ISSN(O): 3107-7889

Jana Nexus: Journal of Health and Medicine

Publisher's Name: Jana Publication and Research LLP

https://www.jananexushm.com

REVIEWER'S REPORT

Manuscript No.: JNHM-106

Title: Correlation between neopterin and some acute phase proteins in women with PCOS,

Recommendation:
Accept after minor revision……

Rating	Excel.	Good	Fair	Poor
Originality			✔	
Techn. Quality			✔	
Clarity		✔		
Significance	✔			

Reviewer's ID: JPR-Bilqees Hamza

Detailed Reviewer's Report

The manuscript under review investigates an exceptionally critical, complex, and evolving frontier in reproductive endocrinology: the role of chronic low-grade inflammation and cellular immune activation in the pathogenesis and phenotypic expression of Polycystic Ovary Syndrome (PCOS). The authors properly frame the inquiry by moving past historical, narrow definitions of PCOS as a simple ovulatory or cosmetic disorder. Instead, they position it as a systemic metabolic-endocrine syndrome characterized by a complex interplay of hyperandrogenism, insulin resistance, and immune system dysregulation. The clinical significance of this study rests on its investigation of serum neopterin—a biochemical marker synthesized by human macrophages upon stimulation by interferon-gamma—alongside traditional acute-phase proteins, specifically C-reactive protein (CRP), serum amyloid A (SAA), and fibrinogen.

By evaluating these specific inflammatory biomarkers within a clinical cohort in Al-Najaf City, Iraq, the paper addresses a vital question in modern metabolic medicine: can markers of macrophage activation serve as distinct diagnostic or prognostic indicators for cardiovascular and metabolic risks across different PCOS phenotypes? The scope of the paper successfully bridges basic laboratory biochemistry with clinical phenotype tracking, providing a valuable comparative analysis that helps clarify the inflammatory foundations of the disease. This makes it highly relevant to contemporary endocrinologists and clinical investigators looking to identify low-cost, high-yield serum biomarkers for metabolic risk stratification.

ISSN(O): 3107-7889
Jana Nexus: Journal of Health and Medicine
Publisher's Name: Jana Publication and Research LLP
https://www.jananexushm.com

REVIEWER'S REPORT

Methodologically, the study utilizes a case-control, cross-sectional design, evaluating a total sample size of 120 individuals, which includes 58 women with a confirmed clinical diagnosis of PCOS and 62 age-matched, healthy control subjects. The clinical setting is well-defined, with recruitment taking place at the Al-Najaf Teaching Hospital from July 2025 to February 2026. A notable methodological strength of the study is its adherence to the internationally recognized Rotterdam criteria for the diagnosis of PCOS, requiring the presence of at least two out of three classic features: oligo- or anovulation, clinical or biochemical signs of hyperandrogenism, and polycystic ovarian morphology via pelvic ultrasonography. Furthermore, the authors take an analytical step forward by sub-classifying the patient cohort into distinct phenotypic subgroups, specifically focusing on Phenotypes A, C, and D, which allows for a more granular investigation of inflammatory variation.

The laboratory methodologies described are standard and robust: serum concentrations of neopterin and SAA were quantified using Enzyme-Linked Immunosorbent Assays (ELISA), while CRP and fibrinogen levels were determined via standard immunoturbidimetric and colorimetric laboratory assays. This multi-marker approach provides a balanced view of both corporate hepatic acute-phase responses (CRP, SAA, fibrinogen) and upstream cellular immune activation (neopterin). However, while the physical execution of the laboratory tests is sound, the presentation of the statistical analysis and the handling of confounding baseline clinical characteristics require a substantial upgrade to meet the rigorous publication standards of a top-tier international endocrinology journal.

The central thesis of the manuscript posits that serum neopterin levels are significantly elevated in women with PCOS compared to healthy controls, and that this elevation correlates positively with classical acute-phase proteins, reflecting a state of chronic, macrophage-mediated immune activation. The authors construct this argument by suggesting that neopterin can serve as an early, highly sensitive mirror of low-grade tissue inflammation, potentially outperforming or complementing traditional markers like CRP, which can fluctuate due to non-specific systemic triggers.

Operating within the established biochemical mechanisms of adipose tissue dysfunction, the paper links these elevated inflammatory markers to insulin resistance and hyperandrogenism. The author implies that hypertrophied visceral adipocytes in PCOS patients recruit and activate macrophages, creating a chronic inflammatory loop where elevated interferon-gamma drives neopterin synthesis while simultaneously altering theca and granulosa cell function in the ovaries. The manuscript effectively concludes that tracking the correlation between neopterin and downstream acute-phase proteins provides a clearer window into the inflammatory severity of the patient's specific phenotype, helping identify individuals at a higher risk for long-term metabolic and cardiovascular complications.

ISSN(O): 3107-7889
Jana Nexus: Journal of Health and Medicine
Publisher's Name: Jana Publication and Research LLP
https://www.jananexushm.com

REVIEWER'S REPORT

Recommendations for Manuscript Improvement

Controlling and Disaggregating the Confounding Effects of Body Mass Index

The primary and most critical methodological recommendation to elevate the manuscript's validity centers on the statistical management of Body Mass Index (BMI). It is widely established in obesity and metabolic syndrome literature that adipose tissue expansion independently drives the hepatic synthesis of CRP, SAA, and fibrinogen, while also increasing systemic macrophage infiltration. The current draft fails to sufficiently separate whether the observed elevations in neopterin and acute-phase proteins are a direct feature of PCOS pathology or simply a reflection of a higher prevalence of obesity within the patient cohort. To resolve this ambiguity, the authors must perform a rigorous multi-variable regression analysis or an Analysis of Covariance (ANCOVA), utilizing BMI as a continuous confounding covariate. Disaggregating the data into lean versus obese PCOS subgroups and comparing them to lean and obese controls will allow the authors to definitively demonstrate whether neopterin elevation persists independently of adiposity, which is vital for establishing the biomarker's unique clinical utility.

Expanding the Statistical Presentation and Power Analysis Documentation

The reporting of the quantitative data in the current text relies heavily on surface-level correlation coefficients, leaving the empirical presentation incomplete for a peer-reviewed laboratory medicine journal. The authors need to introduce comprehensive baseline data tables detailing the exact mean values, standard deviations, and ninety-five percent confidence intervals for all biochemical markers across the healthy control group and each individual PCOS phenotype group (A, C, and D). Furthermore, the methodology section must be updated to include a formal post-hoc statistical power analysis. Given that the sub-grouping of fifty-eight patients into three distinct phenotypes results in small cell sizes, documenting the statistical power is necessary to prove that the study was adequately powered to detect true, statistically significant variations between phenotypes, thereby shielding the manuscript from criticisms regarding type-two statistical errors.

Providing Physiological Justification for the Exclusion of Phenotype B

When detailing the sub-classification of the patient cohort according to the Rotterdam phenotypic criteria, the manuscript notes the inclusion of Phenotypes A, C, and D, but completely omits any mention or representation of Phenotype B (ovulatory hyperandrogenism and polycystic ovaries). In a comprehensive clinical trial evaluation, leaving out an entire diagnostic category without explanation compromises the integrity of the research design. The authors must insert a dedicated narrative clarification within the methods section explaining the total absence of Phenotype B individuals. They should clarify whether this was due to an explicit exclusion criterion in the study design, a zero-incidence rate during the

ISSN(O): 3107-7889
Jana Nexus: Journal of Health and Medicine
Publisher's Name: Jana Publication and Research LLP
https://www.jananexushm.com

specific hospital recruitment timeline, or an intentional focus on classic anovulatory phenotypes. Providing this context is essential for maintaining transparent, accurate clinical research reporting.

Deepening the Discussion on Adipocyte-Macrophage Crosstalk Mechanisms

While the discussion section correctly identifies chronic low-grade inflammation as an important factor in PCOS, the explanation of the underlying cellular mechanisms remains largely descriptive and superficial. The authors should expand this section into a sophisticated biochemical commentary exploring the exact cross-talk mechanisms that occur between dysfunctional adipocytes, macrophage activation, and ovarian tissue. The text should explicitly map out how visceral fat hypoxia triggers the release of chemoattractant factors, leading to the polarization of M1 macrophages which then synthesize neopterin and release inflammatory cytokines like tumor necrosis factor-alpha and interleukin-six. The authors should then discuss how these specific circulating cytokines damage insulin signaling pathways in skeletal muscle and stimulate excess androgen production within the ovarian theca cells, turning the manuscript from a basic correlation study into a deep, mechanism-driven piece of pathophysiological scholarship.

Standardizing and Completing the Bibliographic Metadata Records

A thorough audit of the concluding reference bibliography reveals numerous incomplete citations, missing metadata fields, and minor formatting errors across several entries, including recent 2021 through 2024 publications on chronic inflammation. Multiple references lack crucial publication details, such as missing specific volume designations, issue numbers, exact page numbers, or valid digital object identifiers (DOIs), while some author names feature inconsistent capitalization and punctuation. The authors must systematically review and correct the entire reference list to ensure that every entry conforms perfectly to a singular, standardized academic citation manual, such as the APA seventh edition or the Vancouver style worksheet. This standardization is mandatory for the manuscript to be indexed correctly in international biomedical and clinical science databases.

Cleaning Minor Typographical Slippages and Visual Layout Artifacts

Finally, the review copy contains minor mechanical formatting issues, uneven line spacing around major section boundaries, and occasional paragraph alignment shifts that affect its professional presentation. There are a few instances where punctuation marks are placed incorrectly next to ELISA and immunoturbidimetric acronyms, along with minor typing slips within the introductory abstract paragraphs. The authors must carefully proofread the entire document to eliminate these visual processing remnants. Ensuring that the manuscript possesses a flawless visual layout will provide a polished, highly professional appearance that matches the clinical importance of the biochemical data.

ISSN(O): 3107-7889
Jana Nexus: Journal of Health and Medicine
Publisher's Name: Jana Publication and Research LLP
https://www.jananexushm.com

REVIEWER'S REPORT

Editorial Recommendation

This manuscript is recommended for **publication with major revisions**. The authors have selected a highly valuable, original, and impactful topic by investigating the diagnostic utility of serum neopterin alongside traditional acute-phase proteins within a well-defined clinical cohort in Iraq. The use of the Rotterdam criteria for phenotyping is highly appropriate, the multi-marker approach is well-conceived, and the emphasis on cellular immune activation addresses an important missing link in current PCOS risk assessments.

However, to make the paper suitable, the authors must address the confounding influence of body mass index, provide a clear explanation for the missing phenotype cohort, and expand their statistical reporting beyond basic correlations. Once the text is updated to include multivariate regression matrices, a formal power analysis, a deeper discussion of macrophage polarization mechanics, and a completed and standardized reference bibliography, this manuscript will be a strong, highly analytical, and relevant addition to the scholarship on reproductive immunology.