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Original Article

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Comparison of clinical and biochemical parameters in the ovulatory and anovulatory phenotypes of polycystic ovary syndrome

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ABSTRACT

Aims: We aimed to compare the clinical and the biochemical features of the ovulatory versus anovulatory phenotypes of polycystic ovary syndrome (PCOS).

Methods: This is a retrospective controlled trial conducted among the women who applied to the İstanbul Liv Vadi Hospital between 2021 and 2023 August and diagnosed as PCOS. PCOS patients (n=290) were diagnosed according to the Rotterdam 2003consensus criteria. Women's clinical and biochemical parameters such as age, height, weight, body mass index (BMI), waist, hip, waist/hip ratio (WHR), fasting blood sugar (FBS), insulin, homeostatic model-assessment-insulin resistance (HOMA-IR), antimullerian hormone (AMH), follicle stimulating hormone (FSH), luteinizing hormone (LH), estradiol (E2) total cholesterol, triglyceride, dehydroepiandrosterone (DHEAS), high-density lipoprotein (HDL) and low-density lipoprotein (LDL) of participants were compared between ovulatory and anovulatory phenotypes.

Results: The findings of the study did not demonstrate a statistically significant correlation between ovulatory and anovulatory phenotypes in relation to various factors, including height, weight, BMI, waist circumference, hip circumference, WHR, insulin levels, HOMA-IR, AMH, FSH, E2, TSH, total cholesterol, testosterone, free testosterone, DHEAS, LDL and cholesterol (p-value>0.05). A statistically significant difference was observed between the groups in terms of age, FBS, BMI, LH, and HDL levels.

Conclusion: In conclusion, there is no significant difference in PCOS's ovulatory and anovulatory phenotypes in essential parameters such as insulin resistance and BMI.

Keywords: Polycystic ovary syndrome, PCOS phenotypes, insulin resistance, women, ovulatory and anovulatory phenotypes

INTRODUCTION

Being recognized as one of the most common endocrine problems, polycystic ovary syndrome (PCOS) is associated with a high variety of symptomatology.^{1,2} Women with PCOS are at increased risk of fertility problems due to anovulation but also may be presented with menstrual disorders, acne, hirsutismus, metabolic problems such as insulin resistance, type 2 diabetes, obesity, high blood pressure, and mental disorders (anxiety, depression, and stress).³ Longterm medical therapy, diet and phsyical activity regulations, managing metabolic diseases, arranging regular periods and achieving fertility goals are the well know targets in controlling the complexity of this debilitating endocrine problem.⁴ The prevalence of PCOS ranges from 5-13% in women of reproductive age, and approximately 75% suffer from infertility due to lack of ovulation.⁵

Almost 30% of all infertility is infertility with no ovulation, and the cause of about 90% of this infertility is PCOS.⁶ Controlling this syndrome and its signs and symptoms improves the quality of life in affected women effectively. Many women with PCOS need long-term treatment.⁷⁻⁹ Commonly available drugs are effective on PCOS, but they have many side effects, and this issue has made non-pharmacological treatment strategies to be investigated and studied more.^{10,11} The cause of PCOS is not fully understood. However, it seems to have a genetic basis, and fat plays a role in the pathogenesis or other factors in the disease. Identifying risk factors and factors affecting this disease can help provide more effective treatments.¹²

Based on the Rotterdam 2003 consensus, PCOS is usually represented by ovulatory dysfunction that results in oligo



or amenorrhea. Most symptoms will also rely on whether PCOS is explored in an internal gynecology, dermatology, or medicine background.¹³ Women with PCOS often find out about their disease in infertility clinics. These patients have had infertility problems for years due to the anovulation. These anovulatory women seem to have a different phenotype than ovulatory women with PCOS, including clinical, metabolic, and biochemical parameter differences.¹⁴

Whether these two phenotypes represent a similar spectrum of conditions in terms of clinical and biochemical parameters is still ambiguous. More work must be done to study the different clinical and biochemical parameters in the ovulatory and anovulatory phenotypes. This study aims to compare the differences among the clinical and biochemical parameters profile of different PCOS phenotypes. This comparison may help understand PCOS phenotype characteristics.

METHODS

The study was carried out with the permission of İstinye University Ethics Committee (Date: 22.09.2023, Decision no: 2023/09). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki and documented declared permission was received from all women.

The examination sample consisted of women witholigomenorrhea or amenorrhea, who visited İstanbul Liv Vadi Hospital between Aug 2021 and August 2023. In this study, women who had been analyzed with WHO anovulation and who fulfilled the diagnostic standards of PCOS employed the Rotterdam 2003 consensus.

Women who had a diagnosis of Cushing syndrome, androgen-secreting neoplasia, congenital adrenal hyperplasia, any malignancy and women with a history of oral glucocorticoid or oral contraceptive medication and who were already on antidiabetic treatment were excluded from the study. The inclusion criteria for the study are listed as follows: Women who were between the ages of 18-40, being diagnosed with PCOS, menstrual irregularity, hirsutism, acne, polycystic ovarian morphology, and who had provided the complete demographic and laboratory data.

This study divided women with PCOS into two groups: anovulatory (n=180) and ovulatory (n=110). In this study, progesterone measurement processed on the twenty-one day of menstrual cycle was used to divide women into two groups. During previous examinations and treatments, women were diagnosed ovulatory polycystic ovary syndrome (PCOS) on the 21st day of their menstrual cycle or when their randomly checked progesterone levels reached a minimum of 10 nmol/ liter.^{14,15} The remaining women were classified as anovulatory PCOS.

The participants in the research were subjected to a preliminary examination in the first stage. The next step was to measure height and weight, calculate BMI, and collect information about menstruation. Then, blood samples were taken from the patients and processed on the third day of the menstrual cycle. Serum FBS, insulin, HOMA-IR, AMH, follicle stimulating hormone (FSH), luteinizing hormone (LH), estradiol (E2),thyroid-stimulatinghormone (TSH),total cholesterol, triglyceride, Testosterone, freetestosterone, dehydroepiandrosterone (DHEAS), high-density lipoprotein (HDL) and low-density lipoprotein (LDL)" were measured.

Statistical Analysis

The SPSS version 26 was used for statistical analysis. The normality of data was tested by the Shapiro-Wilk test and graphic investigations. Descriptive statistical methods were utilized to assess the data. The comparison of normally distributed quantitative variables between the two groups was performed using the Student's t-test. The Mann-Whitney U test was deployed to approximate the non-normally distributed quantitative variables between the two groups. The Pearson chi-square test was used to compare qualitative data.

To calculate the sample size with the G-Power 3.2 program, difference between two independent proportions was measured based on the Pearson's Chi-Square Test of Association with the power of 80%, effect size of 50%, and 0.25 type 1 error for at least 228 patients.¹⁶

RESULTS

A total of 290 women with PCOS participated in this study. Table 1 shows the comparison of ovulatory and anovulatory phenotypes in women with PCOS in study parameters.

The mean age and body mass index (BMI) of the women with PCOS were 26.57 years and 28.85 kg/m² (SD = 5.59 and 6.09). The mean height and weight of the women with PCOS were 160.86 cm and 74.67 kg (SD=5.7 and 16.54). The mean waist and hip of participants in the study were 87.91 cm and 107.17 kg (SD=14 and 12.42). Table 1 shows explanatory details of investigation variables in total and each group. For study parameters with normal distribution, mean (M), and standard deviation (SD), and for non-normal distribution, median and interquartile range (IQR) were used to show descriptive information.

In order to compare the age of ovulatory and anovulatory phenotypes an independent-samples t-test was conducted. There was a statistically significant association between ovulatory and anovulatory phenotypes in women with PCOS regarding age (p<0.05). It indicated that the age of the ovulatory group (M=27.93, SD=5.47) was higher than the anovulatory group (M=25.74, SD=5.51).

As shown in Table 1, there was no statistically significant association between ovulatory and anovulatory phenotypes in women with PCOS regarding height, weight, BMI, waist, hip, and waist/hip ratio (p>0.05).

As is shown in Table 1, there was not a statistically significant association between ovulatory and anovulatory phenotypes in women with PCOS in terms of FBS and HOMA-IR (p>0.05). There was a statistically significant association between the two groups in women with PCOS in terms of insulin (p<0.05). We found that the insulin of the ovulatory group (M=10.1, SD=4.98) was lower than that of the anovulatory group (M=12.24, SD=8.48).

Controversies in Obstetrics & Gynecology and Pediatrics

Table 1. The comparison of ovulatory and anovulatory phenotypes in women with PCOS in study parameters (n=290).					
Study parameters		Total n=290	Ovulatory n=110	Anovulatory n=180	p-value
Age (years)	Mean±SD	26.57±5.59	27.93±5.47	25.74±5.51	0.001*
Height (cm)	Mean±SD	160.86±5.7	160.98±6.15	160.79±5.43	0.780*
Weight (kg)	Mean±SD	74.67±16.54	74.42±16.52	74.83±16.59	0.838*
BMI (kg/m²)	Mean±SD	28.85±6.09	28.7±6.04	28.95±6.14	0.740*
Waist (cm)	Mean±SD	87.91±14	88.28±14.93	87.68±13.44	0.725*
Hip (cm)	Mean±SD	107.17±12.42	107.54±13.92	106.95±11.45	0.697*
Waist/Hip ratio	Mean±SD	0.82±0.07	0.82±0.07	0.82±0.07	0.926*
FBS (mg/dL)	Mean±SD	95.95±16.41	96.21±19.74	95.78±14.04	0.830*
Insulin (mL)	Mean±SD	11.43±7.42	10.1±4.98	12.24±8.48	0.017*
HOMA-IR	Mean±SD	2.87±2.28	2.64±2.33	3.01±2.23	0.059**
AMH (ng/mL)	Mean±SD	5.01±2.31	4.82±2.36	5.13±2.28	0.141**
FSH (mIU/mL)	Mean±SD	6.61±1.64	6.68±1.72	6.57±1.59	0.589*
LH (IU/L)	Mean±SD	10.74±5.15	9.93±5.62	11.24±4.78	0.037*
E2 (pg/mL)	Mean±SD	58.02±35.21	54.99±33.42	59.87±36.22	0.098**
TSH (mIU/mL)	Mean±SD	2.42±1.98	2.29±1.12	2.49±2.36	0.865**
Testosteron (nmol/L)	Mean±SD	1.29±6.85	0.85±0.67	1.56±8.68	0.245**
FreeTestosteron (pg/ml)	Mean±SD	2.69±1.28	2.5±1.14	2.81±1.35	0.061**
DHEAS	Mean±SD	253.54±102.41	246.9±101.41	257.5±103.1	0.416*
Total Cholesterol	Mean±SD	177.73±39.79	178.52±43.95	177.24±37.14	0.792*
HDL (mmol/L)	Mean±SD	48.31±12.95	50.32±13.44	47.08±12.53	0.039*
LDL (mmol/L)	Mean±SD	106.62±33.81	106.78±36.84	106.52±31.93	0.948*
Triglyceride	Mean±SD	124.11±103.63	117.17±89.65	128.34±111.34	0.025**
*Independent t test, **Mann Whitney U test +Chi Square test. "BMI, body mass index; FBS, fasting blood sugar; HOMA-IR, homeostatic model-assessment-insulin resistance; AMH, Anti-mullerian					

In order to compare the LH value of ovulatory and anovulatory phenotypes, an independent-sample t-test was conducted. There was a statistically significant association between ovulatory and anovulatory phenotypes in women with PCOS in terms of age (p<0.05). It showed that the LH of the ovulatory group (M=9.93, SD=5.62) was lower than the LH of the anovulatory group (M=11.24, SD=4.78).

There was a statistically significant association between ovulatory and anovulatory phenotypes in women with PCOS in terms of HDL (p<0.05). It showed that HDL of the ovulatory group (M=50.32, SD=13.44) was higher than LH of the anovulatory group (M=47.08, SD=12.53).

There was not a statistically significant association between ovulatory and anovulatory phenotypes in women with PCOS in terms of AMH, FSH, E2, TSH, Testosterone, free testosterone, DHEAS, total cholesterol, and LDL (p>0.05).

In order to compare the triglyceride value of ovulatory and anovulatory phenotypes, the Whitney U test was conducted. There was a statistically significant association between ovulatory and anovulatory phenotypes in women with PCOS in terms of triglyceride (p-value<0.05). It showed that the triglyceride of the ovulatory group (Median=94.5) was lower than the triglyceride of the anovulatory group (Median=103.5).

DISCUSSION

The present study expanded the previous findings, and based on the comparison findings of mentioned parameters

between the two subgroups, no significant relationship was observed in most of the parameters. In our study, BMI, waist/ hip ratio, FBS, HOMA-IR, AMH, FSH, E2, TSH, testosteron, free Testosteron, DHEAS, total cholesterol, and LDL were similar between ovulatory and anovulatory phenotypes. This study showed statistically significant difference between the two phenotypes in age, insulin, LH, HDL, triglyceride parameters. Age of women suffering from PCOSwas relatively low in anovulatory compared to the ovulatory group. The insulin valuewas relatively high in anovulatory in comparison to ovulatory group. The LH and triglyceride values were relatively low in ovulatory in comparison to anovulatory group. The HDL value was relatively high in ovulatory contrasted to anovulatory group.

Clinical, biochemical parameters and metabolic distinctions between PCOS subgroups have been expressed in various research. Panidis et al.¹⁷ compared insulin resistance (IR) and endocrine characteristics of the different phenotypes (severe PCOS, anovulation and hyperandrogenemia, ovulatory PCOS, and mild PCOS). Severe PCOS is associated with more IR. IR also describes the anovulation and hyperandrogenemia with obesity. In contrast, ovulatory PCOS is not associated with IR. The results of the present study are compatible with this study, and no significant relationship was observed between the two phenotypes in terms of IR.

We did not find a significant difference between HOMA-IR and PCOS phenotypes (ovulatory and anovulatory groups), which is consistent with some Controversies in Obstetrics & Gynecology and Pediatrics

previous studies.^{18,19} Gupta et al.¹⁹ evaluated the BMI, AMH and IR in three PCOS phenotypes and reported that no correlation of IR among the different phenotype groups. Hosseinpanah et al.¹⁸ in a retrospective study with 915 women, compared metabolic features, HOMA-IR and fasting insulin among four PCOS phenotypes. They reported no significant difference between PCOS phenotypes and study parameters. Contrary results were presented by Al-Jefout et al.20 who reported that IR and obesity in severe PCOS phenotype were significantly higher than other three main PCOS phenotypes. Shirazi et al.²¹ showed a higher risk of IR in the phenotype oligomenorrhea/ amenorrhea (O), hyperandrogenism (H), and polycystic ovary morphology (P). These result has been repeated in other studies.^{22,23} This disagreement may result from various analysis methodologies, PCOS type standards, determining standards for IR, and cut-off values for HOMA-IR.

We did not find a significant difference between clinical and biochemical parameters (expect insulin, LH, HDL and triglyceride) and PCOS phenotypes (ovulatory and anovulatory groups), which is consistent with a previous study. Mansour et al.²⁴ in a cross-sectional secondary analysis with 125 Iranian women, compared twentyfour clinical and biochemical parameters among PCOS phenotypes. They reported no significant difference in all parameters except fasting blood sugar.Guastella et al.²⁵ assessed the endocrine and clinical distinctions between four PCOS phenotypes. They showed nosignificant difference between PCOS two most common phenotypes (type I classic PCOS and type II classic PCOS) in terms of endocrine and clinical parameters. Burgers et al.¹⁵ in a retrospective cohort study with 1750 women, compared endocrine, ultrasound, and clinical parameters between anovulatory and oligoovulatory women with PCOS. They reported that women suffering from oligoovulatory phenotypes show a milder ovarian dysfunction phenotype than anovulatory PCOS patients.

Limitations of the study

This study has some limitations. Characterization of features associated with PCOS phenotypes has varied between studies. This situation caused difficulties in comparing our study with previous studies. To our knowledge, this is the first study to comparatively examine clinical and biochemical parameters in a cohort of Turkish women and specifically focus on identifying differences between anovulatory and ovulatory individuals.

CONCLUSION

There is no significant difference in PCOS's ovulatory and anovulatory phenotypes in essential parameters such as insulin resistance and BMI. More extensive and complete studies are needed to investigate the differences in phenotypes regarding metabolic, clinical, and biochemical parameters.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of İstinye University Ethics Committee (Date: 22/09/2023, Decision No: 2023/09).

Informed Consent: Because the study was designed retrospectively, no writtenin formed consent form was obtained from patients.

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The authors have no conflicts of interestto declare.

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Author Contributions: All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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Controversies in Obstetrics & Gynecology and Pediatrics

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I was originally born in 1975 in İstanbul. After graduating from Uludağ University Faculty of Medicine, I successfully completed my obstetrics and gynecology specialization training in İstanbul SSK Okmeydanı Hospital in 2004. I continued mycareer in private hospitals providing tertiary health care services, and during this time. I had the opportunity to work and learn with experts who are appreciated in their field. I have attended trainings on minimally invasive surgery abroad and in the country. I have attended more than 50 national and international congresses. Recently, I have published articles of which I am the author or contributed, and there are 4 book chapters of which 2 of them are in the process of publication. Finally, I have been working actively at Liv Hospital Vadİstanbul Hospital in affiliation with the University of İstinye with my experience of more than 15 years, while continuing my academic studies. My command in English is very good. I am married and have one daughter.

