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Original Research Article

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

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Abstract:

Background: One significant issue facing infertile women with polycystic ovarian disease (PCOD) is clomiphene resistance. Patients would have a better prognosis if the causes were identified. The purpose of this study was to identify the various PCOD phenotypes and how they affected infertile women's clomiphene resistance.

Methods: The Department of Obstetrics and Gynaecology, SKMCH, Muzaffarpur, Bihar, referred 100 consecutive PCOD women with infertility who was taking clomiphene from Sadar Hospital and private nursing homes between August 2023 and January 2024. The study was a descriptive-comparative cross-sectional study. The impact of various PCOD phenotypes on these women's clomiphene resistance was evaluated.

Results: According to the findings, 39 (39.0%), 7 (7.0%), 26 (26.0%), and 28 (28.0%) patients, respectively, exhibited the A, B, C, and D phenotypes. Resistance was present in 31 patients (31%). A (HA+OA+PCO) was the most prevalent PCOD phenotype, observed in 48.4% of patients, while D (OA+PCO) was shown in 25.8% of patients. However, there was no significant difference in the phenotypes (P=0.064).

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

PCOD, which affects 6–10% of women in their reproductive age range, is the most prevalent endocrinological condition [1]. Hyperandrogenism and prolonged anovulation are two characteristics of PCOD [2]. The 2003 Consensus of the European Society of Human Reproductive and Embryology/American Society for Reproduction Medicine states that patients with at least two of the following three criteria—1) oligo-ovulation/unovulations; 2) hyperandrogenism symptoms in the laboratory or clinical setting; and 3) polycystic ovary in ultrasonography (volume and number of antral follicles)—would be classified as PCOD [3].

In India, the prevalence estimates are between 8.2% and 22.5% depending on the diagnostic criteria used. [4] Insulin resistance is a typical symptom of PCOD, although its underlying origin is unknown. It appears to have evolved in the hyperandrogenism that follows this disease in both obese and non-obese women [5]. Clomiphene is one drug that is used to treat PCOD, and it has a 20–50% success rate in causing pregnancy [6–9]. These days, clomiphene resistance is increasing, which could cause issues with PCOD treatment [10–13].

The PCOD phenotypes are as follows: B (hyperandrogenism plus oligo/anovulation), C (hyperandrogenism plus polycystic ovarian in ultrasonography), D (oligo-anovulation plus polycystic ovarian in ultrasonography), and A (hyperandrogenism plus oligo-anovulation plus polycystic ovarian in ultrasonography) [14,15].

These four phenotypes and their significance, particularly in clomiphene resistance, are poorly understood. Furthermore, it is challenging to compare the available data due to the disparity in diagnostic criteria and the absence of global agreement on certain criteria [16–19]. Therefore, the purpose of this study was to identify the various PCOD phenotypes and how they affected infertile women's clomiphene resistance.

Materials and Methods

From August 2023 to January 2024, 100 consecutive women with PCOD were included in this descriptive-comparative cross-sectional study conducted in the Department of Obstetrics and Gynecology at Sri Krishna Medical College and Hospital in Muzaffarpur, Bihar. Following an initial diagnosis based on the Rotterdam criteria, each patient was categorized into four distinct phenotypes based on laboratory, clinical, and ultrasonographic criteria.

Following this, the patients were administered clomiphene. Age range of 20 to 40 years, non-male factor infertility, and fallopian tube patency were the inclusion criteria. Male factor infertility, fallopian tube obstruction, uterine structural problems, and dissatisfaction with study enrollment were the exclusion criteria. The clinical criteria (hirsutism according to Ferriman Score > 8, acne, and alopecia) and biochemical criteria (total testosterone level > 0.5 ng/ml or free testosterone > 3.5 pg/ml) were employed for the assessment of hyperandrogenism. Menstrual irregularities and patterns were classified as either amenorrhea (absence of menses for more than six months) or oligomenorrhea (intervals between menses longer than 35 days).

PCOD was identified in patients with 12 or more cysts in each ovary, each with a diameter of 2 to 10 mm and a volume of 10 cm^3 or more, based on transvaginal ultrasound evaluation. 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) are some of the different PCOD phenotypes [14,15]. The patients received 100 mg of clomiphene daily for five days as part of Ovulation Induction (OI), and transvaginal ultrasonography was used to evaluate the patients' reaction on the fourteenth and sixteenth days of their menstrual cycle. Growth of at least one dominant follicle with a diameter of 15 to 16 mm was considered the response. If there was no improvement, a 100 mg daily clomiphene course was given, and the ultrasound evaluation was done again on the 14th and 16th day of the menstrual cycle. The most prevalent phenotypes were identified in instances that did not respond to clomiphene, which were classified as resistant cases.

The SPSS version 25.0 program was used to analyze the data. The numerical variables were represented by the mean plus standard deviation, whereas the categorical variables were represented by frequency and percentage. P values less than 0.05 were regarded as statistically significant when applying the chi-square and ANOVA, independent t-test, and logistic regression techniques.

Results

With mean ages of 27.89, 26.77, 29.86, and 28.37 years for A, B, C, and D phenotypes, respectively, the four phenotypes had the same mean age of 28.5 ± 4.9 years, ranging from 18 to 41 years (Figure 1). Furthermore, the average body mass index (BMI) was 28.3 ± 3.5 kg/m^2, with a range of 19.5 to 41.9 kg/m^2. This BMI was not different for the four phenotypes (A, B, C, and D phenotypes, respectively; Figure 2). The average age and BMI of the phenotypes A, B, C, and D were not statistically significant (P>0.05), according to the data.

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.

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

Phenotype		No.	Minimum	Maximum	Mean ±SD	P value
Age	A	39	18.00	40.00	27.89±4.491	0.074
	B	7	18.00	36.00	26.76±5.81	
	C	26	20.00	41.00	29.86±4.84	
	D	28	18.00	37.00	28.36±4.97	
BMI	A	39	19.49	34.89	27.97±3.49	0.282
	B	7	24.24	41.91	29.63±4.99	
	C	26	19.53	40.39	28.83±3.91	
	D	28	19.49	33.59	28.16±2.63	

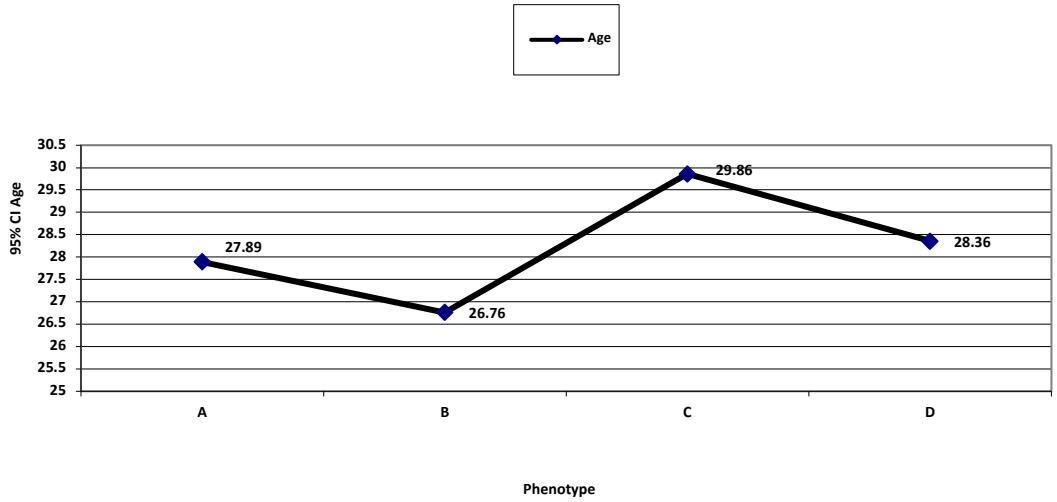

Figure 1: Age distribution of the patients in PCOD phenotypes

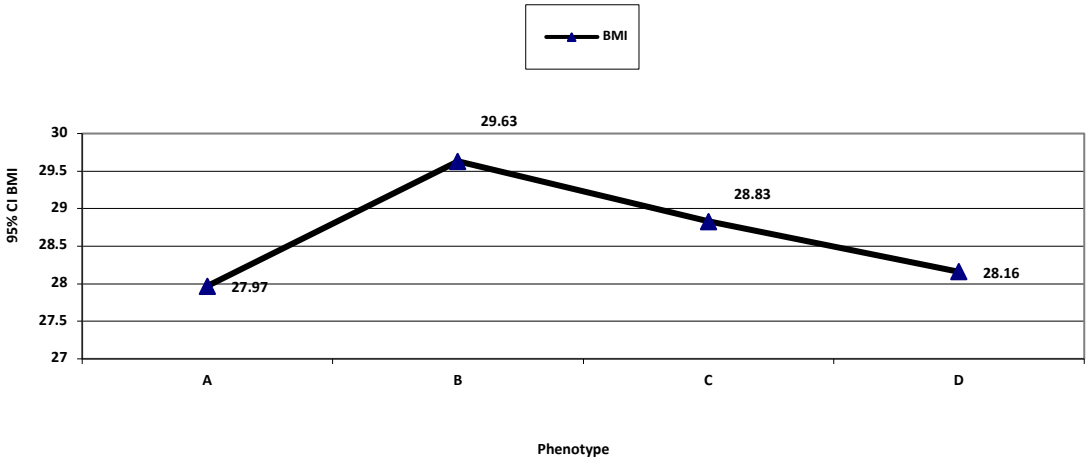

Figure 2: BMI distribution of the patients in PCOD phenotypes

The age and BMI showed non-significant P values of 0.875 and 0.272 in the logistic regression analysis. According to this study, 31 patients (31.0%) had resistance to clomiphene, while 69 patients (69.0%) responded to it. The most prevalent PCOD phenotype was A (HA+OA+PCO), observed in 48.4% of patients, whereas D (OA+PCO) was observed in 25.8% of patients. However, there was no statistically significant difference between the phenotypes (P=0.065). Additionally, 3.2% and 25.8% of people had the B and C phenotypes, respectively. Additionally, 48.4%, 3.2%, 19.4%, and 25.8% of the population showed resistance to the A, B, C, and D phenotypes, respectively. Phenotypes and resistance did not significantly correlate, yet it appears that patients with normal ovarian function respond better 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).

Table 2: Clomiphene resistance according to PCOD phenotypes

Phenotype		Clomiphene	P value
	Resistant	**Sensitive**	
A	15 (48.4%)	24 (52.6%)	0.065
B	1 (3.2%)	6 (96.8%)	
C	6 (19.4%)	20 (80.6%)	
D	8 (25.8%)	20 (74.2%)	

Discussion

PCOD phenotypes and their impact on clomiphene resistance were evaluated in this investigation. The current cross-sectional study's findings showed that there is no significant correlation between the PCOD phenotype and clomiphene resistance; instead, the A (48.4%) and D (25.8%) phenotypes exhibited the highest levels of resistance. Similar to our work, Seyedoshohadaei et al. [16] reported that in an interventional investigation including 150 patients with the B phenotype, 26.6% of them showed clomiphene resistance.

A and C phenotypes were associated with greater levels of Anti-Mullerian Hormone (AMH), and patients with A and B phenotypes had a considerably reduced conception rate, according to research by Ramezanali et al. [17] comparing 386 PCOD patients to 350 subjects with male factor infertility. It is therefore likely that these traits could influence the AMH pathway's role in clomiphene resistance.

As demonstrated in our clomiphene study, phenotype A is associated with a higher rate of resistance to metabolic therapies, according to Ciftci et al. [18] report on 150 patients in a Turkish population. While A and D phenotypes showed higher resistance in our investigation, Pehlivanov et al. [19] observed that metabolic therapies caused greater resistance in PCOD patients with phenotypes A and B. The study included 70 patients in Bulgaria. According to a study by Nestler et al., metformin can reduce insulin production, which in turn can increase response to clomiphene in obese women with polycystic ovarian syndrome [20].

This study demonstrates the use of adjuvant medicine as a substitute strategy to boost clomiphene responsiveness. It should be mentioned that in women with clomiphene-resistant PCOS, short-term usage of rosiglitazone and clomiphene is more effective than metformin and clomiphene in inducing ovulation [21]. Therefore, the combination of medications is crucial. Furthermore, there is currently no particular advice on the use of metformin or clomiphene as first-step medications [22]. Amenorrhea, BMI, total testosterone, anti-Müllerian hormone, ovarian volume, ovarian stromal artery pulsatility index, and visceral fat area are among the factors that have been shown to predict the likelihood of developing resistance to clomiphene.

These factors can also predict the response to clomiphene-citrate treatment in patients with PCOS who are infertile [23]. Only the phenotypes were evaluated in terms of frequency in our study, which revealed that the A and D subtype of PCOD are the most prevalent in clomiphene-resistant cases. The results of a study by Abu Hashim et al. provide compelling evidence that the use of gonadotropins in the event that no response is observed is an additional treatment option for clomiphene-resistant polycystic ovarian syndrome, with metformin plus clomiphene being the major relevant combination [24].

In summary, the findings of this cross-sectional study suggest that various PCOD phenotypes need to be evaluated and treatment options need to be taken into account. Despite the lack of a significant correlation, it appears that patients with normal ovaries respond better to clomiphene. Based on our findings as well as those from earlier research, it appears that patients with polycystic ovaries are more likely to experience resistance rate, symptom manifestations, metabolic diseases, and unfavorable side effects. Therefore, it is advised to give treatment and assessment courses extra thought.

Conclusion

A and D subtypes are the most prevalent PCOD phenotypes in clomiphene-resistant instances (P=0.065). However, future research with a bigger sample size and multi-center sampling would be beneficial to obtain more conclusive findings and identify the precise causes of clomiphene resistance. It would benefit PCOD patients' overall prognosis and course of treatment.

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