OA) was defined as cycle lengths >35 days for oligomenorrheic women and >3 months for secondary amenorrhea.

Ethical consent:

An approval of the study was obtained from Zagazig University Academic and Ethical Committee. Every patient signed an informed written consent for acceptance of the participation in the study. This work has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for studies involving humans.

Statistical Analysis:

The statistical significance level was set at P0.05 for all analyses carried out with SPSS v.27. Frequency and percentage were employed to assess the prevalence of various PCOS characteristics. Quantitative data were presented as mean, standard deviation (SD), and range and were compared by one-way ANOVA by Welch and the post-hoc Games-Howell tests. P value < 0.05 was considered significant.

RESULTS

The mean age of the studied cases was 26.25 years. Regarding educational level it was low in 37.5% and the mean infertility duration among the studied cases was 3.85 years. Type of fertility was primary in 52.1% of the patients. Finally, 41.7% of the cases were suffering of oligomenorrhea (Table 1).

Table (1): Demographic data and history of the studied patients

Variable	I**(n=48)**	
Age: (year)		
Mean ± SD	26.25±5.45	
Range	19-37	
	N	**%**
Educational level:		
Low	18	37.5
Moderate	13	27.1
High	17	35.4
Infertility duration: (year)		
Mean ± SD	3.85±1.35	
Range	2-6	
	No	%
Infertility type:		
1ry	25	52.1
2ry	23	47.9
Menstrual history:		
Amenorrhea	15	31.2
Irregular cycle	13	27.1
Oligomenorrhea	20	41.7

The current results showed most frequent type found among the studied cases was type A (**Table 2)**

Table (2): PCO type of the studied patients

Variable	**(n=48)**	
	N	**%**
PCO phenotype:		
Type A (HA+AO+PCO)	24	50
Type B (AO+HA)	3	6.3
Type C (HA+PCO)	14	29.2
Type D (AO+PCO)	7	14.5

There was no statistically significant difference between different types of PCO regarding age, infertility duration, educational level, type of infertility, and menstrual history **(Table 3).**

Table (3): Comparison between different PCO types in demographic and history data

Variable	Type A (n=24)		Type B (n=3)		Type C (n=14)		Type D (n=7)		F	p
Age: (year)										
Mean ± SD	24.63±4.44		29±6.08		27.93±6.52		27.29±5.5		1.55	0.22
Range	19-35		22-33		20-37		20-35			
Infertility duration: (year)										
Mean ± SD	3.75±1.57		3.67±1.53		4.07±1.21		3.86±0.9		0.18	0.91
Range	2-6		2-5		2-6		2-5			
Variable	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**	**χ^2**	**p**
Educational level:										
Low	6	25	2	66.7	6	42.9	4	57.1	6.43	0.38
Moderate	8	33.3	1	33.3	4	28.6	0	0		
High	10	41.7	0	0	4	28.6	3	42.9		
Infertility type:										
1ry	15	62.5	1	33.3	7	50	2	28.6	3.04	0.39
2ry	9	37.5	2	66.7	7	50	5	71.4		
Menstrual history:										
Amenorrhea	5	20.8	1	33.3	5	35.7	4	57.1	7.19	0.30
Irregular	6	25	1	33.3	3	21.4	3	42.9		
Oligo menorrhea	13	54.2	1	33.3	6	42.9	0	0		

There was no statistically significant difference between different types of PCO regarding lipid profile while there was a statistically significant increase in FBS among type C in comparison to type A and B and also among type D in comparison to type B **(Table 4).**

Table (4): Comparison between different PCO types regarding blood sugar and lipid profile

Variable	Type A (n=24)	Type B (n=3)	Type C (n=l4)	Type D (n=7)	F	p
FBS: (mg/di) Mean ± SD	95.88±13.32	84.33±14.84	106.41±11	103.29±15.5	3.45	0.03*
Cholesterol: **(mg/dl)** Mean ± SD	185.09±39.83	172.7±41.01	195.29±28 .86	177.17±42.61	0.55	0.65
TG: (mg/dl) Mean ± SD	168.15±31.6	137.27±13.06	181.95±31.86	164.7±8.12	1.60	0.20
HDL: (mg/dl) Mean ± SD	43.87±7	43.13±4.88	42.78±6.78	42±5.63	0.17	0.91
LDL: (mg/dl) Mean ± SD	155.99±31.29	169.67±20.98	174.96±30.05	162.91±28.22	1.22	0.32

Table 5 revealed that there was no statistically significant difference between different types of PCO in prolactin, FSH, free testosterone and cortisol but there was a statistically significant increase in LH among type D in comparison to other types, there was a statistically significant increase in total testosterone among type A in comparison to other types and finally there was a statistically significant decrease in 17 α -OHP among type D in comparison to other types.

Table (5): Comparison between different PCO types regarding hormonal profile

Variable	Type A (n=24)	Type B (n=3)	Type C (n=l4)	Type D (n=7)	F or KW	p
Prolactin: (ng/ml) Mean ± SD	15.87±4.32	17.53±1.96	13.91±3.05	17.17±3.05	1.12	0.35
FSH: (mIU/ml) Mean ± SD	5.78±2.16	6.97±0.21	6.44±1.82	5.44±1.69	2.54	0.47
LH: (mIU/ml) Mean ± SD	9.01±2.14	7.63±1.82	7±1.14	10.37±2.64	4.05	0.02*
T. Testosterone: (ng/ml) Mean ± SD	2.9±0.23	1.72±0.08	2.66±0.17	2.22±0.50	3.95	0.04*
F. Testosterone: (ng/ml) Mean ± SD	3.56±0.38	2.4±0.46	3.58±0.3	2.83±0.07	2.14	0.25
DIIEAs:(ng/dl) Mean ± SD	224.31±6.35	202.6±8.99	231.14±6.67	202.81±33.6	0.48	0.70
17 α OHP:(ng/dl) Mean ± SD	2.25±0.53	2.87±0.31	2.61±0.5	1.8±0.08	4.14	0.01 *
Cortisol:(ng/dl) Mean ± SD	11.24±2.31	10.8±2.43	11.55±2.33	11.06±1.8	0.14	0.94

*: Significant

There was no statistically significant difference between different types of PCO in ovarian volume but there was a statistically significant increase in antral follicle count on right side among type A in comparison to other types and there was a statistically significant increase in antral follicle count on left side among type A and D in comparison to other types **(Table 6).**

Table (6): Comparison between different PCO types regarding ovary volume and antral follicle count

Variable	Type A (n=24)	Type B (n=3)	Type C (n=14)	Type D (n=7)	F	p
Right ovary volume: (ml) Mean ± SD	10.11±1.83	9.93±2.66	10.39±2.92	9.3±1.86	0.38	0.77
Left ovary volume: (ml) Mean ± SD	10.68±2.38	12±2.85	9.39±2.86	11.27±2.45	1.31	0.29
Right ovarian antral follicle count: Mean ± SD	18.38±2	15.33±2.31	17.21±2.49	16.86±1.95	3.65	0.04
Left ovarian antral follicle count: (Mean ± SD)	18.83±1.37	17±3	16±2.32	18.86±2.19	7.35	<0.001*

*: Significant

DISCUSSION

PCOS, or polycystic ovarian syndrome, is a hormonal and metabolic condition that affects many women [(13)]**.** PCOS is defined by a combination of androgen excess and ovarian dysfunction symptoms in the absence of other possible diagnosis. PCOS is thought to be caused by a combination of genetic and environmental factors, including a person's diet and lifestyle choices[(14)]**.**

Predicting the illness course and reproductive outcomes, as well as determining treatment options, are dependent on the ability to distinguish distinct PCOS phenotypes. In contrast, metabolic dysfunction is more common in the classic form than in the nonclassic form of PCOS. This demands constant monitoring and careful hormonal control [(9)]**.**

Regarding the demographic data the mean age was 26.25 years and ranged from 19-37 years, educational level in 37.5% of studied patients was low, in 27.1% was moderate and in 35.4% was high. Regarding the clinical history, the current study showed that the infertility duration among the studied patients ranged from 2 to 6 years with mean of 3.85 years.

Regarding type of infertility: 52.1% had primary infertility, 41.7% of the cases were suffering of oligomenorrhea, amenorrhea was found in 31.3% patients, and irregular cycle was present in 27.1% of these patients. Our results were in accordance with the study [(15)]**,** which demonstrated that the duration of infertility ranged from 2 - 8 years with mean of 3 years and the type of fertility was a primary fertility.

Regarding the frequencies of PCOS phenotypes, the current study demonstrated that, most

frequent phenotypes found among the studied cases were phenotypes A and C (50% and 29.2% respectively), phenotype D was found in 14.6%, while type B was found in only 6.3%. These results are supported by the study conducted by **Gluszak and colleagues** [16] in which the prevalence rates for phenotype were A (60.2%), B (16.1%), C (18.3%), and D (5.4%).

Pehlivanov and Orbetzova[17] found the same results in their study**.** Regarding the descriptive information of demographic and history data, the current study observed no statistically significant difference between different types of PCOS in age, duration of infertility, educational level or menstrual history. Also, the primary infertility was more common among phenotype A while secondary infertility was more common among phenotypes B and D but without statistically significant difference. These finding were in accordance with **Amini *et al.* (18)**.

Regarding the distribution of ultrasound findings, the current study demonstrated that there was no statistically significant difference between different phenotypes of PCOS in ovarian volume; but there was a statistically significant increase in ovaries antral follicle count of right side among phenotype A compared to other phenotypes and there was a statistically significant increase in ovaries antral follicle count of left side among phenotypes A and D compared to other phenotypes. These findings were consistent with the study of **Guraya** [19] **and Ali *et al.*** [20]**.**

CONCLUSION

The study suggests that phenotypic group A is the most prevalent phenotype of PCOS. The introducer of phenotype classification of PCOS patients may have implications in future management plans and follow up of each type. But due to the small number of patents in the study we can't reach a definitive conclusion regarding these points.

Financial support and sponsorship: Nil.
Conflict of interest: Nil.

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