ISSN: 1607-8322, e-ISSN: 2220-5799 Anaesthesia, Pain & Intensive Care
Vol 29(4); July 2025 DOI: 10.35975/apic.v29i4.2812

ORIGINAL RESEARCH OBSTETRIC ANESTHESIA

Integrative analysis of inflammatory biomarkers and clinical features in endometriosis: insights into pain severity and diagnostic utility

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ABSTRACT

Background & objective: Endometriosis is an estrogen-dependent inflammatory condition linked with chronic pelvic pain and infertility. It is usually associated with considerable morbidity, and offers diagnostic dilemmas. Biochemical analysis for inflammatory biomarkers can help the clinicians in early identification of this debilitation condition. This study aimed to explore the inflammatory profile in endometriosis by integrating clinical, demographic, and biomarker data.

Methodology: A case-control study was conducted involving 90 premenopausal women; 45 with laparoscopically confirmed endometriosis and 45 age-matched controls) between October 2023 and December 2024 at specialized clinics in Al-Sadr Teaching Hospital, Iraq. Clinical data—including smoking status, infertility, and pain severity (assessed via a 10-point Visual Analog Scale)—were collected. Fasting serum samples obtained during the early follicular phase were analyzed for IL-6, TNF-α, LIF, and CRP using ELISA and immunoturbidimetric assays. Multivariable regression evaluated associations with pain severity. ROC analysis assessed diagnostic performance.

Results: Women with endometriosis showed significantly elevated IL-6, TNF-α, CRP, and LIF levels. Inflammatory markers, more than BMI or age, were primary contributors to the pain severity. ROC analysis revealed moderate diagnostic accuracy for individual biomarkers.

Conclusion: Our integrative study highlights the central role of inflammation in endometriosis and suggests that multi-marker panels may enhance diagnostic and prognostic strategies.

Abbreviations: BMI: Body mass index, CRP: C-reactive protein, IL-6: interleukin-6, LIF: Leukemia inhibitory factor, TNF-α: tumor necrosis factor-alpha, VAS: Visual Analog Scale, VEGF: vascular endothelial growth factor

Keywords: Endometriosis; Inflammatory Biomarkers; Pain Severity; Cytokines; Diagnosis

Citation: Yaseen BR, Mohammed AJ, Salman SA, Alredha RDA. Integrative analysis of inflammatory biomarkers and clinical features in endometriosis: insights into pain severity and diagnostic utility. Anaesth. pain intensive care 2025;29(4):276-82. **DOI:** 10.35975/apic.v29i4.2812

Received: March 30, 2025; **Revised:** April 20, 2025; **Accepted:** April 20, 2025

1. INTRODUCTION

Endometriosis is a prevalent gynecological disorder affecting an estimated 10% of women of reproductive age, characterized by the ectopic presence of endometrial-like tissue outside the uterine cavity. This condition is often accompanied by chronic pelvic pain, dysmenorrhea, and infertility, all of which can severely impair quality of life.[1,2] Despite extensive research, the precise etiology of endometriosis remains elusive, with current evidence strongly implicating an interplay of hormonal, genetic, and immunological factors in its pathogenesis.[3] In particular, chronic inflammation has emerged as a key contributor, with dysregulated immune responses and an aberrant cytokine milieu fostering the establishment and progression of ectopic lesions.[4]

Recent advances have highlighted the role of inflammatory mediators in the development and symptomatology of endometriosis.[5,6] Pro-inflammatory cytokines such as interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF-α) have been found at elevated levels in the peritoneal fluid and serum of affected women, suggesting that these molecules not only contribute to local inflammatory processes but also mediate systemic effects.[7,8] IL-6 is known to orchestrate immune responses and promote angiogenesis through vascular endothelial growth factor (VEGF) pathways, thus facilitating lesion growth and sensitizing nociceptive pathways.[9] Similarly, TNF-α is instrumental in recruiting immune cells and amplifying inflammatory cascades, which may exacerbate tissue injury and chronic pain.[10] Additionally, C-reactive protein (CRP), a well-established marker of systemic inflammation, reflects the broader inflammatory state associated with endometriosis.[11] Leukemia inhibitory factor (LIF), a cytokine critical for endometrial receptivity, has also been implicated; its dysregulation in endometriosis could underlie both the impaired implantation observed in these patients and its association with pain through neuroimmune interactions.[12]

While prior studies have often focused on single biomarkers or limited clinical features, there remains a significant gap in the literature regarding an integrative evaluation of multiple inflammatory markers alongside clinical and demographic variables. Pain, a predominant and debilitating symptom of endometriosis, has been variably correlated with lesion burden and hormonal profiles, yet the precise contribution of inflammatory pathways to pain severity is not fully understood.[13] Our study addresses this gap by simultaneously assessing IL-6, TNF-α, CRP, and LIF in a well-characterized cohort of endometriosis patients. By correlating these markers with clinical parameters such as pain severity, infertility, and lifestyle factors like smoking, we aim to provide a comprehensive picture of the inflammatory milieu in endometriosis.

Furthermore, employing multivariable regression analysis allows us to delineate the independent contributions of these inflammatory mediators relative to traditional factors such as body mass index (BMI) and age. Our study uniquely integrates sensitivity and specificity analyses of these biomarkers, thereby offering novel insights into their potential diagnostic utility.

2. METHODOLOGY

2.1. Study Design and Participants

This case-control study was conducted between October 2023 and December 2024 at specialized clinics in Al-Sadr Teaching Hospital, Basrah, Iraq. The study enrolled 45 premenopausal women with laparoscopically and histologically confirmed endometriosis and 45 age-matched control subjects undergoing routine gynecological examinations. Participants were aged 18–45 years. Exclusion criteria included autoimmune diseases, recent anti-inflammatory therapy, and malignancies. Ethical approval was granted by the Institutional Review Board (Ministry of Health, Najaf Health Directorate, Approval Number: 1542), and all participants provided written informed consent before their inclusion in the study. The research protocol was designed and conducted in accordance with the ethical principles outlined in the Declaration of Helsinki.[14]

2.2. Clinical Evaluation / Data Collection

Detailed clinical data were collected using structured questionnaires, which captured demographic information, reproductive history (with emphasis on infertility), and lifestyle factors (e.g., smoking status). Body mass index (BMI) was calculated as weight (kg) divided by height (m^2).[15] Pain severity was assessed using a 10-point Visual Analog Scale (VAS), with 0 representing no pain and 10 indicating the worst imaginable pain.[16] Endometriosis staging was performed based on the revised American Society for Reproductive Medicine (rASRM) classification system.[17]

2.3. Blood Sample Collection / Processing

Fasting venous blood samples were drawn during the early follicular phase (days 2–5 of the menstrual cycle) using BD Vacutainer® serum separator tubes (Becton Dickinson, Cat. No. SST-II). After allowing clot formation at room temperature for 30 min, samples were

centrifuged at 3000 rpm for 10 min. The resulting serum was aliquoted and stored at –80°C until analysis.

Serum concentrations of the inflammatory biomarkers were measured as follows:

2.3.1. Interleukin-6 (IL-6)

Quantified using the Human IL-6 Quantikine HS ELISA Kit (R&D Systems, Catalog No. HS600B). This high-sensitivity assay has a detection limit of 0.5 pg/mL.

2.3.2. Tumor Necrosis Factor-Alpha (TNF-α)

Measured with the Human TNF-alpha Quantikine ELISA Kit (R&D Systems, Catalog No. DTA00C), which offers a detection limit of 1.0 pg/mL.

2.3.3. Leukemia Inhibitory Factor (LIF)

Assessed using the Human Leukemia Inhibitory Factor (LIF) Quantikine ELISA Kit (R&D Systems, Catalog No. DLF00) with a detection limit of 2.0 pg/mL.

For all ELISA assays, samples were run in duplicate. Calibration curves were constructed using the standards provided in each kit, and the intra-assay and inter-assay coefficients of variation were maintained below 10% and 15%, respectively.

2.3.4. Serum C-reactive protein (CRP)

CRP levels were determined using an immunoturbidimetric assay on the Beckman Coulter AU5800 Clinical Chemistry Analyzer. Quality control procedures were implemented as per the manufacturer's guidelines to ensure assay reliability and reproducibility.

2.4. Statistical Analysis

Data were analyzed using SPSS version 25.0 (IBM Corp., Armonk, NY). Continuous variables were expressed as mean ± standard deviation (SD) and categorical variables were presented as frequencies and percentages. Group comparisons were performed using independent-samples t-tests or Mann-Whitney U tests for continuous variables and chi-square or Fisher's exact tests for categorical variables. Multiple linear regression analyses were used to evaluate the association between inflammatory biomarkers and VAS pain scores, adjusting for confounders such as age and BMI. Additionally, receiver operating characteristic (ROC) curve analysis was performed to assess the diagnostic performance (sensitivity and specificity) of each biomarker in distinguishing endometriosis patients from controls. A $P < 0.05$ was considered statistically significant.[18]

Table 1: Comparative demographic and clinical factors between two groups

Factors		Patients	Controls	P-value
Age (year)	< 30	17 (37.78)	15 (33.33)	192 NS
	30-40	11 (24.44)	20 (44.44)	
	> 40	17 (37.78)	10 (22.22)	
Smoking		37 (83.33)	35 (77.78)	0.0084 **
Infertility History		17 (37.78)	6 (13.33)	0.0001 **

*[a] P-values calculated using the chi-square test; * P < 0.01 indicates a statistically significant difference.Data presented as n (%)*

3. RESULTS

In Table 1 the age distribution did not differ significantly between patients and controls ($P = 0.192$). However, a notably higher proportion of patients reported smoking (83.33% vs. 77.78%) and had a history of infertility (37.78% vs. 13.33%) compared to controls, both differences reaching statistical significance ($P < 0.01$).

In Table 2, among the 45 patients diagnosed with endometriosis, Stage II was the most common (31.11%), followed by Stage IV (26.67%), Stage III (22.22%), and Stage I (20.00%). The distribution across stages was not statistically significant ($P = 0.726$).

Table2: Distribution of endometriosis stages among patients

Endometriosis Stage	No of patients (%)	P-value
Stage I	9 (20.00)	0.726
Stage II	14 (31.11)	
Stage III	10 (22.22)	
Stage IV	12 (26.67)	
Total	45 (100)	

P-value calculated using chi-square test; NS: Not Significant (P > 0.05).

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In Table 3, Serum IL-6, TNF-α, CRP, and LIF levels were all significantly higher in patients with endometriosis compared to controls ($P < 0.01$).

Table 3: Comparison of serum inflammatory markers between endometriosis patients and control

Group	IL-6 (pg/mL)	TNF-α (pg/mL)	CRP (mg/L)	LIF (pg/mL)
Patients	60.48 ± 4.48	30.85 ± 2.16	12.17 ± 0.94	8.82 ± 0.66
Control	5.18 ± 0.54	2.07 ± 0.22	1.152 ± 0.11	0.526 ± 0.06
T-test	**8.979 ****	**4.329 ****	**1.890 ****	**1.327 ****
P-value	0.0001	0.0001	0.0001	0.0001

*P-values calculated using two-tailed independent t-tests; ** P < 0.01 indicates a statistically significant difference.*

Table 4. Multiple linear regression of VAS score on clinical and inflammatory factors in endometriosis patients

Variables (X)	Regression coefficient-b	Linear equation	R2
IL-6	0.088 **	Y^= 0.669 + 0.088X	0.93
TNF-α	0.178 **	Y^= 0.499 + 0.178X	0.89
CRP	0.406 **	Y^= 1.05 + 0.406X	0.88
LIF	0.577 **	Y^= 0.917 + 0.577X	0.87
BMI	0.046 NS	Y^= 4.74 + 0.046X	0.06
Age	-0.0068 NS	Y^= 6.24 - 0.0068X	0.05
Multiple equation	Y^ = 2.12 + 0.004 IL6 + 0.027 TNF + 0.041 CRP +0.046 LIF + 0.008 +0.0007 BMI - 0.012 Age **		0.98

*P-values from multiple linear regression models. NS = Not Significant (P > 0.05); ** = P < 0.01; R^2 = Coefficient of determination*

Table 5: Sensitivity and specificity of inflammatory markers for distinguishing endometriosis patients from controls

Parameters	Group	Sensitivity	Specificity
IL-6	Patients	0.41	0.73
	Control	0.66	0.42
TNF-α	Patients	0.38	0.75
	Control	0.69	0.37
CRP	Patients	0.48	0.63
	Control	0.72	0.38
LIF	Patients	0.46	0.73
	Control	0.69	0.38

[a]*Sensitivity and specificity derived from ROC curve analysis using Youden's Index.*

Table 4. using Multiple linear regression analysis revealed that IL-6, TNF-α, CRP, and LIF were significantly and positively associated with VAS score ($P < 0.01$), while BMI and Age did not show a significant effect. Despite the nonsignificant contributions of BMI and Age, the final model explains a large portion of the variance in VAS score (R^2=0.98), highlighting the dominant predictive role of inflammatory markers in endometriosis symptom severity.

Each biomarker (IL-6, TNF-α, CRP, and LIF) demonstrated moderate sensitivity and specificity in differentiating endometriosis patients from controls, with none exhibiting both high sensitivity and specificity simultaneously. Sensitivity values ranged from 0.38 to 0.66, while specificity ranged from 0.37 to 0.75, indicating variable performance across markers (Table 5).

4. DISCUSSION

The present study comprehensively evaluated key demographic, clinical, and immunological parameters in women with endometriosis compared to a control group, and further explored how these parameters relate to pain severity. Overall, our findings revealed higher rates of smoking and infertility among patients, a non-significant distribution of endometriosis stages, significantly elevated inflammatory markers in affected women, and a strong positive association between those markers and pain scores. These results underscore the pivotal role of inflammation in the pathophysiology of endometriosis, while highlighting potential risk factors (e.g., smoking) and clinical features (e.g., infertility) that may inform disease management.

Our observation that women with endometriosis had higher rates of smoking and infertility is broadly consistent with earlier epidemiological investigations.[19,20] Some studies suggest that tobacco use can alter estrogen metabolism and compromise local immune responses, thereby promoting endometriotic lesion formation or progression.[21] However, conflicting data also exist, with certain cohorts reporting no significant association between smoking and endometriosis.[22] These discrepancies may reflect differences in study design, genetic predisposition, or unmeasured lifestyle confounders (e.g., diet, exercise). The increased prevalence of infertility among patients aligns with well-documented evidence linking endometriosis to subfertility.[23] Mechanistically, the presence of ectopic endometrial tissue can distort pelvic anatomy, provoke chronic inflammation, and potentially reduce endometrial receptivity, thus impacting fertility outcomes.[4]

In terms of disease stage distribution, our study did not find a statistically significant predominance of any single stage within the endometriosis patients. This result mirrors findings from other clinical series demonstrating considerable heterogeneity in disease presentation.[24] Importantly, stage-based classification does not always correlate with symptom severity or fertility impairment, indicating that a more nuanced understanding of individual lesion characteristics, immune response, and lesion location may be required to fully capture disease burden.

A major contribution of this work is the demonstration of significantly elevated inflammatory markers IL-6, TNF-α, CRP, and LIF in patients compared to controls, alongside their strong positive association with pain severity. These findings fit within a broader framework positioning endometriosis as an estrogen-dependent inflammatory disorder, characterized by immune dysregulation in both the peritoneal cavity and ectopic endometrial tissues.[25] IL-6 is a pleiotropic cytokine that regulates the acute-phase response and influences both innate and adaptive immunity.[9] In endometriosis, IL-6 can be secreted by ectopic endometrial stromal cells and resident immune cells, perpetuating a pro-inflammatory milieu and this cytokine not only drives local infiltration of macrophages and neutrophils but also enhances angiogenesis by stimulating vascular endothelial growth factor (VEGF) pathways.[26] Through these mechanisms, IL-6 facilitates lesion proliferation, supports local neuroangiogenesis (which can heighten pain perception), and amplifies the systemic inflammatory burden.[27]

TNF-α is a key regulator of inflammation and tissue remodeling and elevated TNF-α in endometriosis lesions has been shown to increase the recruitment of immune cells—particularly macrophages—leading to the release of additional inflammatory mediators such as IL-1β, IL-8, and matrix metalloproteinases.[10] This cascade fosters an environment of ongoing tissue damage and repair, thereby promoting lesion growth and the ingrowth of nerve fibers that contribute to chronic pelvic pain.[28] Furthermore, TNF-α may enhance estrogen production via local aromatase activation, creating a feedback loop that perpetuates both hormonal and inflammatory processes.[29]

CRP is an acute-phase reactant produced predominantly in the liver in response to IL-6 and other pro-inflammatory cytokines, although CRP is a more general marker of systemic inflammation, its elevation in women with endometriosis points to a heightened inflammatory state beyond the pelvis.[11] Chronic exposure to elevated CRP has been associated with endothelial dysfunction, oxidative stress, and other systemic sequelae, implying that endometriosis might have health implications extending beyond the reproductive system.[30]

LIF is crucial for embryo implantation and endometrial receptivity, and disruptions in its expression can contribute to infertility.[12] In endometriosis, aberrant LIF levels within ectopic and eutopic endometrium may impair normal endometrial remodeling, reduce implantation success, and exacerbate pain through neuroimmune interactions.[12] The strong correlation between LIF and pain scores in our data highlights how dysregulated immune-endocrine crosstalk in endometriosis may drive both symptom severity and subfertility.

Our findings underscore the need for a multidisciplinary approach to endometriosis management. Elevated inflammatory markers, coupled with higher smoking rates and a strong association with infertility, point to the benefit of early lifestyle interventions—such as smoking cessation—and a thorough fertility evaluation. The significant correlation of IL-6, TNF-α, CRP, and LIF with pain severity suggests that monitoring these markers could aid in assessing disease activity or guiding personalized treatment strategies. Although our sensitivity and specificity data indicate that none of these markers alone is sufficient for a definitive diagnosis, their combined use in multi-marker panels could enhance diagnostic confidence. In clinical practice, these panels could be integrated into early screening workflows for patients with suspected endometriosis, especially in primary care or gynecology settings. Paired with imaging findings and patient-reported symptom scales, such biomarker assessments could support clinicians in making more timely and targeted therapeutic decisions. Future clinical protocols might also benefit from incorporating these biomarkers into electronic decision-support tools, potentially improving

individualized care and long-term outcomes. A notable strength of this study is its multifaceted approach, examining demographic, clinical, and biomarker data within a single cohort. This design enabled sufficient modeling of how multiple variables collectively influence symptom severity, as evidenced by the high coefficient of determination in our regression analysis.

5. LIMITATIONS

Nevertheless, certain limitations should be acknowledged. First, the case-control design precludes evaluation of longitudinal changes in inflammatory markers or their response to interventions. Second, the sample size—while sufficient to detect statistically meaningful differences—may not capture the full heterogeneity of endometriosis presentations. Third, single time-point cytokine measurements might miss dynamic fluctuations associated with menstrual cycle phases or treatment regimens. Larger, multicenter, and longitudinal studies will be necessary to validate these findings and explore the stability of biomarker levels over time.

6. CONCLUSION

This study highlights the complex relationship between inflammatory mediators, lifestyle factors, and clinical symptoms in women with endometriosis. The increased levels of IL-6, TNF-α, CRP, and LIF are closely associated with pain severity, supporting the role of inflammation in the disease's pathogenesis. While these biomarkers hold potential for improving understanding and guiding personalized treatment, further research is needed to validate their application in routine clinical practice. Deepening insights into the underlying mechanisms and enhancing diagnostic accuracy could pave the way for more targeted and effective therapeutic strategies for this challenging gynecological condition.

7. Data availability

Numerical data generated in this research is available with the corresponding author, and can be requested for study.

8. Acknowledgments

We would like to express their sincere gratitude to the medical and administrative staff at Al-Sadr Teaching Hospital, Iraq for their invaluable support throughout the study. We extend our appreciation to the Institutional Review Board for granting ethical approval and to all participants who generously contributed their time and effort.

9. Conflict of Interests

We declare that there are no conflicts of interest associated with this manuscript.

10. Financial Disclosures

We declare that this research did not receive any specific grant or funding from public, commercial, or non-profit organizations.

11. Authors contribution

BRY: Conceptualization, methodology, formal analysis, and manuscript writing.

AJM: Data collection, investigation, and software analysis.

SAS: Literature review, validation, and manuscript editing.

RDA: Supervision, project administration, and final manuscript review.

12. REFERENCE

1. Al Hussaini HAD, Alatawi ESE, Shabani JAJ, Edhrabooh MIH, Alhawaj SAA, Almahfoodh MS, et al. Management of endometriosis-related pain: comparing the effectiveness of hormonal therapy, surgical interventions, and complementary therapies. Cureus. 2024;16(12). [PubMed] DOI: 10.7759/cureus.75590

2. Saunders PT, Horne AW. Endometriosis: etiology, pathobiology, and therapeutic prospects. Cell. 2021;184(11):2807–24. [PubMed] DOI: 10.1016/j.cell.2021.04.041

3. Kobayashi H, Imanaka S, Yoshimoto C, Matsubara S, Shigetomi H. Rethinking the pathogenesis of endometriosis: complex interactions of genomic, epigenetic, and environmental factors. J Obstet Gynaecol Res. 2024;50(10):1771–84. [PubMed] DOI: 10.1111/jog.16089

4. Sisnett DJ, Zutautas KB, Miller JE, Lingegowda H, Ahn SH, McCallion A, et al. The dysregulated IL-23/TH17 axis in endometriosis pathophysiology. J Immunol. 2024;212(9):1428–41. [PubMed] DOI: 10.4049/jimmunol.2400018

5. Wei Y, Zhao X, Li L. The effect of circulating inflammatory proteins on endometriosis: a Mendelian randomization study. Immunotargets Ther. 2024:585–93. [PubMed] DOI: 10.2147/ITT.S486139

6. Griffiths MJ, Horne AW, Gibson DA, Roberts N, Saunders PT. Endometriosis: recent advances that could accelerate diagnosis and improve care. Trends Mol Med. 2024;30(9):875-889. [PubMed] DOI: 10.1016/j.molmed.2024.06.008

7. Jiang J, Jiang Z, Xue M. Serum and peritoneal fluid levels of interleukin-6 and interleukin-37 as biomarkers for endometriosis. Gynecol Endocrinol. 2019;35(7):571–5. [PubMed] DOI: 10.1080/09513590.2018.1554034

8. Yu PH, Chou PY, Li WN, Tsai SJ, Wu MH. The pro-inflammatory and anti-inflammatory role of hyaluronic acid in endometriosis. Taiwan J Obstet Gynecol. 2021;60(4):711–7. [PubMed] DOI: 10.1016/j.tjog.2021.05.022

9. Mir MA, Bashir M, Jan N. The role of interleukin (IL)-6/IL-6 receptor axis in cancer. In: Cytokine Chemokine Netw Cancer.Springer; 2023. pp.137–64. DOI:10.1007/978-981-99-4657-0_5

10. Kelkar RA, Kaye AD, Perilloux DM, Hawkins AM, Wester GC, Ragland AR, et al. Evolving role of immunology in chronic pain medicine: tissue necrosis factor and interleukin modulatory treatments. Explor Immunol. 2024;4(4):523–32. DOI: 10.37349/ei.2024.00156

11. Kokot I, Piwowar A, Jędryka M, Sołkiewicz K, Kratz EM. Diagnostic significance of selected serum inflammatory markers in women with advanced endometriosis. Int J Mol Sci. 2021;22(5):2295. [PubMed] DOI: 10.3390/ijms22052295

12. Zutautas KB, Sisnett DJ, Miller JE, Lingegowda H, Childs T, Bougie O, Lessey BA, et al. The dysregulation of leukemia inhibitory factor and its implications for endometriosis pathophysiology. Front Immunol. 2023;14:1089098. [PubMed] DOI: 10.3389/fimmu.2023.1089098

13. Gorun OM, Ratiu A, Citu C, et al. The role of inflammatory markers NLR and PLR in predicting pelvic pain in endometriosis. J Clin Med. 2024;14(1):149. [PubMed] DOI: 10.3390/jcm14010149

14. Shrestha B, Dunn L. The declaration of Helsinki on medical research involving human subjects: a review of seventh revision. J Nepal Health Res Counc. 2020;17(4):548-552. [PubMed] DOI: 10.33314/jnhrc.v17i4.1042

15. Zierle-Ghosh A, Jan A. Physiology, Body Mass Index. In: StatPearls. Treasure Island (FL): StatPearls Publishing; 2025. Available from: https://www.ncbi.nlm.nih.gov/books/NBK535456/

16. Bjornholdt T, Andersen CW. Measurement of acute postoperative pain intensity in orthopedic trials: a qualitative concept elicitation study. Acta Orthop. 2024;95:625. [PubMed] DOI: 10.2340/17453674.2024.42182

17. Hudelist G, Valentin L, Saridogan E, Condous G, Malzoni M, Roman H, et al. What to choose and why to use–a critical review on the clinical relevance of rASRM, EFI and Enzian classifications of endometriosis. Facts Views Vis ObGyn. 2021;13(4):331. [PubMed] DOI: 10.52054/FVVO.13.4.041

18. George D, Mallery P. IBM SPSS statistics 26 step by step: a simple guide and reference. Routledge; 2019. DOI: 10.4324/9780429056765

19. Al-Lami RA, Taha SA, Jalloul RJ, Taylor HS. Women with endometriosis in the United States: National Survey of Family Growth, 2011–2019. J Endometr Uterine Disord. 2024;8:100081. DOI: 10.1016/j.jeud.2024.100081

20. Peng L, Luo X, Cao B, Wang X. Unraveling the link: environmental tobacco smoke exposure and its impact on infertility among American women (18–50 years). Front Public Health. 2024;12:1358290. [PubMed] DOI: 10.3389/fpubh.2024.1358290

21. Bravi F, Parazzini F, Cipriani S, Chiaffarino F, Ricci E, Chiantera V, et al. Tobacco smoking and risk of endometriosis: a systematic review and meta-analysis. BMJ Open. 2014;4(12):e006325. [PubMed] DOI: 10.1136/bmjopen-2014-006325

22. Hemmert R, Schliep KC, Willis S, Peterson CM, Louis GB, Allen-Brady K, et al. Modifiable life style factors and risk for incident endometriosis. Paediatr Perinat Epidemiol. 2019;33(1):19–25. [PubMed] DOI: 10.1111/ppe.12516

23. Haydardedeoglu B, Zeyneloglu HB. The impact of endometriosis on fertility. Womens Health (Lond). 2015;11(5):619–23. [PubMed] DOI: 10.2217/whe.15.48

24. Shadjoo K, Gorgin A, Maleki N, Mohazzab A, Armand M, Hadavandkhani A, et al. Pregnancy-related complications in patients with endometriosis in different stages. Contracept Reprod Med. 2024;9(1):23. [PubMed] DOI: 10.1186/s40834-024-00280-0

25. Garvey M. Endometriosis: future biological perspectives for diagnosis and treatment. Int J Mol Sci. 2024;25(22):12242. [PubMed] DOI: 10.3390/ijms252212242

26. Castle RD. IL-6 signaling pathway differentiation for endometriosis and inflammatory diseases. Explor Immunol. 2024;4(4):476–89. DOI: 10.37349/ei.2024.00153

27. Jones SA, Jenkins BJ. Recent insights into targeting the IL-6 cytokine family in inflammatory diseases and cancer. Nat Rev Immunol. 2018;18(12):773–89. [PubMed] DOI: 10.1038/s41577-018-0066-7

28. Varnosfaderani AS, Kalantari S, Ramezanali F, Shahhoseini M, Amirchaghmaghi E. Increased gene expression of LITAF, TNF-α and BCL6 in endometrial tissues of women with endometriosis: a case-control study. Cell J. 2024;26(4):243–9. [PubMed] DOI: 10.22074/cellj.2024.2022348.1503

29. To SQ, Simpson ER, Knower KC, Clyne CD. Involvement of early growth response factors in TNFα-induced aromatase expression in breast adipose. Breast Cancer Res Treat. 2013;138:193–203. [PubMed] DOI: 10.1007/s10549-013-2413-5

30. Gleason JL, Thoma ME, Zukerman Willinger N, Shenassa ED. Endometriosis and uterine fibroids and their associations with elevated C-reactive protein and leukocyte telomere length among a representative sample of US women: data from the National Health and Nutrition Examination Survey, 1999–2002. J Womens Health (Larchmt). 2022;31(7):1020–8. [PubMed] DOI: 10.1089/jwh.2021.0044

