

PAPER DETAILS

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AUTHORS: Murat Önal, Halime Çali Öztürk

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Anti-Müllerian hormone and HOMA-IR in different phenotypes of polycystic ovary syndrome on insulin resistance

✉ Murat Önal, ✉ Halime Çalı Öztürk

¹Obstetrics and Gynecology Specialist, Gynolife IVF Clinic, Lefkosa, Cyprus

²Department of Obstetrics and Gynecology, Faculty of Medicine, Bezmialem University, İstanbul, Turkey

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ABSTRACT

Aims: To examine the link between serum anti-mullerian hormone (AMH) levels and homeostatic model assessment of insulin resistance (HOMA-IR) in different phenotypes of polycystic ovary syndrome (PCOS).

Methods: This retrospective study included 120 patients aged 18-30 who visited our polyclinics between June 2021 and December 2022. Patients were divided into four groups based on the Rotterdam criteria for PCOS phenotypes. A control group of 24 individuals was also included. Clinical data, hormonal profiles, and metabolic parameters were obtained from medical records.

Results: There were significant differences in AMH, follicle stimulating hormone (FSH), luteinizing hormone (LH), and high-density lipoprotein (HDL) levels among the PCOS phenotypes and control group. AMH levels were highest in phenotype 1 (oligo/anovulation + hyperandrogenism + polycystic ovaries) and lowest in the control group. FSH were highest in phenotype 4 (oligo/anovulation + polycystic ovaries) and lowest in the control group. LH were highest in phenotype 2 (oligo/anovulation + hyperandrogenism). HOMA-IR was highest in phenotype 1. However, there were no significant differences in AMH or HOMA-IR levels among the PCOS phenotypes.

Conclusion: Our study found hormone level differences among PCOS phenotypes but no significant differences in AMH or HOMA-IR. This suggests AMH may not distinguish between phenotypes and insulin resistance may not differ significantly among phenotypes.

Keywords: PCOS phenotypes, anti-mullerian hormone, insulin resistance, HOMA-IR, biomarkers

INTRODUCTION

Polycystic ovarian syndrome (PCOS) is an endocrine disorder that is frequently encountered and affects approximately 5-10% of women of reproductive age worldwide.¹ It is characterized by a heterogeneous collection of signs and symptoms, including menstrual irregularities, hyperandrogenism, and polycystic ovaries.² Insulin resistance (IR) is a crucial feature of PCOS, with up to 70% of affected women exhibiting this metabolic abnormality.¹ There is a correlation between IR in PCOS and a heightened risk of developing type 2 diabetes, cardiovascular disease, and other adverse health outcomes in the long run.³

The homodimeric glycoprotein known as anti-mullerian hormone (AMH) is a member of the transforming growth factor- β family and is expressed in the granulosa cells of secondary, preantral, and small antral follicles that have a

diameter of 4 mm or less.⁴ AMH has been implicated in the regulation of ovarian function and folliculogenesis, with elevated serum AMH levels observed in women with PCOS compared to age- and body mass index (BMI)-matched controls.⁵ However, the effectiveness of AMH as a diagnostic criterion for PCOS is a topic that is still under debate.⁴

The homeostasis model assessment of insulin resistance (HOMA-IR) is a commonly employed instrument to evaluate IR in clinical and research settings.⁶ The assessment is based on the measurement of fasting glucose and insulin levels and has been shown to correlate well with more invasive measures of IR, such as the hyperinsulinemic-euglycemic clamp.⁷ HOMA-IR has been used to investigate the relationship between IR and various clinical features of PCOS, including hyperandrogenism and menstrual irregularities.^{6,7}

Corresponding Author: Murat Önal, muratonal@yahoo.com



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Despite the well-established associations between PCOS, IR, and elevated AMH levels, few studies have explored the link between AMH and HOMA-IR in various PCOS phenotypes. This represents a significant gap in the current literature, as understanding the interplay between these factors may provide valuable insights into the underlying pathophysiology of PCOS and inform the development of more targeted therapeutic interventions.

The primary objective of this study is to investigate the relationship between serum AMH levels and HOMA-IR in women with different phenotypes of PCOS. Specifically, we aimed to determine whether AMH and HOMA-IR are independently associated with specific PCOS phenotypes and whether their combined assessment improves the prediction of these phenotypes.

METHODS

The study was carried out with the permission of Bezmialem Vakıf University Non-interventional Clinical Researchs Ethics Committee (Date: 14.06.2023, Decision No: 2023/191). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

This retrospective study included 120 patients aged 18-30 who visited our polyclinics between June 2021 and December 2022. The study population consisted of patients aged 18-30 who visited our polyclinics with menstrual irregularity and a desire to have children. A total of 120 patients were divided into four groups according to their PCOS phenotypes, as determined by the study criteria. Additionally, 24 individuals were included as a control group. The study's eligibility requirements were determined by evaluating the patient's medical history, physical exam, and ultrasonography results, which were obtained from the outpatient clinic records during the specified dates. The diagnosis of PCOS was made if the patients met at least two of the 2003 Rotterdam Consensus criteria.

Based on a specific set of inclusion and exclusion criteria, 120 participants were selected for the study. The study included only patients who were between the ages of 18 and 30 and unable to conceive despite wanting a child for at least one year. They also needed to be diagnosed with PCOS, meeting at least two of the 2003 Rotterdam Consensus criteria.⁸ In this consensus it was stated that for the diagnosis of PCOS, the patient should have at least two of the three major criteria. 1. Oligo/anovulation 2. Hyperandrogenism (clinical or biochemical findings) 3. Polycystic ovaries (determined by ultrasound) and other androgen excess disorders should be excluded. The presence of at least two of these three findings makes the diagnosis of PCOS after excluding Cushing's syndrome, congenital adrenal hyperplasia, hyperprolactinemia, and androgen-secreting tumors.

Thus, PCOS patients can be categorized into four distinct phenotypes:⁸

- "Phenotype 1: Oligo/anovulation + hyperandrogenism + polycystic ovaries
- Phenotype 2: Oligo/anovulation + hyperandrogenism
- Phenotype 3: Hyperandrogenism + polycystic ovaries
- Phenotype 4: Oligo/anovulation + polycystic ovaries"

We divided our participants into four groups according to this classification.

Participants were required to undergo an oral glucose tolerance test (OGTT) to assess glucose tolerance. Participants with a fasting glucose level ≥ 126 mg/dl or a 2-hour glucose level ≥ 200 mg/dl were excluded from the study due to the presence of diabetes. Participants with a fasting glucose level between 100-125 mg/dl or a 2-hour glucose level between 140-199 mg/dl were excluded due to the presence of impaired glucose tolerance. In addition, patients with a history of thyroid dysfunction, hyperprolactinemia, and hypercortisolism were excluded. Patients could not have taken oral contraceptives or any medication known to alter hormone, lipid, or insulin metabolism within three months before the study and had to be non-smokers. Patients with PCOS needed to have similar mean age and body mass index (BMI) across their phenotypes, while individuals with a BMI of 23-25 were also included.

Exclusion criteria for the study were those who did not agree to participate in the study, smokers, individuals diagnosed with hypertension or diabetes, and those with any endocrinopathy. Patients who had taken oral contraceptives in the last three months, used insulin-sensitizing medications, or medications for hyperlipidemia were also excluded. Patients with vitamin B6 or B12 deficiency, or those who had taken vitamin supplements to treat these deficiencies within the last six months, were also excluded, as these may influence homocysteine metabolism. We also considered 24 healthy participants for the control group.

On the third day of the patients' menstrual cycle, several measurements were recorded in the case report form, including their age, BMI, Luteinizing Hormone (LH), Estradiol (E2), levels of Follicle Stimulating Hormone (FSH), Free T4, Prolactin, Thyroid Stimulating Hormone (TSH), Hemogram, Biochemistry (total cholesterol, LDL, HDL, Triglyceride), AMH, fasting insulin, fasting blood sugar (FBS), and HOMA-IR values. The study aimed to evaluate the relationship between AMH and HOMA-IR among the four different phenotypes of PCOS patients and the control group (healthy) concerning IR.

Statistical Analysis

To examine the study results, the SPSS statistical package program for Windows (version 22.0, SPSS Inc., Chicago, Illinois, USA) was used. Numeric variables were reported

as either mean±standard deviation or median (minimum-maximum), while categorical variables were expressed as the number and/or percentage of patients in the form of descriptive statistics. The mean±standard deviation was used to report continuous data. For comparative analysis of continuous data, the Mann-Whitney U test was used.

RESULTS

Table 1 represents the baseline clinical and hormonal profile of the study population. The study parameters include age, BMI, hormone levels like AMH, FSH, LH, E2, prolactin, TSH, FT4, lipid profile including triglycerides, total cholesterol, HDL, LDL, fasting blood sugar, fasting insulin, HOMA-IR, CRP, liver function tests, complete blood count, renal function tests, and platelet indices.

Study parameters	Median (Min.-Max.)	mean±standart deviation
Age	24(18-30)	24.41±2.75
BMI	25(23-25)	24.28±0.83
AMH	4(2-8)	3.76±1.4
FSH	6.59(3.96-12)	6.85±1.48
LH	7.23(2.75-15.2)	7.48±2.63
E2	32(14.04-73)	35.5±11.35
PRL	13(5-28.6)	13.39±4.99
TSH	1.93(0.01-4.83)	1.81±0.72
FT4	1(0.31-2.66)	1.08±0.28
Total cholesterol	221(123-352)	225.31±52.95
Triglycerides	120(48-228)	123.09±31.61
LDL	135(46-191)	123.21±38.95
HDL	60(38.6-89)	59.29±11.86
FBS	84(71-99)	85.71±8.28
Fasting Insulin	15(7.2-36.8)	15.98±5.21
HOMA-IR	3.15(1.58-9.08)	3.53±1.43
CRP	1(0.01-6.3)	1.5±1.19
ALT	14(9-23)	14.51±3.36
AST	14(9-30)	14.52±4.02
BUN	20(4.6-36)	18.39±5.69
Creatinine	0.78(0.42-1)	0.76±0.1
Leukocyte	6.73(3.54-18.45)	7.7±2.57
Neutrophil	3.86(0.62-15.93)	4.74±2.59
Lymphocyte	2.12(0.04-30.03)	2.42±2.21
Monocyte	0.54(0.01-6.7)	0.58±0.49
Basophil	0.06(0.01-1.83)	0.12±0.27
Hemoglobin	12.9(10-14.8)	12.67±1.23
RDWSD	33.6(30.8-49.1)	34.37±3
Platelet	247000(136000-434000)	249093.26±57339.37
MPV	9.8(0-13.1)	9.43±1.49
PDW	12(0-22.5)	13.63±4.03

BMI;body mass index, AMH; anti-mullerian hormone, FSH; follicle-stimulating hormone, LH; luteinizing hormone, E2 ; estradiol, PRL; prolactin, TSH; thyroid-stimulating hormone, FT4; free thyroxine, LDL; low-density lipoprotein, HDL; high-density lipoprotein, FBS; fasting blood sugar, HOMA-IR; Homeostatic Model Assessment of Insulin Resistance, CRP; C-Reactive Protein, ALT; alanine aminotransferase, AST; aspartate aminotransferase, BUN; blood urea nitrogen, RDWSD; Red Cell Distribution Width-Standard Deviation, MPV; Mean Platelet Volume, PDW; Platelet Distribution Width.

The first set of parameters listed in the table relates to demographics, including age and BMI. The study population had a median age of 24 years, with a range between 18 and 30 years, with a mean value of 24.41±2.75. The median BMI was 25 kg/m², with a range of 23-25 kg/m², indicating that the study participants had normal weight or were slightly overweight. The mean BMI was 24.28±0.83, which falls within the normal range.

Next, the table shows the hormone levels of the study participants, which include AMH, FSH, LH, E2, and prolactin. The median AMH value was 4 ng/ml, with a range of 2-8 ng/ml, showing the ovarian reserve of the participants. The mean FSH level was 6.85±1.48 mIU/ml, and the mean LH level was 7.48±2.63 mIU/ml. The median E2 level was 32 pg/ml, with a range of 14.04-73 pg/ml, and the median prolactin level was 13 ng/ml, with a range of 5-28.6 ng/ml. These hormone levels fall within the normal ranges for premenopausal women.

The lipid profile of the study population is also included in the table, including total cholesterol, triglycerides, LDL, and HDL. The median total cholesterol level was 221 mg/dl, with a range of 123-352 mg/dl, and the mean value was 225.31±52.95 mg/dl. The median triglyceride level was 120 mg/dl, ranging from 48-228 mg/dl, with a mean value of 123.09±31.61 mg/dl. The median LDL value was 135 mg/dl, ranging from 46-191 mg/dl, with a mean value of 123.21±38.95 mg/dl. The median HDL level was 60 mg/dl, with a range of 38.6-89 mg/dl, and the mean value was 59.29±11.86 mg/dl.

The fasting blood sugar level of the participants was measured, with a median value of 84 mg/dl, ranging from 71-99 mg/dl, and a mean value of 85.71±8.28 mg/dl. The median fasting insulin level was 15 µIU/ml, with a range of 7.2-36.8 µIU/ml, and a mean value of 15.98±5.21 µIU/ml. The HOMA-IR value, which assesses IR, had a median of 3.15, ranging from 1.58-9.08, and a mean value of 3.53±1.43. These values suggest that the study participants had some degree of IR.

The liver function tests, including ALT and AST levels, were also measured. The median ALT level was 14 U/L, with a range of 9-23 U/L, and a mean value of 14.51±3.36 U/L. The median AST level was 14 U/L, ranging from 9-30 U/L, with a mean value of 14.52±4.02 U/L. The renal function tests, including BUN and creatinine levels, had median values of 20 mg/dl and 0.78 mg/dl, respectively. The complete blood count and platelet indices, including leukocyte, neutrophil, lymphocyte, monocyte, basophil, hemoglobin, RDWSD, platelet, MPV, and PDW, were also measured.

Table 2 presents a comparison of various study parameters among different phenotypes of PCOS patients and a control group. The table shows the mean values and standard deviation of each parameter for four different phenotypes of PCOS patients, as well as a control group.

The analysis of the table reveals that the age and BMI of PCOS patients are similar across all four phenotypes and the control group. As expected, the levels of AMH, FSH, LH, and HOMA-IR differ significantly among the four phenotypes of PCOS patients compared to the control group. In particular, AMH levels are highest in phenotype 1 and lowest in the control group, while FSH levels are highest in phenotype 4 and lowest in the control group. LH levels are highest in phenotype 2, and HOMA-IR is highest in phenotype 1.

The table also shows that HDL levels are significantly lower in phenotype 4 compared to the control group, while fasting blood sugar (FBS), platelet count, mean platelet volume (MPV), and red cell distribution width-standard deviation (RDWSD) are significantly higher

in this phenotype than in the control group. Moreover, phenotype 4 has a higher hemoglobin level than the other phenotypes, and phenotype 1 has a higher neutrophil count than the control group.

However, there were no significant differences in AMH levels among different phenotypes of PCOS patients. This suggests that AMH may not be a useful biomarker for distinguishing between different phenotypes of PCOS. Furthermore, the results found no significant differences in HOMA-IR levels among the different phenotypes of PCOS patients. This implies that insulin resistance may not differ significantly among the different phenotypes of PCOS patients. However, the study did find that fasting blood sugar levels were significantly higher in Phenotype 1 (oligo/anovulation + hyperandrogenism + polycystic ovaries) compared to other phenotypes. This finding may suggest that Phenotype 1 is associated with a higher fasting blood sugar and greater risk of developing diabetes. The difference of AMH and HOMA-IR in different PCOS phenotypes in this study are shown in **Figure 1**.

Study parameters	Phenotype 1	Phenotype 2	Phenotype 3	Phenotype 4	p value	Control	p value
Age	24.32±2.74	24.46±1.81	24.42±2.78	24.56±2.73	0.949	24.41±2.75	0.991
BMI	24.28±0.86	24.31±0.85	24.25±0.87	24.38±0.79	0.967	24.26±0.84	0.978
AMH	5.06±1.13	4.77±0.83	4.67±0.78	4.44±0.56	0.121	2.47±0.50	<0.001
FSH	6.37±1.27	6.42±1.84	6.44±1	6.5±1.39	0.768	7.37±1.48	<0.001
LH	7.57±2.57	9.03±3.01	8.03±3.05	6.3±1.99	0.017	7.56±2.64	0.044
E2	35.27±12.45	34.95±9.07	35.33±6.76	35.33±12.99	0.986	35.79±11.06	0.999
Prolactin	13.49±4.88	13.65±6	13.25±4.24	13.26±3.42	0.981	13.36±5.55	0.999
TSH	1.84±0.89	1.81±0.6	1.79±0.65	1.84±0.7	0.999	1.78±0.65	1.000
FT4	1.07±0.32	1.08±0.17	1.06±0.2	1.05±0.17	0.967	1.09±0.33	0.988
Total Cholesterol	224.38±59.67	224.15±69.86	226.33±34.1	226.88±29.74	0.910	225.30±55.82	0.952
Triglycerides	126.8±25.91	123.85±26.06	124±17.45	124.38±14.95	0.916	120.22±40.44	0.765
LDL	127.4±41.15	124.92±22.11	124.58±24.84	124.84±32.11	0.847	119.71±43.61	0.887
HDL	55.79±10.89	57.38±10.25	57.75±5.75	56.22±9.43	0.786	62.97±13.14	0.006
FBS	92.8±4.01	89.38±7.68	86±8.33	87.03±8.49	0.007	80.50±6.50	<0.001
Fasting Insulin	17.81±7.23	15.03±7.6	14.48±4.03	14.94±3.54	0.223	15.65±3.65	0.204
HOMA-IR	4.09±1.6	3.97±1.85	3.75±1.17	3.5±1.11	0.561	3.12±1.28	0.006
CRP	1.62±1.46	1.54±0.69	1.58±0.51	1.53±0.76	0.592	1.41±1.29	0.195
ALT	14.7±3.46	14.23±3.7	14.5±2.68	14.59±3.85	0.961	14.42±3.22	0.984
AST	14.14±3.48	14.31±3.84	14.25±3.72	14.81±3.68	0.820	14.70±4.52	0.946
BUN	18.55±6.8	18.68±6.41	18.62±3.52	18.56±4.67	0.859	18.15±5.58	0.957
Creatinine	0.76±0.11	0.73±0.12	0.77±0.16	0.73±0.11	0.223	0.77±0.08	0.103
Leukocyte	7.73±2.67	6.24±1.34	5.91±0.81	8±2.75	0.018	8.04±2.61	0.005
Neutrophil	5.01±2.92	3.83±1.09	3.19±0.59	4.97±2.62	0.076	4.85±2.65	0.082
Lymphocyte	2.44±1.03	2.14±0.8	1.9±0.64	2.28±0.97	0.276	2.59±3.14	0.390
Monocyte	0.55±0.22	0.53±0.15	0.49±0.14	0.74±1.11	0.888	0.56±0.24	0.657
Basophil	0.1±0.17	0.09±0.18	0.11±0.19	0.06±0.05	0.638	0.17±0.36	0.027
Hemoglobin	12.11±1.31	12.67±1.5	12.5±1.16	12.51±1.18	0.402	13.08±1.04	0.001
RDWSD	34.92±2.63	36.67±2.23	36.53±2.01	33.88±2.32	<0.001	33.58±2.32	<0.001
Platelet	245300±53437	211692±20673	208000±35411	258062±55436	0.001	25934±6196	0.001
MPV	9.48±1.59	9.7±1.41	9.98±1.08	9.49±1.25	0.173	9.27±1.58	0.048
PDW	13.66±3.58	13.3±3.28	12.8±2.8	11.84±2.73	0.054	14.44±4.70	0.070

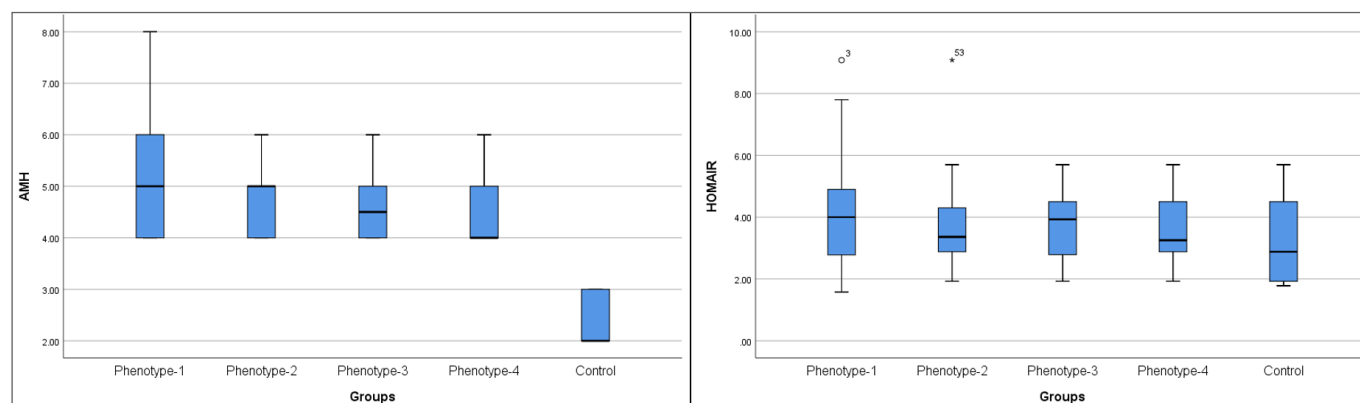


Figure 1. The difference of AMH and HOMA-IR in different PCOS phenotypes

DISCUSSION

The present study investigates whether AMH and HOMA-IR are independently associated with specific phenotypes of PCOS and whether their combined assessment improves the prediction of these phenotypes. Understanding the associations between PCOS phenotypes, AMH, and HOMA-IR is crucial for better diagnosis and management of this complex endocrine disorder. PCOS is a condition that frequently affects women during their reproductive years, which is associated with various symptoms, including irregular menstrual cycles, hirsutism, and infertility.⁶ Identifying the underlying hormonal and metabolic factors that play a role in the onset and advancement of PCOS is essential for the development of targeted therapeutic interventions.⁹

Our study found significant differences in the levels of AMH, FSH, LH, and HDL among the four phenotypes of PCOS patients compared to the control group. Phenotype 1 had the highest AMH levels, while the control group had the lowest. FSH levels were highest in phenotype 4 and lowest in the control group. LH levels were highest in phenotype 2, and HOMA-IR was highest in phenotype 1. These results align with prior research studies that have reported varying hormone levels among different PCOS phenotypes.⁹⁻¹² The observed differences in hormone levels among the phenotypes may provide insights into the underlying pathophysiology of PCOS and help clinicians better understand the heterogeneity of this disorder. Furthermore, these differences may have implications for the development of targeted treatment strategies for each phenotype.

Despite previous research suggesting insulin resistance is associated with PCOS,^{13,15} our study found no significant differences in HOMA-IR levels among the different PCOS phenotypes. However, we did observe that in comparison to other phenotypes, Phenotype 1 had significantly higher fasting blood sugar levels. This

finding aligns with a previous study that reported higher HOMA-IR levels in more severe PCOS phenotypes.¹⁴⁻¹⁶ The lack of significant differences in HOMA-IR levels among the phenotypes may indicate that IR is a common feature of PCOS, regardless of the specific phenotype. Alternatively, it may suggest that other factors, such as obesity or genetic predisposition, play a more significant role in the development of IR in PCOS patients. Further research is needed to elucidate the relationship between IR and PCOS phenotypes.

The finding that AMH levels are highest in phenotype 1 is consistent with previous studies indicating that AMH levels are elevated in PCOS patients,^{17,18} particularly those with hyperandrogenism and polycystic ovaries. AMH is produced by small follicles present in the ovaries, and its levels are indicative of ovarian reserve and follicular activity. In PCOS patients with hyperandrogenism and polycystic ovaries, there is an increase in the number of small follicles and a reduction in the growth and maturation of larger follicles, leading to elevated AMH levels.^{18,19}

The finding that HOMA-IR is highest in phenotype 1 is also consistent with previous studies showing that IR is more pronounced in PCOS patients with hyperandrogenism and polycystic ovaries.^{20,21} Insulin resistance is a hallmark of PCOS and is associated with hyperinsulinemia, which in turn, contributes to hyperandrogenism and ovulatory dysfunction. The primary cause of insulin resistance in PCOS is thought to be related to deficiencies in insulin signaling pathways, defects in glucose transport, and increased lipolysis in adipose tissue.^{20,22}

However, the difference in AMH levels among different phenotypes of PCOS patients was not significant, suggesting that AMH may not be a useful biomarker for distinguishing between phenotypes. This finding is in line with previous research that reported a lack of correlation between AMH and PCOS phenotypes.^{23,24} The inability of AMH to differentiate between PCOS

phenotypes may be because AMH levels are influenced by various factors, such as age, body mass index, and ovarian reserve. Additionally, AMH levels may not accurately reflect the severity of PCOS symptoms or the presence of specific phenotypic features. As a result, clinicians may need to rely on a combination of clinical, hormonal, and metabolic markers to accurately diagnose and classify PCOS phenotypes.

This study's conclusions could be useful in the clinical setting for the diagnosis and management of PCOS. Understanding the associations between hormone levels, IR, and PCOS phenotypes can help clinicians better tailor treatment plans for patients. However, our study has limitations, such as a relatively small sample size and a retrospective design. Future research should focus on larger, longitudinal studies to further explore the relationships between AMH, HOMA-IR, and PCOS phenotypes, as well as the potential utility of other biomarkers for distinguishing between phenotypes.

CONCLUSION

Our study found significant differences in hormone levels among PCOS phenotypes, but no significant differences in AMH or HOMA-IR levels among the different phenotypes. These findings suggest that AMH may not be a useful biomarker for distinguishing between PCOS phenotypes, and insulin resistance may not differ significantly among phenotypes. Further investigation is required to improve our understanding of the associations between hormone levels, insulin resistance, and PCOS phenotypes, as well as to identify potential biomarkers for improved diagnosis and management of this complex endocrine disorder.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of Bezmialem Vakıf University Non-interventional Clinical Researchs Ethics Committee (Date: 14.06.2023, Decision No: 2023/191).

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

Referee Evaluation Process: Externally peer-reviewed.

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