Correlation between neopterin and some acute phase proteins in women with PCOS.

Abstract

Background: Polycystic ovary syndrome (PCOS) is a complex endocrine and metabolic disorder, typically characterized by chronic mild inflammation, hyperandrogenism, insulin resistance, obesity, infertility, and anovulation. Emerging evidence indicates a potential mechanistic role of immune activation and acute phase proteins in the pathogenesis and progression of PCOS.

Objectives: This study was designed to assess serum levels of neopterin with other selected acute phase proteins, namely, C-reactive protein (CRP), serum amyloid A (SAA), and fibrinogen in women with PCOS and their relationship with different PCOS phenotypes and inflammation activity.

Methods: This case–control cross-sectional study included 58 women with a clinical diagnosis of PCOS that attended Al-Najaf Teaching Hospital, in Al-Najaf City, Iraq during the period from July 2025 to February 2026. It included 62 controls with normal health. Diagnosis and classification The diagnosis of PCOS was made according to the Rotterdam criteria. Patients were divided into phenotype A, C and D groups, using PCOS phenotypic criteria. Serum concentrations of both neopterin and SAA were measured by ELISA, while CRP and fibrinogen were determined with standard immunoturbidimetric and colorimetric methods.

Results: Between the two groups, serum neopterin, CRP and SAA levels were significantly increased in PCOS women compared to healthy controls ($p < 0.01$).In contrast, fibrinogen levels showed no statistically significant difference between the two groups ($p = 0.32$). Among PCOS phenotypes, phenotype A demonstrated the highest levels of neopterin and acute phase proteins, followed

by phenotype C and phenotype D, with statistically significant differences observed for neopterin, CRP, and SAA ($p < 0.05$).

Conclusion: Serum neopterin and selected acute phase proteins were significantly increased in women with PCOS, supporting the presence of chronic mild inflammation and immune activation in PCOS pathophysiology. The higher inflammatory biomarker levels observed in phenotype A suggest greater inflammatory and metabolic disturbances in this phenotype.

Keywords:PCOS, Neopterin, CPR, SAA, Fibrinogen

Introduction

Polycystic ovary syndrome (PCOS) is a significant global public health problem that is considered one of the most common hormonal disorders affecting women, often becoming apparent during the reproductive years. An estimated 10–13% of women globally are thought to have PCOS, but up to 70% of affected women are undiagnosed. PCOS is a complex disease that mainly manifests as hyperandrogenism, and ovulatory dysfunction, which also causes menstrual irregularities, infertility, insulin resistance (IR), obesity and polycystic ovarian morphology (Armstrong et al., 2025). Besides reproductive disorders, PCOS is now recognized as a systemic inflammatory and metabolic disorder linked to cardiovascular complications, dyslipidemia, type 2 diabetes mellitus, and endothelial dysfunction. In the recent past, a considerable amount of evidence has raised the possibility that chronic low-grade inflammation and immune dysregulation might be central in the pathogenesis and progression of PCOS (Bajuk Studen & Pfeifer, 2018; Hosseini et al., 2026).

Neopterin is an inflammatory biomarker that receives increasing attention as a sensitive marker of cellular immune activation. Neopterin, a pteridine derivative that is most commonly increased due to activation of macrophages and monocytes after stimulation with interferon-gamma (IFN-γ) released from activated T-helper lymphocytes. Neopterin levels are elevated in cellular

immune activation, correlated with inflammatory, autoimmune, infectious and metabolic diseases (Heneberk et al., 2023). Besides that, as an immune marker neopterin is also associated with oxidative stress since reactive oxygen species are produced by activated macrophages along with the production of neopterin. Thus, increased levels of neopterin might reflect both immune activation and oxidative tissue damage (Murr et al., 2002; Rudnicka et al., 2021).

Chronic mild inflammation has emerged as a fundamental pathophysiological mechanism for ovarian dysfunction and metabolic abnormalities in women with PCOS. Dysfunction of adipose tissue, insulin resistance, hyperandrogenism and modification of cytokine production led to a pathway's activation inflammatory in PCOS (Dong & Rees, 2023). In a number of studies, increased circulating levels of inflammatory cytokines such as interleukin-6 (IL-6), tumor necrosis factor-alpha (TNF-α) and C-reactive protein (CRP) have been shown in women with PCOS compared to healthy individuals. Such inflammatory mediators may disturb insulin signaling, modify ovarian steroidogenesis and cause reproductive dysfunction (Bansal et al., 2025).

The acute phase response (APR) is a key feature of the innate immune system, which consists of an immediate and coordinated systemic response to infection, tissue damage, neoplasia and other types of inflammation. These proteins undergo a significant increase or decrease in their concentration within the serum, following stimulation of inflammation which is mainly induced by cytokines (Chabuk et al., 2025). Acute phase proteins like C-reactive protein (CRP), serum amyloid A (SAA) and fibrinogen are among the most clinically important. CRP is one of the most sensitive inflammatory biomarkers and has been evaluated in numerous studies in women with PCOS. High sensitive CRP (HS-CRP): HS-CRP is a marker of chronic low-grade inflammation, and increased levels have been found in patients with PCOS; it was also associated with obesity, insulin resistance, endothelium dysfunction and higher rate of cardiovascular risk. What is already known on this topic A systematic review

and meta-analysis has shown that women with PCOS have circulating CRP levels much higher than those of non-obese controls (independent of obesity) supporting the notion that inflammation is an intrinsic part of the pathophysiology of PCOS (Aboeldalyl et al., 2021).

Serum amyloid A (SAA) is another prominent acute phase reactant that is synthesized in response to inflammation. In SAA for immune regulation, lipid metabolism and chemotactic recruitment of inflammatory cells. SAA concentrations levels have been shown to correlate with insulin resistance, obesity, and cardiovascular disease from common metabolic disturbances that occur in PCOS (den Hartigh et al., 2023). In women with SLE, the high levels of SAA may be associated with vascular dysfunction and persistent inflammation in the endothelium. In addition, fibrinogen an acute phase protein related to coagulation has been recently stated to be elevated in inflammatory and metabolic disorders including PCOS. Since higher fibrinogen levels increases hypercoagulability, endothelial damage and cardiovascular disturbances among PCOS women showing association of inflammation with thrombotic risk (Ali et al., 2016; Wang et al., 2020).

Although there is growing evidence about the role of inflammatory pathways in PCOS, there is little data on neopterin and acute phase proteins in women with this condition. Neopterin is an indicator of cellular immune activation, while CRP, SAA and fibrinogen are markers reflecting systemic inflammatory responses; therefore, examining the relationship between these factors may help elucidate the inflammation mechanisms that characterize PCOS. Furthermore, the association between neopterin and acute-phase proteins may also help develop new biomarkers for early diagnosis, disease tracking, and prediction of metabolic- or cardiovascular-related processes (Agacayak et al., 2015).

The aim of the present study was to analyze serum neopterin and selected acute phase proteins in relation to C-reactive protein (CRP), serum amyloid A (SAA) and fibrinogen in women with polycystic ovary syndrome (PCOS). Assessing

these biomarkers may deepen our understanding of the inflammatory and immunological changes that play a role in PCOS pathogenesis, and may also lead to clinically useful parameters for managing this condition.

Methods

Patients and data collection

A case–control cross-sectional study was carried out at Al-Najaf Teaching Hospital in Al-Najaf City, Iraq for the period from July 2025 to February 2026. A total of 120 subjects were enrolled in the study, including 58 women clinically diagnosed with PCOS and 62 apparently healthy/no previous related studies control subjects.Patients were recruited from the Gynecology and obstetrics outpatient clinic of Al-Najaf Teaching Hospital. PCOS patients were classified according to the Rotterdam phenotypic criteria into phenotype A, phenotype C, and phenotype D. Phenotype A included patients presenting with hyperandrogenism, ovulatory dysfunction, and polycystic ovarian morphology. Phenotype C was characterized by hyperandrogenism and polycystic ovaries with preserved ovulation, whereas phenotype D included patients with ovulatory dysfunction and polycystic ovarian morphology without evidence of hyperandrogenism. Phenotype B was excluded from the present study.The control group comprised apparently healthy age-matched women who had regular menstrual cycles and no clinical or laboratory evidence of endocrine, inflammatory, autoimmune or metabolic disorders.

Inclusion Criteria

Participants included in the study were qualified based on the following factors:Women aged between 18–45 years. Clinically diagnosed PCOS based on Rotterdam criteria. No acute bacterial or viral infection in the last 4 weeks. Absence of hormonal or anti-inflammatory therapy during the 3 months prior to recruitment. Written informed consent prior to participation.

Exclusion Criteria

Chronic diseases like diabetes mellitus, hypertension or chronic kidney disease. Cardiovascular or hepatic diseases. Malignancy or history of cancer. Acute infection or sepsis. Smoking or alcohol consumption. Corticosteroid, immunosuppressive agent, or antioxidant supplement use in the last 3 months.

Clinical Data Collection

Demographic and clinical data were obtained via standardized questionnaires and medical records. Information was collected on age, BMI, menstrual history, length of symptoms (previous menarche), family history of PCOS and treatment history. Clinical examinations were conducted by specialist gynecologists when the samples were obtained. Phenotype B was excluded from the present study.

Blood Collection and Sample Preparation

Each subject underwent an overnight fasting, blood was then aseptically collected from a peripheral vein using a sterile disposable syringe (about 5 mL). Approximately 20–30 min at room temperature blood samples were placed in sterile plain tubes to obtain clots. Serum was separated by centrifugation of the samples at 3000 pm for 10 minutes.Freshly isolated serum samples were divided into sterile Eppendorf tubes and stored at −20°C until any biochemical examination. At the same time, multiple freeze-thaw cycles were not conducted to maintain biomarker stability and assay specificity.

Measurement of Serum Biomarkers

Neopterin

Serum neopterin concentrations were measured using a commercially available enzyme-linked immunosorbent assay (ELISA) kit, carried out according to the manufacturer's instructions. Absorbance at 450 nm on a microplate reader was later used to calculate concentrations based on standard calibration curves.

C-Reactive Protein (CRP)

An immunoturbidimetric assay kit (HumaCount – Germany)designed based on the formation and clearing of antigen–antibody complex was used to measure serum CRP levels. The measurements procedure was performed according to the instructions of the manufacturer.

Serum Amyloid A (SAA)

Serum amyloid A concentrations were measuredby ELISA kit (HumaCount – Germany). The assay was conductedaccording to the manufacturer's protocol, and the optical density was measured at 450 nm.

Fibrinogen

The serum fibrinogen was measured by a standard coagulation-based colorimetric assay method(HumaCount – Germany). Concentrations were measured spectrophotometrically in accordance with kit instructions and expressed in mg/dL.

Ethical Considerations

The study protocol was approved by the Research Ethics Committee of Al-Najaf Teaching Hospital, Al-Najaf, Iraq (2025). All subjects provided written informed consent prior to enrollment. All procedures were conducted in accordance with the ethical standards of the Declaration of Helsinki as it relates to research involving human subjects.

Statistical Analysis

Statistical analysis was performed using IBM SPSS Statistics version 26. Continuous variables were expressed as mean ± standard deviation (SD) and categorical variables were presented as frequencies and percentages. Biomarker levels were compared between PCOS patients and healthy controls using independent sample t-test. To examine the correlation between neopterin and CRP, SAA, and fibrinogen, Pearson correlation term was used. For categorical variables, Chi-square test was performed. Statistical significance was defined as a p-value less than 0.05.

The Results

Table 1 shows the distribution of age groups and residence among women with PCOS and healthy controls. The results showed that there is no statistical significant difference between the two groups regarding age distribution (P = 0.643), so that both groups were age-matched. The majority of women in both groups were within the age range of 25–31 years.Regarding residence, most participants in both the PCOS and control groups were from urban areas (62.1% and 69.4% respectively).

Table 1. Assessment of ageand residencein bothPCOS Patients and control

Items		PCOS Patients (N= 58)		Control (N= 62)		(P value)
		Freq.	%	Freq.	%	
Age	18-24	17	29.3	19	30.6	0.643
	25-31	21	36.2	24	38.7	
	32-38	13	22.4	11	17.7	
	39-45	7	12.1	8	12.9	
Residence	Rural	22	37.9	19	30.6	0.232
	Urban	36	62.1	43	69.4	

The distribution of women according to type of PCOS demonstrates that phenotype C was the predominant clinical presentation, accounting for 55.8% of the studied cases, whereas phenotype Drepresented 25.5%, and phenotype Aconstituted only 18.7% (figure 1)

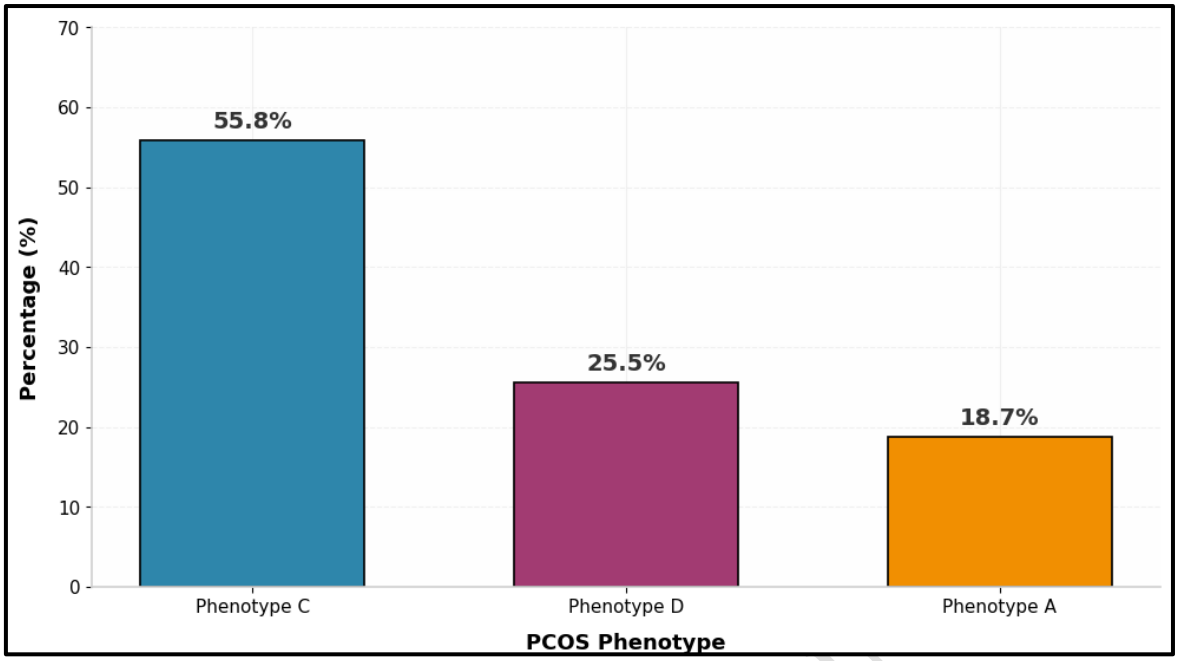

Figure 1. Distribution of PCOSwomen according to the type of PCOS

Table 2 Comparison of serum neopterin and selected acute phase proteins in PCOS women and control subjects. Neopterin, CRP and SAA demonstrated statistically significant differences when comparing PCOS patients with controls; while the levels of fibrinogen showed no statistically significant difference between these groups.

Table 2. Comparison of neopterin and acute phase proteinsbetween PCOSwomen and healthy control

Biomarkers	PCOS Patients (N= 58)		Control (N= 62)		(P value)
	Mean	SD	Mean	SD	
Neopterin (nmol/L)	13.74	3.16	8.92	2.21	< 0.005*
CRP (mg/L)	9.48	2.74	4.13	1.65	< 0.003*
SAA (nmol/mL)	16.85	4.22	9.37	2.88	<0.004*
Fibrinogen (mg/dL)	328.44	52.61	314.27	48.35	0.32

*** High Significant at P value <0.01**

Table 3 presents the comparison of serum neopterin and selected acute phase proteins among PCOS patients according to PCOS phenotypes. Statistically

significant differences were observed among PCOS phenotypes regarding neopterin, CRP, and SAA levels, whereas fibrinogen levels did not show a statistically significant difference between the studied phenotypes.

Table 3. Comparison of neopterin and acute phase proteinsamongPCOSpatientsclassified according to type of PCOS

Biomarkers	Phenotype C (N= 32)		Phenotype D (N= 15)		Phenotype A (N= 11)		(P value)
	Mean	SD	Mean	SD	Mean	SD	
Neopterin (nmol/L)	12.41	2.68	10.95	2.34	16.82	3.27	< 0.012*
CRP (mg/L)	8.16	2.11	6.94	1.88	12.38	2.96	< 0.013*
SAA (nmol/mL)	14.74	3.65	12.62	2.91	19.85	4.11	<0.014*
Fibrinogen (mg/dL)	321.56	44.38	314.82	40.17	337.91	51.64	< 0.32

*** Significant at P value <0.05**

Pearson correlation analysis of serum neopterin levels and acute phase proteinsbiomarkers among PCOS patients are shown in Table 4. Consequently, those results showed highly significant positive correlation between neopterin, and CRP levels (r = 0.442, P = 0.004). Moreover, serum neopterin displayed a moderate positive correlation with SAA levels (r = 0.332, P = 0.002). On the other hand, the association between neopterin and fibrinogen was weak and statistically non-significant (r = 0.078, P = 0.423).

Table 4.Pearson correlation coefficient between neopterin and acute phase proteins

Markers	Neopterin	
	r	P value
CRP (mg/L)	0.442	0.004*
SAA (nmol/mL)	0.332	0.006*
Fibrinogen (mg/dL)	0.078	0.423

*** High Significant at P value <0.01**

Discussion

The present study investigated the association between serum neopterin and selected acute phase proteins, including C-reactive protein (CRP), serum amyloid A (SAA), and fibrinogen, in women with polycystic ovary syndrome (PCOS). The findings demonstrated significantly elevated levels of neopterin, CRP, and SAA in PCOS patients compared with healthy controls, while fibrinogen levels showed no statistically significant difference. Furthermore, significant variations in neopterin and acute phase proteins were observed among different PCOS phenotypes, with phenotype A showing the highest biomarker levels. Overall, these results strengthen the accumulating evidence linking chronic low-grade inflammation and immune activation as critical components of the pathophysiology of PCOS.

No significant differences regarding age and residence distribution were observed when comparing the PCOS patient groups with healthy controls. Such comparability reduces the contribution of demographic confounding variables to the inflammation markers. For both groups, the majority of women were within the reproductive age interval (age 25–31 years), which is similar to that period most frequently affected by PCOS (Inoue et al., 2021).

The current study specifically highlights the markedly raised levels of serum neopterin in women with PCOS. Neopterin has been regarded as a sensitive biomarker of cellular immune activation, being released from activated macrophages stimulated by interferon-gamma secreted in turn by activated T lymphocytes. Increased neopterin levels thus suggest sustained stimulation of immune system and inflammation pathways. Low-grade chronic inflammation has emerged as one of the most important contributors to the pathophysiology of PCOS, especially in thinking about these components together as insulin-resistant, obesity and hyperandrogenism (Aboeldalyl et al., 2021)

The high neopterin levels seen in this study may indicate the activation of monocytes and macrophages in patients with PCOS. The systemic inflammation

and immune activation even in young adulthood might be promoted by adipose tissue dysfunction and excess visceral fat deposition that can stimulate the release of inflammatory cytokines such as interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF-α), which is similar with common features of patients with polycystic ovarian syndrome(PCOS) (Deng et al., 2024). Yilmaz et al. (2012) reported similar observations where increased levels of neopterin were reported in women with PCOS, and this increase was proposed as critical element involved in metabolic derangement associated to the diseas.

In the current study, an increase in plasma CRP was found in women with PCOS compared to healthy controls. CRP is synthesized in the liver as a response to inflammatory cytokines (especially IL 6). Increased CRP concentrations are interpreted as markers of persistent low grade systemic inflammation and have been associated with an elevated cardiovascular risk, as well as the development of insulin resistance. The increase in CRP regarding progressive PCOS patients showed is similar with previous studies which indicate that raised levels of CRP among patients. Systematic Review and Meta-analysis by Aboeldalyl et al. (2021) has additionally observed elevated CRP levels in females having PCOS independently of obesity which points to the inflammation is intrinsically related to the pathogenesis of PCOS and is not due merely secondary to adiposity.

Also, much higher levels of serum amyloid A (SAA) were observed in the patients with PCOS than controls. Streptococcal Ag-Ab complexesSAA is an immune regulation acute phase reactant, which plays a role in lipid transportation and inflammatory cell recruitment. Increased levels of SAA in PCOS probably represents ongoing inflammatory stimuli and endothelial dysfunction. High levels of SAA have been associated with insulin resistance and the development of the metabolic syndrome, processes that often accompany PCOS. The marked elevation of SAA shown in this work reinforces the concept that inflammatory and metabolic derangements exist together within

PCOS and may be responsible for the long-term cardiovascular morbidities (Zhu et al., 2022).

On the other hand, serum fibrinogen levels significantly did not differ between PCOS patients and healthy controls. Despite being an important acute phase protein involved in both coagulation and inflammation, this study did not find significance for fibrinogen; however, low sample size, variations in severity of disease, body mass index (BMI) and other lifestyle factors may explain these results. Previous studies have indicated that women with PCOS were more likely to have high plasma fibrinogen especially in those who are obese or with severe metabolic disturbances but other researches do not support such substantial differences (Escobar-Morreale et al., 2011). Accordingly, increase of fibrinogen in PCOS possibly related to the underlying cardiovascular or metabolic risk factors.

One of the most important findings in the present study is pronounced differences in neopterin, CRP and SAA levels between different PCOS phenotypes. Compared with phenotypes C and D, the levels of inflammatory biomarkers are higher in phenotype A as well (Cohen O et al., 2017). Increased inflammation activity in a phenotype A might reflect an organopathy triggered by metabolic disturbances, hormone imbalance and dysregulation of the immunity. To identify this gradient in the data, we included RHI technology and separated populations into classical or non-classical PCOS phenotypes (as per ESHRE/ASRM criteria) when possible — these findings areconsistent with previously reported data that higher degrees of systemic inflammation are associated with classic phenotypes characterized by hyperandrogenism and severe reproductive dysfunction (Rudnicka et al., 2021).

This finding reinforces the concept of a close interaction between immune activation and systemic inflammation in PCOS. Inflammatory cytokines released from activated macrophages and other immune cells incite hepatic acute phase protein synthesis (e.g., C-reactive protein [CRP], serum amyloid A

[SAA]) while also enhancing neopterin production. This systemic inflammatory response might provide one possible mechanism tying insulin resistance, endothelial dysfunction, ovarian abnormalities and cardiovascular risk in the PCOS patients (Dhital et al., 2026).

The results from the current investigation highlight the significance of inflammatory biomarkers in elucidating PCOS pathophysiology. High levels of neopterin, CRP and SAA may be used as useful markers to assess inflammatory burden and identify women at higher risk for metabolic and cardiovascular complications. This study has some important strengths in spite of some limitations that need to be recognized. The small sample size and single-center design may limit the application of the findings. Moreover, hormonal and metabolic parameters including insulin resistance indices, androgen levels, and lipid profiles were not thoroughly assessed. Females with Polycystic Ovarian Syndrome (PCOS) have an increase in inflammatory cytokines and acute phase response.Cytokine levels are not significantly associated with PCOS. What we found was that increased immune activation level markedly correlates the severity of metabolic features of PCOS and may play a role in increasing the risk for long term cardiovascular consequences in females with PCOS). Better studies implicating much bigger study populations alongside other biomarkers may needed to do better clarifications to understand the relationship between complex nature of immune activation accessory kinases axis site along possible acute phase responses on different best phenotypes relative with women from idol if PCOS.

Conclusion

This study demonstrated enhanced neopterin levels, as well as acute-phase proteins markers (C-reactive protein, serum amyloid A, in patients with polycystic ovary syndrome, reflecting their role in the inflammatory processes and pathophysiology of PCOS. A correlation analysis was performed between

serum levels of neopterin and each of CPR and SAA. Fibrinogen played a weak role in the curating of PCOS.

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