Research Article (Araştırma Makalesi)

Evaluating The Diagnostic Potential of Angptl2 and Angptl8 in Women with Polycystic Ovary Syndrome

Polikistik Over Sendromlu Kadınlarda Angptl2 ve Angptl8'in Tanı Potansiyelinin Değerlendirilmesi

Zeki UGUR[1], Senol SENTURK[1], Medeni ARPA[2], Alperen AKSAN[3]

[1] Recep Tayyip Erdogan University, Faculty of Medicine, Department of Obstetrics and Gynecology, Rize, Türkiye
[2] Recep Tayyip Erdogan University, Faculty of Medicine, Department of Medical Biochemistry, Rize, Türkiye
[3] Department of Gynecology and Obstetrics, Sar Hospital, Rize, Türkiye

Özet

Amaç: Polikistik over sendromu (PCOS), hiperandrojenizm, anovülasyon ve polikistik overlerle karakterize yaygın bir endokrin bozukluktur. Bu hastalığın patogenezinde insülin direnci önemli bir rol oynamaktadır. Bu çalışmanın amacı, PCOS'lu kadınlarda anjiyopoetin-benzeri proteinler (ANGPTL2 ve ANGPTL8) düzeylerini değerlendirmek ve özellikle insülin direnci olmak üzere metabolik ve hormonal parametrelerle olan ilişkisini inceleyerek tanısal potansiyellerini araştırmaktır.

Gereç ve Yöntemler: Bu prospektif klinik çalışmaya 40 PCOS'lu kadın ve 40 sağlıklı kontrol olmak üzere toplam 80 katılımcı dahil edildi. PCOS tanısı Rotterdam kriterlerine göre kondu. Serum ANGPTL2 ve ANGPTL8 düzeyleri ELISA kiti kullanılarak ölçüldü; insülin direnci HOMA-IR yöntemiyle hesaplandı. Tanısal doğruluğu değerlendirmek için korelasyon testleri ve ROC (alıcı işletim karakteristiği) eğrisi analizi yapıldı.

Bulgular: PCOS grubunda ANGPTL2 düzeyleri ile insülin ve HOMA-IR arasında anlamlı bir korelasyon saptandı ($r = 0.42$, $p < 0.01$), ANGPTL8 ise HOMA-IR ile daha zayıf bir ilişki gösterdi ($r = 0.35$, $p < 0.05$). ROC analizi hem ANGPTL2 (AUC = 0.60) hem de ANGPTL8 (AUC = 0.58) için düşük tanısal doğruluk gösterdi; bu da bu proteinlerin PCOS için güvenilir tanı belirteçleri olmadığını göstermektedir.

Sonuç: ANGPTL2 ve ANGPTL8, PCOS'ta insülin direnci ile ilişkili olsa da, tanısal kullanımları sınırlıdır. Bu proteinlerin PCOS'taki rolünü ve olası terapötik potansiyelini daha iyi anlayabilmek için daha geniş katılımlı çalışmalara ihtiyaç vardır.

Anahtar kelimeler: PCOS, ANGPTL2, ANGPTL8, insülin direnci, biyobelirteçler, metabolik bozukluklar

Abstract

Objective: Polycystic ovary syndrome (PCOS) is a common endocrine disorder characterized by hyperandrogenism, anovulation, and polycystic ovaries. Insulin resistance plays a key role in the pathogenesis of this disorder. This study aimed to evaluate the serum levels of angiopoietin-like proteins (ANGPTL2 and ANGPTL8) in women with PCOS and to investigate their correlation with metabolic and hormonal parameters, especially insulin resistance, to assess their diagnostic potential.

Material and Methods: A prospective clinical study included 80 participants: 40 women with PCOS and 40 healthy controls. PCOS diagnosis was based on the Rotterdam criteria. Serum ANGPTL2 and ANGPTL8 levels were measured using ELISA kits, and insulin resistance was calculated using HOMA-IR. Statistical analyses included correlation tests and receiver operating characteristic (ROC) curve analysis to assess diagnostic accuracy.

Results: ANGPTL2 levels showed a significant correlation with insulin and HOMA-IR in the PCOS group ($r = 0.42$, $p < 0.01$), while ANGPTL8 showed a weaker correlation with HOMA-IR ($r = 0.35$, $p < 0.05$). ROC analysis showed low diagnostic accuracy for both ANGPTL2 (AUC = 0.60) and ANGPTL8 (AUC = 0.58), suggesting that they are not reliable diagnostic markers for PCOS.

Conclusion: Although ANGPTL2 and ANGPTL8 are associated with insulin resistance in PCOS, their diagnostic utility remains limited. Further studies with larger populations are needed to better understand their role in PCOS and their potential for therapeutic use.

Keywords: PCOS, ANGPTL2, ANGPTL8, insulin resistance, biomarkers, metabolic disorders.

Correspondence: Senol Senturk, Recep Tayyip Erdogan University, Faculty of Medicine, Department of Obstetrics and Gynecology, Rize, Türkiye

Phone: +90 532 716 6482 **e-mail:** senol.senturk@erdogan.edu.tr

ORCID No (Respectively): 0000-0002-5502-1664, 0000-0001-7712-7278, ORCİD: 0000-0001-8321-4829, 0000-0001-7623-3589

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INTRODUCTION

Polycystic ovary syndrome (PCOS) is traditionally the combination of polycystic ovaries with hyperandrogenism (hirsutism and acne) and anovulation (oligomenorrhea, infertility, and dysfunctional uterine bleeding). On ultrasonography, it is the main gynecological endocrinopathy, affecting 6%-10% of women of reproductive age (1). It is the most common cause of infertility due to anovulation. In many countries, it is the leading cause of female infertility (2). The specific pathophysiology of this syndrome is not yet clear, but it is associated with the presence of insulin resistance, obesity, type 2 diabetes mellitus, dyslipidemia, metabolic syndrome, hypertension, cardiovascular disease, hyperplasia, and endometrial cancer (3). In the presence of menstrual disorders, PCOS is diagnosed in 30-40% of patients with primary or secondary amenorrhea and in 80% of patients with oligomenorrhea (4). PCOS is more common in women of childbearing age, and symptoms vary according to ethnicity. The most widely used tool for the diagnosis of PCOS is still the "Rotterdam criteria"; the prevalence is five times higher than when defined according to the NIH (National Institutes of Health)criteria (5). Only one-third of patients have the classic form of the syndrome described (3).

The concept of PCOS is very broad; clinically, it is characterized by the presence of menstrual irregularities, chronic anovulation, and hyperandrogenism. There are a few epidemiologic studies on PCOS, which are mainly population-based. However, these studies have problems with sampling and classification, generalizability, and comparability (6).

PCOS is a multifactorial disease related to genetic and environmental factors and is associated with obesity, insulin resistance, glucose tolerance, dyslipidemia, and diabetes (4). It is estimated that 105 million women between the ages of 15 and 49 worldwide suffer from PCOS, with 72% to 82% of cases of hyperandrogenism attributable to this condition. Angiopoietin-like 2 (ANGPTL 2) is a proinflammatory protein associated with chronic inflammatory diseases such as diabetes, atherosclerosis, and cancer, and is widely distributed in visceral adipose tissue (Rotterdam, 2004). ANGPTL 2 has important effects on angiogenesis, androgen biosynthesis, adipocyte function, and insulin resistance (6). Angiopoietin-like 8 (ANGPTL 8) is an atypical member of the angiopoietin-like protein family involved in lipid and glucose homeostasis. It has the ability to inhibit lipoprotein lipase activity and induce pancreatic β-cell proliferation in insulin-resistant states. ANGPTL 8 levels have been reported to increase in obesity. ANGPTL 2 and ANGPTL 8 have been reported to be associated with insulin resistance, diabetes, and obesity, and are also effective in inflammation. In this case, it is hypothesized that they may also play a role in the pathogenic mechanisms leading to PCOS. This study aimed to investigate the usefulness of the ANGPTL 2 AND ANGPTL 8 proteins in the diagnosis of PCOS.

MATERIALS AND METHODS

Study design and participants

This prospective clinical study was conducted to investigate the relationship between serum levels of ANGPTL2 and ANGPTL8 in women with PCOS and obesity who presented to the gynecology and obstetrics outpatient clinic between January 2018 and December 2019 were evaluated consecutively. A total of 112 patients were screened; those who did not meet the Rotterdam criteria (n=18), had endocrine disease (n=7), were using hormonal medications (n=5), or did not meet the obesity criteria (n=2) were excluded. As a result, 40 patients with PCOS and 40 control patients were included in the study. PCOS diagnosis was based on the Rotterdam criteria, which require the presence of two out of three characteristics: Oligo- or anovulation, hyperandrogenism (clinical or biochemical), and polycystic ovaries on ultrasound, excluding other causes such as congenital adrenal hyperplasia, androgen-secreting tumors, and Cushing's syndrome.

Ethical approval and informed consent

The study was conducted at the Department of Obstetrics and Gynecology, Recep Tayyip Erdoğan College, after obtaining institutional ethics committee approval(Decision no: 2018/20). All participants provided written informed consent in accordance with the Declaration of Helsinki before enrollment in the study.

Inclusion and exclusion criteria

Women aged 18-35 years with a confirmed diagnosis of PCOS based on the Rotterdam criteria were included. Exclusion criteria were the use of hormone therapy within the last six months, pregnancy, breastfeeding, other endocrine disorders (such as thyroid disease, diabetes mellitus), or systemic diseases. Participants with a body mass index (BMI) outside the range of 18.5–30 kg/m^2 were also excluded to minimize confounding factors.

Data collection

Demographic data, including age, BMI, and menstrual history, were collected from all participants. Clinical characteristics such as hirsutism were assessed using the Ferriman-Gallwey scoring system, with a score of ≥8 indicating hirsutism. Blood pressure, waist circumference, and fasting blood glucose levels were recorded in all subjects.

Blood sample collection and biochemical analysis

Fasting blood samples were collected from all participants between 8:00 and 10:00 am after an overnight fast. The serum was separated by centrifugation and stored at -80°C until analysis. ANGPTL2 and ANGPTL8 levels were measured using commercially available ELISA kits (catalog numbers: XYZ for ANGPTL2 and ABC for ANGPTL8, Manufacturer). In addition to ANGPTL2 and ANGPTL8, serum levels of luteinizing hormone (LH), follicle-stimulating hormone (FSH), estradiol (E2), testosterone, insulin, and glucose were also measured. Insulin resistance was calculated using the HOMA-IR formula (Homeostasis Model Assessment for Insulin Resistance):

HOMA−IR=fasting insulin (μU/mL)×fasting glucose (mg/dL)/405.

Statistical analysis

The data were analyzed using the statistical software package SPSS 26.0. Although a specific power analysis was not performed at the beginning of the study, the sample size was determined based on previous biomarker studies in patients with PCOS. Descriptive statistics were calculated for all variables. Continuous variables were presented as mean ± standard deviation (SD), while categorical variables were presented as frequencies and percentages. The normality of the data distribution was assessed using the Shapiro-Wilk test. Differences between the two groups were analyzed using the t-test for normally distributed variables and the Mann-Whitney U-test for non-normally distributed variables. The chi-square test was used for categorical variables. Correlation analyses between ANGPTL2, ANGPTL8, and clinical parameters (BMI, HOMA-IR, hormone levels) were performed using Pearson's or Spearman's correlation coefficients, as appropriate. A p-value < 0.05 was considered statistically significant.

RESULTS

Demographic and clinical characteristics

A total of 80 participants were included in the study: 40 women with PCOS and 40 healthy controls. The mean age of the PCOS group was 21.65 ± 4.14 years, while the control group had a mean age of 22.9 ± 3.97 years, with no statistically significant difference between the two groups ($p > 0.05$). Both groups had normal body mass index (BMI) values, with no significant differences observed ($p > 0.05$). However, the size of the ovaries was significantly larger in the PCOS group than in the control group ($p < 0.001$, **Table 1**).

Table 1. Demographic Data of Individuals in the Control and PCOS Groups

Parameters	Control Group (n=40)	PCOS Group (n=40)	p-value
	Mean ± Std	Mean ± Std	
Age	22.9 ± 3.97	21.65 ± 4.14	0.173
BMI (<25kg/m^2)	23.27 ± 4.98	24.8 ± 6.10	0.228
Menarche	13.27 ± 1.61	14.8 ± 8.74	0.267
Gravida	0.22 ± 0.73	0.12 ± 0.40	0.452
Parity	0.10 ± 0.37	0.12 ± 0.40	0.776
Abortion	0.12 ± 0.51	0.00 ± 0.00	0.129
Number of Living Children	0.10 ± 0.37	0.07 ± 0.26	0.734
Age of First Pregnancy	21.8 ± 7.45	22.5 ± 5.10	0.293
Menstrual Cycle Duration	30.4 ± 7.17	43.3 ± 17.2	0.000
Duration of Menstruation	6.2 ± 1.71	7.57 ± 6.38	0.192
PED	3.95 ± 3.80	4.37 ± 4.93	0.668

Statistical analysis was performed using the *t-test* for normally distributed data and the *Mann-Whitney U-test* for non-normally distributed data.

p-value < 0.05 was considered significant.

Hormonal and metabolic parameters

Mean luteinizing hormone (LH) levels were significantly higher in the PCOS group than in the control group (8.19 ± 6.52 mIU/mL vs. 4.23 ± 2.15 mIU/mL, $p < 0.01$). Fasting insulin and HOMA-IR levels were also elevated in the PCOS group compared to the control group ($p < 0.05$), indicating a higher prevalence of insulin resistance in women with PCOS **(Table 2)**.

ANGPTL2 and ANGPTL8 levels

As for angiopoietin-like proteins, ANGPTL8 levels showed a weak positive correlation with BMI and HOMA-IR ($r = 0.35$, $p < 0.05$). On the other hand, ANGPTL2 levels showed a significant positive correlation with insulin and HOMA-IR levels ($r = 0.42$, $p < 0.01$), suggesting a stronger association with insulin resistance in the PCOS group. Interestingly, a negative correlation was observed between ANGPTL2 and prolactin levels ($r = -0.27$, $p < 0.05$, **Table 3**).

Table 2. Clinical Characteristics of the Control and PCOS Groups

Parameteres	Control Group (n=40)	PCOS Group (n=40)	p-value
	Mean ± Std	Mean ± Std	
ANGPTL2 (ng/ml)	49.1 ± 1.99	41.14 ± 1.27	0.036
ANGPTL8 (pg/ml)	1793835 ± 99972	2125669 ± 109768	0.180
Ovarian Size	4.93 ± 3.9	9.19 ± 3.4	0.000
Follicle Count	7.35 ± 1.70	13.45 ± 2.12	0.000
WC	75.13 ± 1.06	86.1 ± 1.51	0.006
FG Score	7.67 ± 2.4	14.15 ± 5.47	0.000
Fasting Glucose (mg/ml)	90.3 ± 9.16	90.9 ± 10.35	0.803
Insulin (mIU/ml)	16.62 ± 8.2	13.9 ± 15.1	0.611
HOMA-IR	2.74 ± 2.46	3.5 ± 4.84	0.425
Total Cholesterol (mg/dl)	168.5 ± 2.58	185.85 ± 3.63	0.018
Triglyceride (mg/dl)	82.2 ± 4.30	91.9 ± 4.52	0.337
HDL (mg/dl)	59.40 ± 1.05	65.9 ± 7.66	0.604
LDL (mg/dl)	92.65 ± 2.28	112.6 ± 3.07	0.002
FSH (mIU/ml)	4.86 ± 1.39	4.51 ± 1.22	0.258
LH (mIU/ml)	4.23 ± 2.15	8.19 ± 6.52	0.000

The data represent mean values ± standard deviations. Insulin resistance was calculated using the HOMA-IR formula.

The significance level was set at $p < 0.05$.

Table 3. Correlations of ANGPTL2 and ANGPTL8

Variable	ANGPTL2 (ng/ml) r	ANGPTL2 (ng/ml) p	ANGPTL8 (pg/ml) r	ANGPTL8 (pg/ml) p
Age	-0.003	0.976	-0.166	0.157
BMI (<25kg/m^2)	0.092	0.418	0.257*	0.028
Menarche	-0.022	0.847	0.064	0.592
Gravida	-0.039	0.728	-0.033	0.781
Insulin	0.392	0,001	0,086	0,484
HOMA-IR	0.262	0,032	0.257	0,041

Pearson's correlation coefficient was used to evaluate the relationship between ANGPTL2, ANGPTL8, and various clinical parameters.

p-value < 0.05 was considered statistically significant.

Diagnostic Performance

Receiver Operating Characteristic (ROC) curve analysis was performed to evaluate the diagnostic value of ANGPTL2 and ANGPTL8 in distinguishing between PCOS and healthy controls. The area under the curve (AUC) for ANGPTL2 in the PCOS group was 0.60, while for ANGPTL8, the AUC was 0.58, indicating low diagnostic accuracy for both proteins **(Figures 1 and 2)**.

Sensitivity and specificity analyses showed that neither ANGPTL2 nor ANGPTL8 provided adequate sensitivity and specificity for distinguishing PCOS from healthy controls. The cut-off values identified for ANGPTL2 and ANGPTL8 did not reach statistical significance in the diagnostic evaluation of PCOS ($p > 0.05$).

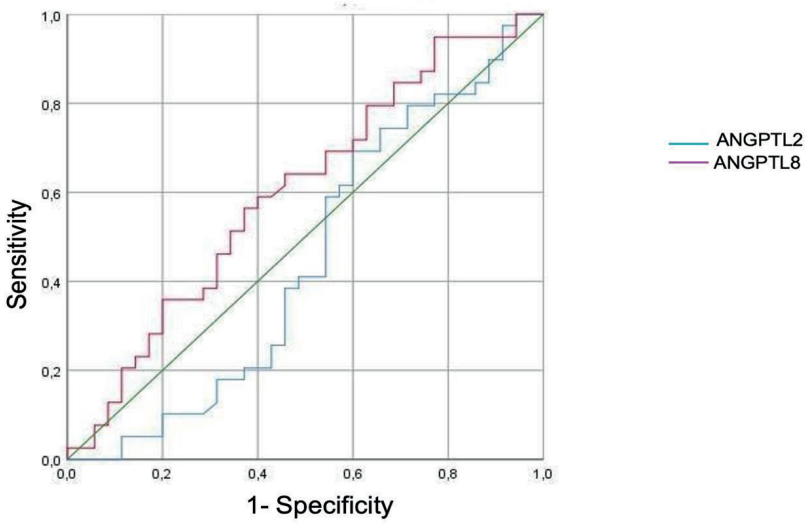

Figure 1. ROC Analysis - Control Group

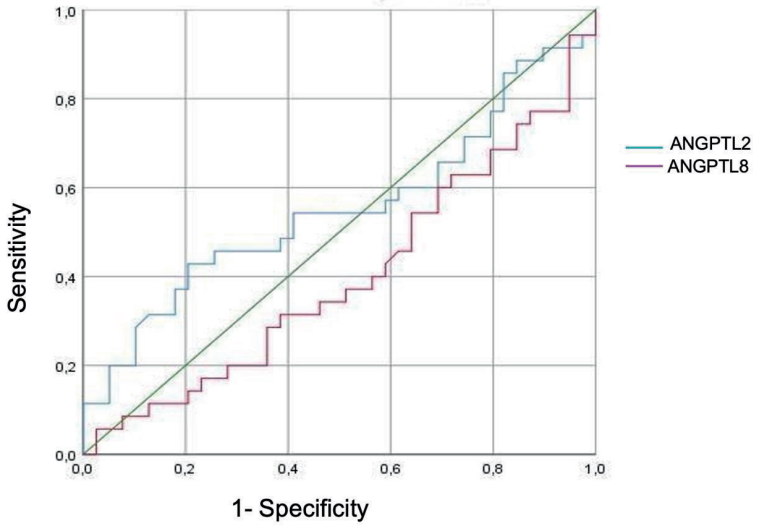

Figure 2. ROC Analysis - PCOS Group

DISCUSSION

PCOS is a complex endocrine and metabolic disorder characterized by chronic anovulation and hyperandrogenism. Insulin resistance is known to play an important role in the pathogenesis of PCOS and metabolic syndrome. ANGPTL2 is a proinflammatory protein associated with chronic inflammatory diseases such as diabetes, atherosclerosis, and cancer, and is highly expressed in visceral adipose tissue. In addition, ANGPTL8 has important effects on angiogenesis, androgen biosynthesis, adipocyte function, and insulin resistance (7). This study aimed to investigate the usefulness of ANGPTL2 AND ANGPTL8 proteins in the diagnosis of PCOS. The clinical characteristics of the patients were evaluated in the groups formed in the study.

In our study, a positive significant association was found between ANGPTL 8 and BMI and HOMA-IR, as well as between ANGPTL 2 and the insulin and HOMA-IR ratio. The sensitivity and specificity analyses performed in the study showed that ANGPTL 2 and ANGPTL 8 were not statistically significant for the diagnosis in the PCOS and control groups.

Sasaki *et al.* reported that high expression of ANGPTL2 leads to inflammation in adipose tissue and impairs insulin sensitivity(8). In addition, Tabata et al. reported that adipose tissue inflammation and insulin resistance are increased in ANGPTL2-deficient mice (9). Previous studies have shown that ANGPTL2 levels are regulated by the degree of obesity. It has been reported that the concentration of this factor decreases with weight loss and correlates significantly with systemic insulin resistance and inflammation (10). Based on these studies, a study conducted on women with PCOS found that there was no significant difference in serum levels of ANGPTL2 in women with PCOS with normal BMI compared to the control group, and that there was also a significant positive correlation between ANGPTL2 and insulin and HOMA-IR. Similar to this study, a positive correlation between ANGPTL2 and insulin and HOMA-IR levels was also found in our study.

ANGPTL8 is also known in the literature as betatrophin. In one study, basal serum betatrophin concentrations were found to be positively correlated only with HOMA-IR among the indirect insulin sensitivity indices. Therefore, it was hypothesized that serum betatrophin concentrations in women with PCOS are dependent on insulin secretion from beta cells (11). Research showed that patients with PCOS have more ANGPTL8 than the control group (12). Further investigation by Varikasuvu et al. showed that the ANGPTL8 levels increased in patients with PCOS, which was also associated with increased age and insulin resistance (13). Kahraman et al. found that in women with PCOS, enhanced ANGPTL8 levels are correlated with LH and fibroblast growth factor-21 (14). Further research has shown that the production of ANGPTL8 levels increases significantly in PCOS patients with insulin resistance relative to healthy women (15). In another study, ANGPTL8 serum concentrations in women with PCOS, linked to insulin resistance and beta-cell function, did not change (11). Researchers have hypothesized that higher levels of ANGPTL8 in women with PCOS may be due to increased resistance of such patients to insulin (16-18).

In our study, similar to the literature, a low positive correlation between ANGPTL8 and the HOMA-IR ratio was found. However, some studies in the literature reported no correlation between ANGPTL8 and HOMA-IR. Since the betatrophin effect may reflect a compensatory response in the insulin-resistant state and has been suggested as a marker of insulin resistance, it is important to consider these indices when comparing the results of different studies (19). Moreover, the influence of ethnicity in the cited studies on serum betatrophin concentrations and the different PCOS phenotypes should not be excluded. However, the role of this hormone in the pathogenesis of insulin resistance in PCOS women has not been clearly established.

This study contributes to the limited body of research investigating the potential diagnostic value of angiopoietin-like proteins (ANGPTL2 and ANGPTL8) in women with polycystic ovary syndrome (PCOS). By focusing on a homogeneous group of participants (women aged 18to 35 years with controlled BMI to minimize confounding factors), the study provides insights into the relationships between these proteins and insulin resistance, an important factor in the pathogenesis of PCOS. The use of established criteria, such as the Rotterdam criteria for PCOS diagnosis and the HOMA-IR formula for insulin resistance, adds methodological rigor to the study. In addition, the prospective design strengthens the reliability of the results and provides a basis for future research into the role of

ANGPTL proteins in PCOS and related metabolic disorders. One of the main limitations of this study is the relatively small sample size, which may limit the generalizability of the results. In addition, although BMI was controlled for in the study, other potential confounders, such as dietary habits, physical activity, or genetic predispositions that could influence ANGPTL levels, were not considered. Another limitation is the fact that the study was conducted at a single center, which may limit the applicability of the results to broader populations with different ethnic backgrounds or different PCOS phenotypes. Finally, the study's inability to establish statistically significant diagnostic value for ANGPTL2 and ANGPTL8 limits its immediate clinical application. Future studies with larger and more diverse populations are needed to further explore these relationships.

In conclusion, this study highlights the possible involvement of angiopoietin-like proteins, particularly ANGPTL2 and ANGPTL8, in the pathogenesis of PCOS through their association with insulin resistance. Although both proteins correlated with metabolic parameters, particularly insulin and HOMA-IR levels, their diagnostic utility in distinguishing women with PCOS from healthy controls was not statistically significant. These results suggest that although ANGPTL2 and ANGPTL8 may play a role in the metabolic disturbances in PCOS, they are not yet reliable biomarkers for clinical diagnosis. Future research with larger, more diverse cohorts and deeper exploration of the molecular mechanisms of these proteins is needed to further elucidate their role and potential therapeutic value in the treatment of PCOS.

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Conflict of Interest: The author declares no conflicts of interest.

Ethics Approval: The study was conducted at the Department of Obstetrics and Gynecology, Recep Tayyip Erdoğan College, after obtaining approval from the institutional ethics committee (Date: 26.01.2018/ Decision no: 2018/20). All participants provided written informed consent in accordance with the Declaration of Helsinki before enrollment in the study.

Author contribution: The corresponding author declares that he contributed to all aspects of the study.

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