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Different Phenotypes of Polycystic Ovarian Disease and Their Effects on Clomiphene Resistance in Infertile Women

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ABSTRACT

Background and Objective: Clomiphene resistance is an important problem among women with Polycystic Ovarian Disease (PCOD) suffering from infertility. Recognition of the causes would result in better prognosis in these patients. This study was performed to determine different PCOD phenotypes and their effects on clomiphene resistance in infertile women.

Methods: In this descriptive-comparative cross-sectional study, 200 consecutive PCOD women with infertility taking clomiphene who were reffered to Akbarabadi hospital in 2017 and 2018 were enrolled. Different PCOD phenotypes and their effects on clomiphene resistance among these women were assessed.

Results: The results showed that A, B, C, and D phenotypes were observed in 79 (39.5%), 13 (6.5%), 51 (25.5%), and 57 (28.5%) patients, respectively. Sixty-one patients (30.5%) had resistance. Despite no significant difference between phenotypes (P=0.064), the most common PCOD phenotype was A (HA+OA+PCO) found in 39.2% and D (OA+PCO) was seen in 29.8% of the patients.

Conclusion: According to the results, there was no significant association between PCOD phenotypes and clomiphene resistance. Finally, A and D phenotypes were frequent types with clomiphene resistance

Keywords Polycystic ovarian disease, Disease Resistance, Phenotypes, Clomiphene

Introduction

Polycystic Ovarian Disease (PCOD) is the most common endocrinological disorder in women of fertility age, seen in 6-10% of this age group **(1)**. PCOD is characterized by chronic anovulation and hyperandrogenism **(2)**. According to the European Society of Human Reproductive and Embryology /American Society for Reproduction Medicine Consensus in 2003, the patients with minimally two out of three criteria would be known as PCOD; 1) oligo-ovulation/unovulations; 2) clinical/laboratory symptoms of hyperandrogenism; 3) polycystic ovary in ultrasonography (volume and number of antral follicles) **(3)**.

Prevalence rate of PCOD in Iran ranges from 5% to 10% **(4)**. The primary cause of PCOD is unknown but insulin resistance is a common feature and it seems that it is evolved in the hyperandrogenism following this syndrome in obese and non-obese women **(5)**. Among some medications used to treat PCOD, clomiphene is utilized in the treatment of PCOD resulting in pregnancy rate of 20 to 50% **(6-9)**. Nowadays, the resistance to clomiphene is raising that would result in some problems in treatment of PCOD **(10-13)**. PCOD phenotypes include A (hyperandrogenism plus oligo-anovulation plus polycystic ovarian in ultrasonography), B (hyperandrogenism plus oligo/anovulation), C (hyperandrogenism plus polycystic ovarian in ultrasonography), and D (oligo-anovulation plus polycystic ovarian in ultrasonography) **(14, 15)**. There are little understanding about these four phenotypes and their role especially in clomiphene resistance. Also, due to dispersion of diagnostic criteria and lack of international consensus for different criteria, comparison of the available data is difficult **(16-19)**. Hence, this study was performed to determine different PCOD phenotypes and their effects on clomiphene resistance in infertile women.

Materials and Methods

This descriptive-comparative cross-sectional study carried out on 200 consecutive women with PCOD in Akbarabadi hospital during 2017 and 2018. All patients initially were diagnosed by Rotterdam criteria and were divided according to laboratory, clinical, and ultrasonographic criteria in four different phenotypes and then the patients received clomiphene. Inclusion criteria included age between 20 and 40 years, non-male factor infertility, and fallopian tube patency. Exclusion criteria were male factor infertility, fallopian tube obstruction, uterine anatomical disorders, and dissatisfaction to be enrolled in the study. For hyper-androgenism assessment, the clinical criteria (hirsutism according to Ferriman Score over 8, acne, and alopecia) and biochemical criteria (total testosterone level over 0.5 ng/ml or free testosterone over 3.5 pg/ml) were used. Pattern of the menses and menstrual irregularity were defined as oligomenorrhea (intervals between menses longer than 35 days) or amenorrhea (lack of menses more than six months).

For ultrasonographic assessment of PCOD, transvaginal approach was used and PCOD was diagnosed in cases with 12 or more cysts with diameters of 2 to 10 mm in each ovary and with volume of 10 cm^3 or more. Different PCOD phenotypes include A (hyperandrogenism plus oligo/anovulation plus polycystic ovarian in ultrasonography), B (hyperandrogenism plus oligo/anovulation), C (hyperandrogenism plus polycystic ovarian in ultrasonography), and D (oligo/anovulation plus polycystic ovarian in ultrasonography) (14, 15). The patients underwent Ovulation Induction (OI) with clomiphene with dose of 100 mg daily for five days and the response was assessed in 14^{th} to 16^{th} days of the menstrual cycle by trans-vaginal ultrasonography. The response was defined as growth of minimally one dominant follicle with diameter of 15 to 16 mm. In cases without response, a seven-day clomiphene course with dose of 100 mg was administered and the ultrasound assessment was repeated in 14^{th} to 16^{th} menstrual days. Cases without response to clomiphene were considered as resistant and most common phenotypes were determined in these cases.

Statistical issue

Data analysis was carried out by SPSS version 25.0 software. The mean plus standard deviation was used to demonstrate the numerical variables and the frequency and percentage were used to show the categorical variables. Chi-square and ANOVA, independent t-test, and logistic regression were applied and a P values less than 0.05 was considered statistically significant.

Results

The mean age was 28.5 ± 4.9 years ranging from 18 to 41 years that was not different between four phenotypes with mean age of 27.89, 26.77, 29.86, and 28.37 years in A, B, C, and D phenotypes, respectively (Figure 1). Also, the mean BMI was 28.3 ± 3.5 kg/m^2 ranging from 19.5 to 41.9 kg/m^2 that was not different between four phenotypes with mean BMI of 27.97, 29.63, 28.83, and 28.16 kg/m^2 in A, B, C, and D phenotypes, respectively (Figure 2). The results showed that the mean age and BMI of the phenotypes A, B, C, and D were not statistically significant (P> 0.05). Table 1 shows the mean and standard deviation of the mean age and BMI of the patients based on four phenotypes A, B, C, and D.

According to logistic regression analysis, the age and BMI had a P value of 0.875 and 0.272 that is not significant. In this study, it was relealed that 139 patients (69.5%) were responder to clomiphene and 61 patients (30.5%) had resistance. Despite no significant difference between phenotypes (P=0.065), the most common PCOD phenotype was A (HA+OA+PCO) found in 39.2% and D (OA+PCO) was seen in 29.8% of patients. Also, B and C phenotypes were seen in 6.5% and 25.5%, respectively. Furthermore, the percentage of resistance for A, B, C, and D phenotypes were seen in 39.2, 7.7%, 23.5%, and 29.8%, respectively. There was no significant association between phenotypes and resistance but it seems that patients with normal ovary have better response to clomiphene. Finally, A and D phenotypes were frequent types with clomiphene resistance. As seen in Table 2, the PCOD phenotypes and clomiphene resistance had no significant association (P=0.065) except when the significance level is not 0.05 but is considered 0.1 (P< 0.1).

Figure 3 shows the resistant and sensitive patients by phenotypes A, B, C, and D.

Table 1. Mean and standard deviation of age and BMI by phenotypes

Phenotype		N	Minimum	Maximum	Mean	SD	P value
Age	A	79	18.00	40.00	27.89	4.491	0.074
	B	13	18.00	36.00	26.76	5.81	
	C	51	20.00	41.00	29.86	4.84	
	D	57	18.00	37.00	28.36	4.97	
BMI	A	79	19.49	34.89	27.97	3.49	0.282
	B	13	24.24	41.91	29.63	4.99	
	C	51	19.53	40.39	28.83	3.91	
	D	57	19.49	33.59	28.16	2.63	

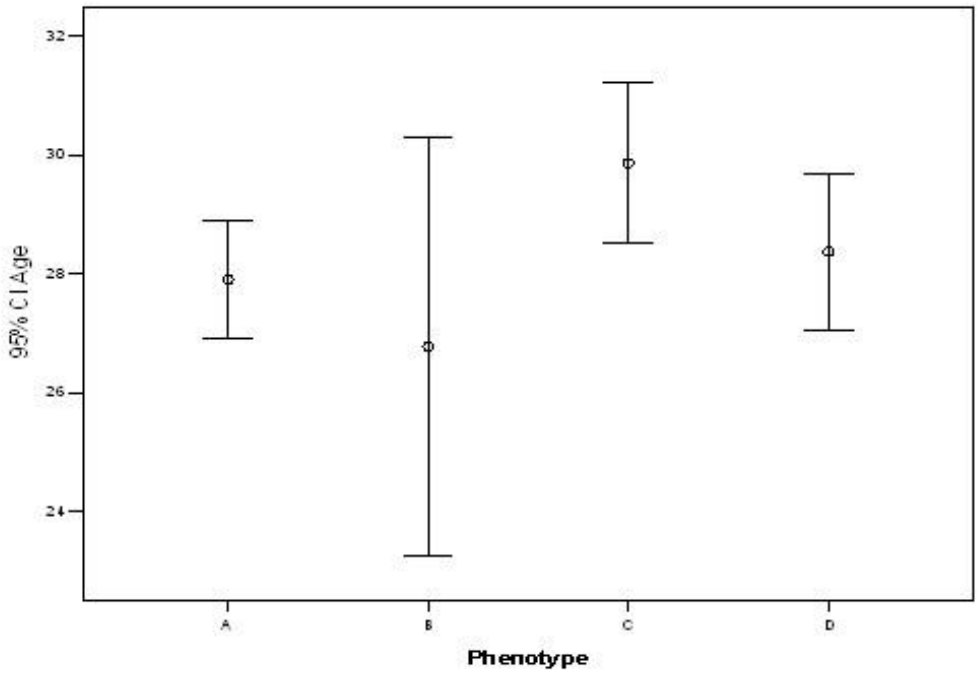

Figure 1. Age distribution of the patients in PCOD phenotypes

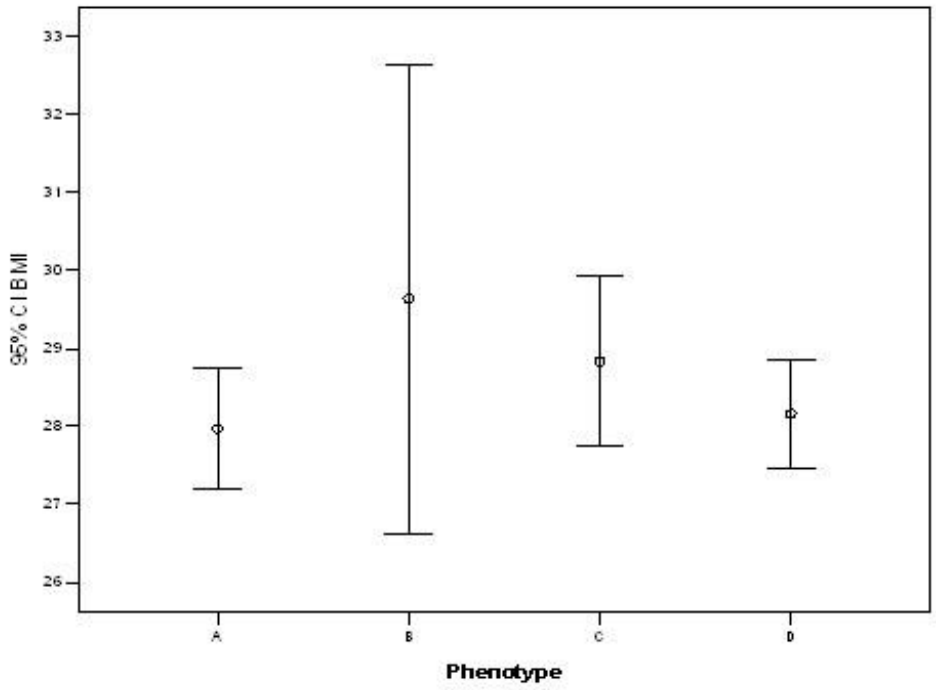

Figure 2. BMI distribution of the patients in PCOD phenotypes

Table 2. Clomiphene resistance according to PCOD phenotypes

Phenotype	Clomiphene		P value
	Resistant	Sensitive	
A	31 (39.2%)	48 (60.8%)	0.065
B	1 (7.7%)	12 (92.3%)	
C	12 (23.5%)	39 (76.5%)	
D	17 (29.8%)	40 (70.2%)	

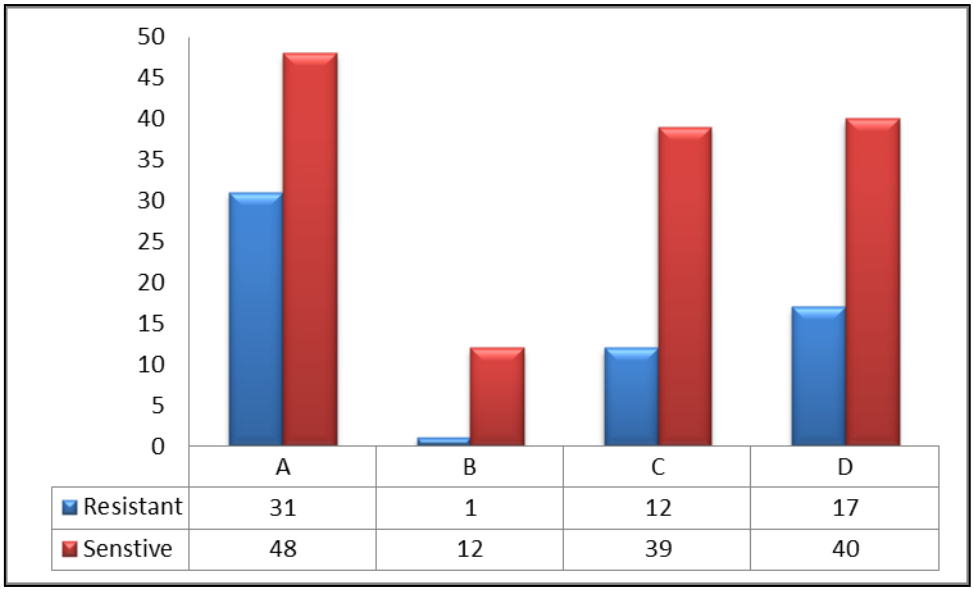

Figure 3. Frequency of resistant and sensitive patients by phenotypes A, B, C, and D

Discussion

In this study, PCOD phenotypes and their effect on clomiphene resistance were assessed. The results of current cross-sectional study demonstrated that there is no significant association between PCOD phenotype and clomiphene resistance but most resistance was seen in A (39.2%) and D (29.8%) phenotypes. Seyedoshohadaei *et al.*, **(16)** in an interventional study reported that among 150 patients with B phenotype the clomiphene resistance was seen in 26.6 % similar to our study.

Ramezanali *et al.*, **(17)** assessed 386 patients with PCOD versus 350 subjects with male factor infertility and reported that A and C phenotypes were accompanied with higher levels of Anti-Mullerian Hormone (AMH) and also the patients with A and B phenotypes had significantly lower pregnancy rate. Accordingly, it is probable that such phenotypes may affect the clomiphene resistance by AMH pathway.

Ciftci *et al.*, **(18)** reported 150 patients in a Turkish population and found that phenotype A is accompanied by higher resistance rate to metabolic treatments as seen in our study for clomiphene. Pehlivanov *et al.*, **(19)** in a Bulgarian population including 70 patients found that metabolic treatments in PCOD patients with phenotypes A and B had higher resistance to metabolic treatments but in our study, A and D phenotypes had higher resistance. In a study of Nestler et al. the results showed that response to clomiphene can be increased in obese women with the polycystic ovarian syndrome by decreasing insulin secretion with metformin **(20)**. This study shows that adjuvant medication in alternative method to increast the response to clomiphene. It should be noted that short-term use of rosiglitazone and clomiphene is more efficacious than metformin and clomiphene in ovulation induction in women with clomiphene-resistant PCOS i.e. the combination of drugs are of great importance as well **(21)**. Also, there is no specific recommendation regarding the use of clomiphene or metformin as first-step drug to date **(22)**. Some factors can predict the chance of resistant to clomiphene e.g. revealed that amenorrhea, level of BMI, total testosterone, anti-Müllerian hormone, ovarian volume, ovarian stromal artery pulsatility index, and visceral fat area can predict clomiphene-citrate treatment response in patients with PCOS suffering from infertility **(23)**. In our study, just the phenotypes are assessed regarding frequency and showed that the most common PCOD phenotypes in clomiphene-resistant cases are A and D subtypes. According to the results of a study done by Abu Hashim et al. there is strong evidence that the metformin in combination with clomiphene is mainly relevant for clomiphene-resistant polycystic ovarian syndrome and, in case of observing no response, other step can be the use of gonadotropins **(24)**. Totally, according to the results of this cross-sectional study, it is concluded that different PCOD phenotypes should be assessed and treatment of them must be considered. However, there was no significant association but it seems that patients with normal ovary have better response to clomiphene and regarding our results and also those attained in previous studies, it seems that resistance rate, symptoms manifestations, metabolic diseases, and adverse therapeutic effects are more common in cases with polycystic ovaries. Hence, special consideration to treatment and assessment course is recommended. The most common PCOD phenotypes in clomiphene-resistant cases are A and D subtypes (P=0.065). However, further studies with larger sample population and multi-center sampling would help to attain more definite results and find the exact causes of clomiphene resistance.

It would help to improve the treatment course and final prognosis in the PCOD patients.

Ethical issue

This investigation was in accordance with the Declaration of Helsinki. The ethical committee of Iran University of Medical Sciences approved this study [IR.IUMS.SMD.REC.1396.9411290015]. Additionally, the authors have entirely observed ethical issues like including plagiarism, data fabrication and double publication.

Acknowledgment

None.

Conflict of interest

None.

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