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Original Article

Evaluation of relationship among polycystic ovary syndrome, atherogenic index of plasma, and high sensitive C reactive protein

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Abstract

Aim: In this study, we aimed to investigate the relationship among cardiovascular risk factors (CRFs), atherogenic index of plasma (AIP) and high-sensitivity C-reactive protein (hs-CRP) levels in polycystic ovary syndrome (PCOS) patients and identify risks earlier.
Materials and Methods: 131 patients diagnosed with PCOS according to Rotterdam criteria and 140 healthy controls were included from August 2019 to October 2019. Blood samples were done in the early follicular phase of the patients and were done after 10-12 hours of fasting.
Results: AIP and hs-CRP levels were higher in PCOS group ($p<0.001$, $p<0.001$, respectively). In PCOS group significantly positive correlation was determined between CRFs and AIP. Significantly positive correlation was determined only between hs-CRP and triglyceride levels ($r=0.280$, $p<0.05$). In PCOS group, there was a significantly positive correlation between hs-CRP levels and AIP ($r=0.372$, $p<0.001$).
Conclusion: AIP and hs-CRP may be beneficial markers for early monitoring of cardiovascular diseases in PCOS patients.

Keywords: Atherogenic index of plasma; cardiovascular risk factors; high-sensitivity C-reactive protein; polycystic ovary syndrome

INTRODUCTION

Polycystic ovary syndrome (PCOS) is a complex metabolic and endocrinological disorder (1). Polycystic appearance of the ovaries in ultrasonography, hyperandrogenism and chronic anovulation are clinical findings seen in PCOS (2). In Turkey, according to three diagnostic criteria of PCOS prevalence (The Rotterdam, Androgen Excess Society and the National Institutes of Health) were determined as 10% (8-13%, n=15), 10% (7-13%, n=10) and 6% (5–8%, n=18) respectively (3).

Although the increased risk of cardiovascular disease (CVD) in patients with PCOS is not fully demonstrated, the data obtained show that the incidence of CVD is increasing. PCOS patients have independent cardiovascular risk factors (CRFs). Dyslipidemia, impaired glucose tolerance, increased abdominal adiposity, insulin resistance, hyperinsulinemia and obesity in patients with PCOS predispose to CVD (4–6).

Lipid profile of serum is the major risk factor and predictor for CVD (7). Despite for LDL-C being primary lipid risk factor, other lipid parameters can also increase coronary heart disease (8). Subclinical atherosclerosis is another risk factor for CVD (9,10). In the development of atherosclerosis, there is a strong correlation between high values of plasma triglyceride (TG), low density of lipoprotein cholesterol (LDL-C), and low values of high-density lipoprotein cholesterol (HDL-C) (11). The atherogenic index of plasma (AIP) is a parameter that is measured in milligrams per deciliter and provides additional benefit when evaluating CRFs. AIP is calculated as the logarithm of the plasma TG/HDL ratio [log (TG/HDL-C)] (12). On the other hand, CRP plays a role in inflammation pathophysiology of atherosclerosis. High-sensitivity C-reactive protein (hs-CRP) is thought to be precursor of future cardiovascular risk (13).

Early detection of CRFs in patients with PCOS can help protect patients from CVD and may reduce the occurrence

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of poor cardiovascular health outcomes. We aimed to show the relationship between AIP and hs-CRP in PCOS patients and to show whether AIP and hs-CRP could be helpful in determining early CVD.

MATERIALS and METHODS

From August 2019 to October 2019, 131 patients diagnosed with PCOS according to Rotterdam criteria and 140 healthy controls with regular menstrual cycle (21-35 days) and had no clinical signs of hyperandrogenism were enrolled in this study. Patients diagnosed with diabetes mellitus (DM), hypertension (HT), chronic kidney failure, hypothyroidism, adrenal and pituitary disease, smokers, patients with systemic inflammation, rheumatoid diseases or autoimmune systemic disorders and using lipid-lowering drugs or oral contraceptives were excluded. The study was approved by Afyonkarahisar Health Sciences University Clinical Research Ethics Committee (Date: 08/02/2019, Decision No: 2019/9-258) and conducted in accordance with the 1975 Helsinki Declaration guidelines. Written informed consent was obtained from all patients.

Height (cm), weight (kg) and waist circumference (cm) were evaluated and body mass index (BMI) was calculated as kg/m² in all patients. According to the World Health Organization (WHO) criteria; patients with BMI ≥25 kg/m² were considered overweight, and 18.5-24.9 kg/m² BMI were considered normal weight (14).

Blood sample was performed in the early follicular phase (2nd to 5th day of the menstrual period). Plasma fasting glucose, insulin, triglyceride (TG), total cholesterol, LDL-C, and HDL-C levels were measured in fasting blood samples of 10-12 hours. Glucose, TG, LDL-C, HDL-C tests (mg/dl), without waiting from the serum sample obtained, were performed by Roche Cobas C501 autoanalyzer using Roche brand commercial kits (Roche Diagnostics International Ltd. Rotkreuz, Switzerland). Total testosterone (ng/dl), free testosterone (ng/dl), androstenedione (ng/mL), dehydroepiandrosterone sulphate (DHEAS, ug/dl), sex hormone binding globulin (SHBG, nmol/L), insulin (µIU/ml), follicle stimulating hormone (FSH, mIU/ml), luteinizing hormone (LH, mIU/ml), and estradiol (pg/mL) were studied by chemiluminescence in the Roche Cobas E601 hormone autoanalyzer with using Roche commercial kits (Roche Diagnostics International Ltd. Rotkreuz, Switzerland). Patients with at least three criteria from Adult Treatment Panel-III criteria were evaluated as metabolic syndrome (15).

Homeostatic Model Assessment for Insulin Resistance (HOMA-IR) = (Fasting plasma glucose (mg/dl) X Fasting plasma insulin (µU/ml))/405. HOMA-IR method was used and the presence of HOMA-IR ≥2.7 was considered insulin resistance (16). AIP were calculated by logarithm of the ratio of TG to HDL-C [log (TG/HDL-C)]. It is associated that low cardiovascular risk if AIP <0.1, moderate cardiovascular risk if AIP between 0.1-0.24, and high cardiovascular risk if AIP>0.24 (17). We measured participant's blood pressure after 5 to 10 minutes rest using digital blood pressure monitors (OMRON-M3 Comfort, Shiokoji Horikawa, Shimogyo-ku, Kyoto, Japan). Hs-CRP (mg/L) measurement was performed by IMMAGE Immunochemistry Systems autoanalyzer (Beckman Coulter, USA). Hs-CRP levels <1, 1-3, >3 mg/L were considered as low, moderate and high-level risk of future heart disease, respectively (18). Ovarian volume and ovarian cyst measurements were performed by abdominal ultrasonography (Hitachi HI VISION Preirus, Tokyo, Japan).

The sample size for the study was calculated using the following formula:

$n = Z^2 \times (p \times q) / e^2$

$= (1.96)2 \times 0.09 \times (1-0.09) / (0.05)^2$

$= 125.85$

$= 126$

Where,

n= sample size

Z= 1.96 at 95% Confidence Interval

p= average prevalence of taken from previous study (9%)[2]

q= 1-p

e= Margin of error (5%)

Statistical analysis

Statistical analysis was performed using IBM SPSS Statistics 22.0 statistical software. Continuous variables with normal distribution were reported as the mean±standard deviation (m±sd) and categorical variables were expressed as the number of patients and percentages. Chi-square test was used to compare percentage distributions between two groups and Mann Whitney-U test was used to compare median values between groups. The correlation of continuous data was evaluated by Spearman test. Correlation coefficient (r); between 0.00–0.24 weak, between 0.25–0.49 moderate, between 0.50–0.74 strong, between 0.75–1.00 were evaluated as a very strong relationship. All tests were two-tailed, and p-value <0.05 was considered statistically significant.

RESULTS

One hundred and thirty one women with PCOS and 140 healthy women were included in this study. There were no significant differences between ages and heights of two groups. But when weights are compared; the weight of PCOS patients were significantly higher than control group (p<0.001). Also, BMI of PCOS patients were significantly higher than control group (p<0.001), (Table 1). Patients with a BMI of more than 25 kg/m² were 60.3% of PCOS group and 15.7% of control group (Table 2). It was determined that the risk of high BMI in PCOS group increased by 8.25 times compared to control group (odds ratio=8.25, p<0.001).

Waist circumference of patients with PCOS was significantly higher than control group (p<.001), (Table 1).

Table 1. Biochemical and hormonal parameter results of groups

Parameter	Control (n=140)(mean±sd)	PCOS (n=131) (mean±sd)	P value
Age (year)	25.34±4.99	24.64±5.02	>0.05
Height (cm)	163±6	162±6	>0.05
Weight (kg)	59.30±9.82	73.43±16.46	<0.001
BMI (kg/m^2)	22.33±3.36	27.79±5.70	<0.001
Waist Circumference (cm)	95.37±5.74	105.52 ±11.48	<0.001
Systolic Blood Press (mm/Hg)	105.42±12.41	115.08±14.29	<0.001
Diastolic Blood Press (mm/Hg)	71.50±7.40	74.06±9.05	<0.05
Fasting Glucose (mg/dl)	78.60±8.36	81.54±8.46	<0.05
Insulin (µIU/ml)	9.26±3.69	17.24±10.79	<0.001
HOMA_IR	1.81±0.79	3.57±2.66	<0.001
FSH (mıu/ml)	6.04±2.79	5.39±1.68	>0.05
LH (mıu/ml)	6.50±4.58	8.58±5.41	<0.001
Estradiol (pg/mL)	88.50±54.03	58.43±34.20	<0.001
DHEAS (UG/dl)	150.11±46.39	302.30±143.02	<0.001
Total testosterone (ng/dl)	27.85±7.45	69.21±26.53	<0.001
Free testosterone (ng/dl)	1.80±0.66	3.00±1.16	<0.001
Androstenedione (ng/mL)	1.70±0.58	4.25±2.13	<0.001
SHBG (nmol/L)	128.15±24.12	58.56±24.95	<0.001
TG (mg/dl)	98.51±46.87	114.43±54.60	<0.05
HDL-C (mg/dl)	56.69±11.99	51.12±11.56	<0.001
Total cholesterol (mg/dl)	160.76±29.50	169.41±30.22	<0.05
LDL-C (mg/dl)	89.71±20.70	105.59±26.50	<0.001
AIP	0.212±0.21	0.314±0.24	<0.001
hs–CRP (mg/L)	1.29±0.59	2.14±1.36	<0.001

Data are median (min-max) unless indicated otherwise. Statistical comparisons by the Mann-Whitney U.
HOMA_IR: Homeostatic Model Assessment for Insulin Resistance; TG: triglyceride; LDL-C: low density lipoprotein cholesterol; AIP: atherogenic index of plasma; HDL-C: high-density lipoprotein cholesterol; hs–CRP: High-sensitivity C-reactive protein; SHBG: Sex hormone-binding globulin, DHEAS: Dehydroepiandrosterone sulfate

Central obesity was observed in 54.1% of PCOS patients, while this rate was 10.7% in control group (p<0.001), (Table 2). Systolic and diastolic blood pressures of PCOS group were significantly higher than control group. Metabolic syndrome was observed in 79.3% of PCOS patients, whereas this rate was 3.6% in control group (p<0.001), (Table 2).

Serum LH, DHEAS, total testosterone, free testosterone and androstenedione levels were significantly higher in PCOS group than control group, whereas estradiol and SHBG levels were significantly lower in PCOS group. After 10-12 hours of fasting, mean plasma fasting glucose and mean plasma insulin levels in PCOS group (81.54±8.46 mg/dl and 17.24±10.79 µIU/ml) and control group (78.60±8.36 mg/dl and 9.26±3.69 µIU/ml) were analyzed respectively. There were significant differences between plasma fasting glucose and plasma fasting insulin levels between two groups (p<0.05, p<0.001). HOMA-IR index were found significantly higher in PCOS group (p<0.001), (Table 1). While insulin resistance was seen 64.8% in PCOS patients, this rate was 14.3% in control group (Table 2).

Table 2. Body mass index, metabolic syndrome, insulin resistance and dyslipidaemia of the groups

Parameter	Control		PCOS		P value
	n	%	n	%	
BMI					
Normal weight	118	84.3	52	39.7	<0.001
Overweight	22	15.7	79	60.3	<0.001
Metabolic Syndrome					
-	135	96.4	27	20.7	<0.001
+	5	3.6	104	79.3	<0.001
Central Obesity					
-	125	89.3	60	45.8	<0.001
+	15	10.7	71	54.1	<0.001
Insulin Resistance					
-	120	85.7	46	35.2	<0.001
+	20	14.3	85	64.8	<0.001
Dyslipidemia					
-	121	86.4	47	35.8	<0.001
+	19	13.6	84	64.1	<0.001

Data are n (%). Statistical comparisons by Mann Whitney-U test was used to compare median values between groups. BMI: Body mass index

When two groups were compared about insulin resistance; the risk of insulin resistance was 10.85 times higher in PCOS group (odds ratio=10.85, p<0.001).

TG, LDL-C and total cholesterol levels were significantly higher in PCOS group (p<0.05, p<0.001, p<0.05, respectively). HDL-C levels were significantly lower in PCOS group (p<0.001), (Table 1). Dyslipidemia was observed 64.1% in PCOS group, while this rate was 13.6% in control group (Table 2). When both groups were evaluated about dyslipidemia, risk of dyslipidemia was 11.4 times higher in PCOS group (odds ratio=11.4, p<0.001).

AIP were calculated. In PCOS group, AIP was 0.314±0.24 while it was 0.212±0.21 in control group (p<0.001). Hs-CRP was 2.14±1.36 mg/L in PCOS group, whereas it was 1.29±.59 mg/L in control group (p<0.001).

When we evaluated the correlation between AIP and CRFs in PCOS group (Table 3), we found significantly positive correlation between systolic blood pressure (r=0.219, p<0.05), BMI (r=0.388, p<0.001), LDL-C (r=0.417, p<0.001), total cholesterol (r=0.291, p<0.05), TG (r=0.887, p<0.001), insulin (r=0.404, p<0.001), waist circumference (r=0.418, p<0.001) and HOMA-IR (r=0.377, p<0.001). We found significantly negative correlation between AIP and HDL-C (r= -0.609, p<0.001).

Table 3. Correlation between AIP and CRFs in PCOS group

Parameters	n	AIP r	P value
Age (year)	131	-0.006	0.948
BMI (kg/m²)	131	0.388	<0.001
Waist Circumference (cm)	131	0.418	<0.001
Systolic Blood Press (mm/Hg)	131	0.219	<0.05
Diastolic Blood Press (mm/Hg)	131	0.106	0.227
Insulin (µIU/ml)	131	0.404	<0.001
HOMA_IR	131	0.377	<0.001
FSH (mıu/ml)	131	0.200	<0.001
LH (mıu/ml)	131	-0.174	<0.001
Estradiol (pg/mL)	131	-0.107	<0.001
DHEAS (UG/dl)	131	-0.020	0.823
Total testosterone (ng/dl)	131	0.125	0.156
Free testosterone (ng/dl)	131	-0.009	0.921
Androstenedione (ng/mL)	131	0.050	0.569
SHBG (nmol/L)	131	-0.042	0.630
TG (mg/dl)	131	0.887	<0.001
HDL-C (mg/dl)	131	-0.609	<0.001
Total cholesterol (mg/dl)	131	0.291	<0.001
LDL-C (mg/dl)	131	0.417	<0.001
hs–CRP (mg/L)	131	0.372	<0.001

Data are n (%). Statistical comparisons by Spearman test.
BMI: Body mass index; HOMA_IR: Homeostatic Model Assessment for Insulin Resistance; TG: triglyceride; LDL-C: low density lipoprotein cholesterol; AIP: atherogenic index of plasma; HDL-C: high-density lipoprotein cholesterol; hs–CRP: High-sensitivity C-reactive protein; SHBG: Sex hormone-binding globulin, DHEAS: Dehydroepiandrosterone sulfate

In PCOS group, there was a significantly positive correlation between hs-CRP and AIP (r=0.372, p<0.001). In PCOS group, there was a significantly positive correlation between hs-CRP and TG (r=0.280, p<0.05). There was a significantly negative correlation between hs-CRP and HDL-C in PCOS group (r=0.242, p<0.05).

When we evaluated the correlation between AIP and CRFs in control group (Table 4), we found significantly positive correlation between BMI (r=0.334, p<0.001), LDL-C (r=0.324, p<0.001), waist circumference (r=0.301, p<0.001), total cholesterol (r=0.202, p<0.05) and TG (r=0.864, p<0.001). There was a significantly negative correlation between AIP and HDL-C (r= -0.593, p<0.001). There was no correlation between hs-CRP and CRFs in control group.

Table 4. Correlation between AIP and CRFs in control group

Parameters	n	AIP r	P value
Age (year)	140	0.158	0.063
BMI (kg/m²)	140	0.334	<0.001
Waist Circumference (cm)	140	0.301	<0.001
Systolic Blood Press (mm/Hg)	140	-0.014	0.865
Diastolic Blood Press (mm/Hg)	140	-0.078	0.359
Insulin (µIU/ml)	140	0.095	0.266
HOMA_IR	140	0.117	0.168
FSH (mıu/ml)	140	0.130	0.126
LH (mıu/ml)	140	-0.137	0.107
Estradiol (pg/mL)	140	-0.134	0.114
DHEAS (UG/dl)	140	0.182	<0.05
Total testosterone (ng/dl)	140	0.067	0.429
Free testosterone (ng/dl)	140	0.019	0.820
Androstenedione (ng/mL)	140	0.189	<0.05
SHBG (nmol/L)	140	0.019	0.820
TG (mg/dl)	140	0.864	<0.001
HDL-C (mg/dl)	140	-0.593	<0.001
Total cholesterol (mg/dl)	140	0.202	<0.05
LDL-C (mg/dl)	140	0.324	<0.001
hs–CRP (mg/L)	140	0.085	0.320

Data are n (%). Statistical comparisons by Spearman test.
BMI: Body mass index; HOMA_IR: Homeostatic Model Assessment for Insulin Resistance; TG: triglyceride; LDL-C: low density lipoprotein cholesterol; AIP: atherogenic index of plasma; HDL-C: high-density lipoprotein cholesterol; hs–CRP: High-sensitivity C-reactive protein; SHBG: Sex hormone-binding globulin, DHEAS: Dehydroepiandrosterone sulfate

DISCUSSION

CVD is the cause of one third of deaths worldwide and CRFs lead to increased mortality from CVD (17). Overweight women with PCOS have evidences of subclinical CVD due to insulin resistance (19). Insulin resistance and compensatory hyperinsulinemia leads to cardiometabolic abnormalities (20). Epidemiological studies have shown the highest rate of CVD in metabolic

syndrome associated with insulin resistance (21). There is a strong positive correlation between insulin resistance and hyperandrogenemia in PCOS patients. It has been shown that hyperinsulinemia has a stimulating effect on androgen production in women with PCOS and cardiovascular functions are negatively affected (22). In our study, insulin resistance and hyperandrogenemia that may increase cardiovascular risk in PCOS patients were higher than healthy participants. Being overweight and the percentage of having metabolic syndrome was higher in PCOS patients.

Talbott et al. compared PCOS patients with control group in the early premenopausal period and they showed that PCOS patients had significantly high CRFs such as increased LDL-C, TG levels, total cholesterol, BMI, systolic blood pressure, insulin, glucose and decreased HDL-C levels (23). In our study, we also determined CRFs increased in PCOS group. Levels of total cholesterol, LDL-C, TG, fasting insulin, fasting glucose, BMI, and systolic blood pressure were higher and HDL-C levels were lower in PCOS patients.

Dyslipidemia is seen more than 70% of PCOS women (24). Although LDL-C is an important risk factor, other lipid panels can also raise coronary heart disease (7). Low HDL-C levels are an independent cardiovascular risk factor. Scientific evidence shows that low HDL-C levels and high LDL-C levels increase the frequency of CVD. LDL-C/HDL-C ratio is usually predicts coronary artery diseases (25). Naito et al. reported that the use of some combined lipoprotein ratios (LDL-C/TG, TG/HDL-C, LDL-C/HDL-C), rather than measuring lipid level alone, were statistically stronger with the prevalence of CVD (26). Atherogenic dyslipidemia, defined as hypertriglyceridemia and a high ratio of LDL-C/HDL-C, is associated with high cardiovascular disease (27). Previous studies have attempted to provide a better ratio of atherogenic dyslipidemia to assess cardiovascular disease risk and treatment response (28). AIP is used to estimate CRFs and refer to true relationship between atherogenic lipids to protective lipids (25). Gaziano et al. showed that AIP was associated with myocardial infarction and coronary disease (29). Tan et al. stated that AIP is a practical and usable parameter for evaluating changes in lipoprotein profile during pioglitazone use (30). Niroumand et al. reported that AIP could be a predictive value for atherosclerosis (28). Khazaál et al. stated that AIP could be an alternative screening tool even in cases where all atherogenic lipid values are normal. They also stated that AIP is a non-invasive way of predicting the presence and degree of coronary atherosclerosis (25).

In our study, in PCOS group, serum AIP was higher. Also, significant positive correlations were observed between AIP and CRFs (such as total cholesterol, LDL-C, TG, waist circumference, BMI, systolic blood pressure, insulin, and HOMA-IR). Negative correlation was observed between AIP and HDL-C. AIP can be used for early impressions of CVD for PCOS patients because AIP is an easy, non-invasive and useful index. AIP can be used as a method for regular CVD monitoring, especially in PCOS patients with other CRFs.

In previous studies, it has been reported that CRP has negative effects on the prognosis of CVD and can be used in women at risk of cardiovascular disease (31,32). It has demonstrated that CRP is a strong independent predictor of future CVD and/or stroke (33). The JUPITER (Justification for the Use of Statins in Primary Prevention: An Intervention Trial Evaluating Rosuvastatin) study suggested that lowering CRP levels could reduce future cardiovascular events in healthy patients (34). But the assay for CRP is difficult to perform accurately, and the currently preferred test is high-sensitivity hs-CRP (35).

Coner et al.'s study on the role of chronic inflammation in the development of coronary artery disease, they included patients with acute coronary syndrome (ACS) without ST segment elevation. They measured hs-CRP levels that used to evaluate subclinical vascular inflammation in these patients. They also measured the soluble form of Lectin-like OxLDL receptor-1 (sLOX-1), which indicates the prognostic prediction of ACS patients with possible underlying atherosclerotic plaque rupture. As a result of this study, in patients with ACS without ST segment elevation found that both hs-CRP and SLOX-1 levels increased gradually with higher modified Gensini scores. However, they stated that hs-CRP measurements have a scattered distribution in clinical studies and this is an important limitation in hs-CRP evaluation (36). For this reason, we did not include patients with systemic inflammation, rheumatoid diseases or autoimmune systemic disorders in our study so that hs-CRP values are not affected.

Studies have reported that PCOS is associated with increased hs-CRP levels (37,38). González et al. stated that PCOS was a pro-inflammatory status. According to the data obtained in this study, it was stated that chronic low-grade inflammation was the basis of ovarian dysfunction and metabolic disorders in PCOS (39).

It has been thought that one of the underlying factors of atherosclerosis in PCOS patients may be a chronic subclinical inflammatory process. Although new inflammatory marker tests are available, the hs-CRP test appears to be a better inflammatory marker. hs-CRP maintains an independent association with cardiovascular events (40). In our study, significantly negative correlation was observed between hs-CRP and HDL-C. There was no correlation between hs-CRP and CRFs except TG. The reason for that may be hs-CRP may retain an independent association with CVD. Also, in our study there was a positive correlation between AIP and hs-CRP in PCOS group. The reason for the positive correlation between AIP and hs-CRP is that TG and HDL-C are used in the calculation of AIP. If the inflammatory process is important for the

initiation and progression of the atherosclerotic process; hs-CRP, an indicator of low level of chronic inflammation, may indicate early inflammation, atherosclerosis, and CVD risk in PCOS patients.

LIMITATIONS

The main limitations of this study are its small sample size and being a single center study. In addition, patients enrolled in the study should be followed up for a long time. Long-term complications can complicate our interpretations, and future research is needed.

CONCLUSION

hs-CRP level, which is the circulating marker of chronic inflammatory condition, and AIP used to predict acute coronary events were increased in PCOS patients. Positive correlation was determined between AIP and CRFs. AIP which is a non-invasive index can be used for early impressions of CVD for PCOS patients. If the inflammatory process is important for the initiation and progression of the atherosclerotic process, hs-CRP, an indicator of low-level chronic inflammation, may help predict the risk of coronary heart disease in PCOS patients. AIP and hs-CRP may be beneficial markers for early monitoring of CVD in PCOS patients. PCOS patients should be informed in terms of potential CRFs.

Competing interests: The authors declare that they have no competing interest.

Financial Disclosure: There are no financial supports.

Ethical approval: The study was approved by Afyonkarahisar Health Sciences University Clinical Research Ethics Committee (Date: 08/02/2019, Decision No: 2019/258). The study was conducted in accordance with the 1975 Helsinki Declaration guidelines and written informed consent was obtained from all patients.

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