E-ISSN 2250-0944
ISSN 2250-1150
doi: 10.31838/ijprt/16.02.477

**Research Article**

# Inflammatory and Oxidative Stress Biomarkers in Women with Endometriosis: Association with Disease Severity

**Hina Pervaiz[1], Asma Iqbal[2], Amna Noor[3*], Ukasha Zaheer[4], Hina Ehsan[5], Imran Mehboob Baig[6]**
[1]Department of Physiology, Fatima Jinnah Medical University Lahore, Pakistan.
[2]Senior Registrar, Department of Obstetrics and Gynaecology, Karachi Medical and Dental College, Karachi.
[3*]Department of Physiology Fatima Jinnah Medical University Lahore, Pakistan.
[4]Medical Officer. Ibn - E - Siena Hospital and Research Institute, Multan. Department of Obstetrics and Gynaecology.
[5]Demonstrator. Department of Physiology, Bakhtawar Amin Medical & Dental College, Multan.
[6]Associate Professor, Department of Physiology, Shahida Islam Medical and Dental College, Lodhran.
**Email:** [1]hinaathar20@gmail.com, [2]asmanadeemkhan@hotmail.com, [3*]nooramna533@gmail.com, [4]ukashamughal23@gmail.com, [5]hinaehsan.hi@gmail.com, [6]imran.physio@simc.edu.pk
**Corresponding Author:** Amna Noor
Department of Physiology Fatima Jinnah Medical University Lahore, Pakistan.
**Email:** nooramna533@gmail.com
Received: 01.07.26, Revised: 03.08.26, Accepted: 05.09.26

**ABSTRACT**
**Background:** Endometriosis is a chronic inflammatory disorder in which oxidative imbalance may support lesion survival and disease progression. Affordable circulating biomarkers may help assess severity in resource-limited settings.
**Objective:** To compare inflammatory and oxidative stress biomarkers in women with and without endometriosis and determine their association with disease severity.
**Methods:** This multicenter analytical cross-sectional study included 240 women undergoing pelvic laparoscopy at three tertiary-care hospitals in Pakistan. Histologically confirmed cases were categorized as revised American Society for Reproductive Medicine stage I–II or stage III–IV. Women without endometriosis served as controls. Serum high-sensitivity C-reactive protein, interleukin-6, tumor necrosis factor-alpha, malondialdehyde, superoxide dismutase and total antioxidant capacity were measured.
**Results:** The study included 160 women with endometriosis and 80 controls. Women with endometriosis had significantly higher inflammatory markers and malondialdehyde, whereas superoxide dismutase and total antioxidant capacity were significantly lower than controls (all $p<0.001$). Biomarker disturbance increased progressively from controls to stage I–II and stage III–IV disease. Interleukin-6, malondialdehyde and total antioxidant capacity remained independently associated with advanced disease. The combined biomarker model effectively distinguished stage III–IV disease, achieving an area under the receiver operating characteristic curve of 0.86.
**Conclusion:** Endometriosis was associated with increased systemic inflammation, lipid peroxidation and impaired antioxidant defense. A combined biomarker panel may support severity assessment but cannot replace clinical evaluation, imaging or histopathology.

**Keywords:** Endometriosis, Inflammation, Oxidative Stress, Interleukin-6, Malondialdehyde, Antioxidant Capacity, Pakistan.

## INTRODUCTION

Endometriosis is a chronic, estrogen-dependent inflammatory disorder characterized by the presence of endometrium-like tissue outside the uterine cavity.[1] It commonly presents with dysmenorrhea, chronic pelvic pain, dyspareunia, infertility and reduced quality of life.[2] The condition affects approximately 10% of women of reproductive age, although its exact prevalence varies according to the population studied and the diagnostic methods employed.[3]

Endometriosis is clinically heterogeneous and may occur as superficial peritoneal disease, ovarian endometrioma or deep infiltrating endometriosis.[4] The severity of pain does not always correspond to the anatomical extent of disease, and some women with advanced lesions may have limited symptoms.[5] Conversely, women with apparently minimal

disease may experience severe pain and infertility.[6]

Although retrograde menstruation is considered an important mechanism, it alone cannot explain why endometriotic lesions develop in only some women.[7] Altered immune clearance, hormonal imbalance, genetic susceptibility, angiogenesis, resistance to apoptosis and abnormal tissue repair contribute to lesion establishment and progression.[8] Endometriosis is therefore increasingly recognized as a systemic disorder involving interactions between endocrine, inflammatory and metabolic pathways.[2]

Macrophages, neutrophils, natural killer cells and lymphocyte populations are altered in women with endometriosis. These immune cells produce inflammatory cytokines and chemokines that support ectopic tissue survival, vascular formation, fibrosis and peripheral nerve sensitization.[6] Interleukin-6 (IL-6) and tumour necrosis factor-alpha (TNF-α) are among the most frequently studied inflammatory mediators in endometriosis.[9] High-sensitivity C-reactive protein (hs-CRP) may also provide an inexpensive indicator of low-grade systemic inflammation.[10]

Repeated bleeding within endometriotic lesions releases haemoglobin, haem and free iron into the surrounding environment. Free iron promotes reactive oxygen species generation and lipid peroxidation, thereby producing oxidative damage to cellular membranes, proteins and nucleic acids.[9] Oxidative stress can also activate nuclear factor-kappa B and other intracellular pathways that enhance inflammation, angiogenesis and cellular proliferation.

Malondialdehyde (MDA) is a commonly measured product of lipid peroxidation and provides an indirect estimate of oxidative injury. Superoxide dismutase (SOD) is an important enzymatic antioxidant that converts superoxide radicals into less reactive compounds, while total antioxidant capacity (TAC) represents the combined activity of circulating antioxidant systems.[10] Increased oxidant activity accompanied by reduced antioxidant defense may contribute to the persistence and progression of endometriotic lesions.

Despite considerable research, no individual blood biomarker has demonstrated sufficient accuracy and reproducibility for the diagnosis or staging of endometriosis.[11] Differences in lesion phenotype, menstrual phase, infertility status, previous treatment, assay technique and control selection contribute to inconsistent findings.[12] Recent evidence therefore supports the evaluation of biomarker panels that represent more than one biological pathway.[13]

Diagnostic delays are especially important in low- and middle-income countries, where menstrual pain may be normalized and access to specialist imaging and laparoscopic surgery remains limited.[14] Biomarkers measured through commonly available immunoassay and spectrophotometric techniques may assist clinical triage in such settings. This study compared inflammatory and oxidative stress biomarkers in women with and without endometriosis and determined their association with disease severity.

## MATERIALS AND METHODS

This multicentre analytical cross-sectional study was conducted in the departments of Obstetrics and Gynaecology, Biochemistry and Physiology of three tertiary-care teaching hospitals in Pakistan from January to December 2025. Approval was obtained from the institutional ethics committees of the participating hospitals. Written informed consent was obtained from every participant before enrolment. The study was conducted according to the ethical principles of the Declaration of Helsinki.

Women aged 18–45 years who were scheduled for laparoscopy because of chronic pelvic pain, infertility, an adnexal mass or suspected endometriosis were screened consecutively. Women were enrolled in the endometriosis group when lesions were identified during laparoscopy and subsequently confirmed by histopathological examination.

The control group consisted of women undergoing laparoscopy for tubal evaluation, sterilization or a benign non-inflammatory gynaecological condition. These women had no visible endometriotic lesions or evidence of active pelvic inflammation during surgery.

Women were excluded if they were pregnant or postmenopausal or had an acute infection, autoimmune disease, chronic inflammatory disorder, malignancy, diabetes mellitus, significant hepatic or renal disease, or another condition likely to influence the biomarkers. Current smokers and women who had taken antioxidant supplements during the preceding eight weeks were excluded. Women who had received hormonal treatment, corticosteroids or regular anti-inflammatory medicines during the previous three months were also excluded.

The sample size was calculated for comparisons among three groups using a moderate

expected effect size, 90% statistical power and a 5% level of significance. Allowance was made for incomplete samples and laboratory errors. A total of 240 women were included, consisting of 160 women with endometriosis and 80 controls.

The extent of endometriosis was assessed during laparoscopy using the revised American Society for Reproductive Medicine classification. Women with stage I or II disease were categorized as having early endometriosis, whereas those with stage III or IV disease were categorized as having advanced endometriosis. Combining adjacent stages provided clinically meaningful groups with sufficient numbers for statistical comparisons.

Demographic and clinical information included age, body mass index, parity, menstrual-cycle phase, infertility status and presenting symptoms. The severity of pelvic pain during the preceding three months was recorded using a 10-point visual analogue scale, on which 0 indicated no pain and 10 indicated the worst imaginable pain.

Fasting venous blood was collected between 8:00 and 10:00 am before anaesthesia and surgical manipulation. Serum was separated within one hour by centrifugation at 3,000 revolutions per minute for 10 minutes. Samples were divided into labelled aliquots and stored at −80°C until analysis. Samples collected at participating centres were transported to the coordinating laboratory on dry ice. Repeated freezing and thawing were avoided.

Serum hs-CRP was measured using immunoturbidimetry. IL-6 and TNF-α were measured using commercially available human enzyme-linked immunosorbent assay kits. Each sample was tested in duplicate according to the manufacturer's instructions. MDA was measured using the thiobarbituric acid-reactive substances method. SOD activity was assessed by inhibition of pyrogallol autoxidation, while TAC was determined using the ferric-reducing antioxidant power method.

Calibrators and two levels of internal quality-control material were included in every analytical run. A duplicate coefficient of variation greater than 10% resulted in repeat analysis. Laboratory personnel were unaware of the laparoscopic findings and disease stage. Assays were selected according to their affordability and availability in public-sector laboratories. The study design, participant grouping, biomarker measurements and primary outcomes are summarized in Table 1**.**

Table 1. Study framework and laboratory measurements

| Variable | Operational approach |
|---|---|
| Control group | Women without laparoscopic evidence of endometriosis |
| Early disease | rASRM stage I–II |
| Advanced disease | rASRM stage III–IV |
| Inflammatory biomarkers | hs-CRP, IL-6 and TNF-α |
| Oxidative stress biomarker | MDA |
| Antioxidant biomarkers | SOD and TAC |
| Primary outcome | Differences in biomarkers according to disease severity |
| Secondary outcome | Independent predictors of stage III–IV disease |

Data were analysed using SPSS version 26.0. Continuous and categorical variables were summarized using appropriate descriptive statistics and compared with parametric or non-parametric tests. Spearman correlation, multivariable logistic regression and ROC analysis assessed biomarker associations and performance. A p-value <0.05 was considered significant.

## RESULTS

A total of 276 women were screened. Twenty-four did not fulfill the eligibility criteria, while 12 were excluded because their specimens were haemolysed or inadequate. The final analysis therefore included 240 participants: 80 controls and 160 women with histologically confirmed endometriosis. Among the women with endometriosis, 78 had stage I–II disease and 82 had stage III–IV disease.

The demographic and clinical characteristics of the participants are presented in Table 2. Age, body mass index and menstrual-cycle phase were comparable among the groups. Infertility and pelvic pain were more frequently observed among women with endometriosis.

Table 2. Demographic and clinical characteristics

| Characteristic | Controls (n=80) | Stage I–II (n=78) | Stage III–IV (n=82) | p-value |
|---|---|---|---|---|

| | | | | |
|---|---|---|---|---|
| Age, years | 31.2 ± 5.8 | 30.7 ± 5.6 | 31.8 ± 5.9 | 0.46 |
| BMI, kg/m² | 25.1 ± 3.9 | 24.8 ± 3.7 | 25.6 ± 4.1 | 0.42 |
| Infertility, n (%) | 18 (22.5) | 43 (55.1) | 49 (59.8) | <0.001 |
| Pelvic-pain score, median (IQR) | 1 (0–2) | 6 (4–7) | 7 (5–9) | <0.001 |
| Follicular-phase sampling, n (%) | 43 (53.8) | 39 (50.0) | 39 (47.6) | 0.74 |

The comparison of circulating biomarkers between all women with endometriosis and controls is shown in Table 3. Women with endometriosis had a consistent pro-inflammatory and pro-oxidative profile accompanied by lower antioxidant defense.

Table 3. Biomarkers in women with endometriosis and controls

| Biomarker | Controls (n=80) | Endometriosis (n=160) | p-value |
|---|---|---|---|
| hs-CRP, mg/L | 1.42 (0.81–2.19) | 3.18 (1.92–5.04) | <0.001 |
| IL-6, pg/mL | 3.6 (2.7–4.9) | 7.9 (5.4–11.8) | <0.001 |
| TNF-α, pg/mL | 8.4 (6.5–10.7) | 13.7 (10.2–18.1) | <0.001 |
| MDA, µmol/L | 2.21 ± 0.61 | 3.74 ± 0.96 | <0.001 |
| SOD, U/mL | 8.92 ± 1.84 | 6.71 ± 1.69 | <0.001 |
| TAC, mmol Trolox equivalent/L | 1.38 ± 0.25 | 0.99 ± 0.24 | <0.001 |

A progressive biomarker disturbance was observed from controls to stage I–II and stage III–IV disease, as presented in Table 4. The most marked differences between early and advanced disease were observed for IL-6, MDA and TAC. The direction of these associations remained unchanged when the analysis was restricted to women sampled during the follicular phase.

Table 4. Biomarker concentrations according to disease severity

| Biomarker | Controls (n=80) | Stage I–II (n=78) | Stage III–IV (n=82) | p-value |
|---|---|---|---|---|
| hs-CRP, mg/L | 1.42 (0.81–2.19) | 2.61 (1.64–3.88) | 3.86 (2.31–5.83) | <0.001 |
| IL-6, pg/mL | 3.6 (2.7–4.9) | 6.3 (4.8–8.4) | 10.2 (7.4–13.9) | <0.001 |
| TNF-α, pg/mL | 8.4 (6.5–10.7) | 12.2 (9.4–15.8) | 15.6 (11.6–20.4) | <0.001 |
| MDA, µmol/L | 2.21 ± 0.61 | 3.28 ± 0.72 | 4.18 ± 0.96 | <0.001 |
| SOD, U/mL | 8.92 ± 1.84 | 7.25 ± 1.54 | 6.20 ± 1.67 | <0.001 |
| TAC, mmol Trolox equivalent/L | 1.38 ± 0.25 | 1.10 ± 0.21 | 0.88 ± 0.22 | <0.001 |

The relationships between biomarker concentrations, operative severity and pain scores are presented in Table 5. IL-6 and MDA demonstrated the strongest positive correlations with rASRM score, whereas TAC showed the strongest inverse relationship. Correlations with pain intensity were comparatively weaker.

Table 5. Correlation of biomarkers with disease severity and pelvic pain

| Biomarker | r with rASRM score | p-value | r with pain score | p-value |
|---|---|---|---|---|
| hs-CRP | 0.39 | <0.001 | 0.28 | <0.001 |
| IL-6 | 0.58 | <0.001 | 0.36 | <0.001 |
| TNF-α | 0.42 | <0.001 | 0.31 | <0.001 |
| MDA | 0.61 | <0.001 | 0.38 | <0.001 |
| SOD | −0.46 | <0.001 | −0.25 | 0.002 |
| TAC | −0.59 | <0.001 | −0.34 | <0.001 |

After adjustment for age, body mass index, infertility, menstrual-cycle phase and participating center, IL-6, MDA and TAC remained independently associated with stage III–IV disease (Table 6). No significant

multicollinearity was observed among the variables included in the final model.

Table 6. Multivariable predictors of stage III–IV endometriosis

| Variable | Adjusted odds ratio | 95% confidence interval | p-value |
|---|---|---|---|
| IL-6, per 2 pg/mL increase | 1.42 | 1.17–1.72 | <0.001 |
| MDA, per 0.5 µmol/L increase | 1.58 | 1.20–2.09 | 0.001 |
| TAC, per 0.1 mmol/L decrease | 1.36 | 1.12–1.66 | 0.002 |
| hs-CRP, per 1 mg/L increase | 1.08 | 0.96–1.22 | 0.19 |
| TNF-α, per 5 pg/mL increase | 1.13 | 0.91–1.40 | 0.27 |
| SOD, per 1 U/mL decrease | 1.12 | 0.94–1.34 | 0.21 |

The individual areas under the receiver operating characteristic curves were 0.78 for IL-6, 0.81 for MDA and 0.79 for TAC. The combined IL-6, MDA and TAC model produced an area under the curve of 0.86 (95% confidence interval: 0.80–0.91). The combined model identified advanced disease with 79.3% sensitivity and 78.2% specificity.

## DISCUSSION

The present study demonstrated significantly increased systemic inflammation and lipid peroxidation in women with endometriosis. Antioxidant defense was simultaneously reduced, and these abnormalities became more pronounced with increasing disease severity. IL-6, MDA and TAC remained independently associated with stage III–IV endometriosis after adjustment for relevant clinical factors.

The inflammatory findings were consistent with current understanding of endometriosis as an immune-mediated disorder involving altered macrophage activity and abnormal cytokine production.[15] Activated immune cells within the peritoneal cavity contribute to inflammation, angiogenesis, fibrosis and the survival of ectopic endometrial tissue.[16] Increased circulating IL-6 and TNF-α may therefore reflect inflammatory activity occurring within endometriotic lesions and the surrounding peritoneal environment.[17]

IL-6 demonstrated a stronger association with disease severity than hs-CRP or TNF-α. This may indicate that IL-6 is more closely related to the active inflammatory pathways involved in lesion progression. hs-CRP increased significantly across the study groups but did not retain an independent association after adjustment. CRP is a nonspecific downstream acute-phase protein and may be affected by obesity, minor infections and other unrecognized inflammatory processes.

The increase in MDA supported the involvement of lipid peroxidation in endometriosis. Repeated bleeding within lesions releases iron, which promotes reactive oxygen species production through iron-dependent chemical reactions.[18] Reactive oxygen species damage cellular lipids and generate MDA and other secondary products. Oxidative injury may subsequently activate inflammatory signalling, angiogenesis and cellular proliferation, creating a self-perpetuating cycle of inflammation and oxidative stress.

MDA showed the strongest correlation with the rASRM score and remained independently associated with advanced endometriosis. Nevertheless, MDA is not specific to endometriosis and can be increased in several metabolic and inflammatory disorders. The thiobarbituric acid-reactive substances method may also detect compounds other than MDA. Strict specimen handling and laboratory quality control are therefore necessary when MDA is used in clinical research.[19]

SOD activity and TAC were significantly reduced among women with endometriosis. Lower SOD activity may decrease the removal of superoxide radicals, while reduced TAC suggests depletion or inadequate activity of circulating antioxidant systems. The progressive reduction in these biomarkers from early to advanced disease supported the presence of increasing redox imbalance. TAC remained independently associated with advanced disease, suggesting that overall antioxidant status may be more informative than a single antioxidant enzyme.

The combined IL-6, MDA and TAC model performed better than any individual biomarker. This finding was consistent with systematic reviews showing that numerous candidate biomarkers have been studied but none has demonstrated adequate reproducibility for routine independent use.[20] Endometriosis involves multiple biological pathways; consequently, a panel incorporating inflammation, oxidative injury and antioxidant defense may reflect disease activity more completely than an isolated measurement.[21]

A recent prospective study reported that selected oxidative stress markers could not reliably distinguish infertile women with endometriosis from women with unexplained infertility.[22] Differences in the study population, control selection, laboratory methods and disease distribution may explain the variation from the present findings. The current study focused mainly on association with disease severity rather than using biomarkers as definitive diagnostic tests.

The correlations between biomarker concentrations and pelvic pain were weaker than their correlations with operative disease severity. Endometriosis-associated pain is influenced by lesion location, deep infiltration, adhesions, peripheral nerve involvement, neurogenic inflammation, central sensitization, and psychosocial factors.[23] Therefore, biomarker concentrations and anatomical stage should not be used to underestimate severe symptoms in women with limited visible disease. Although relugolix combination therapy can reduce endometriosis-associated pain, treatment response does not reliably indicate anatomical disease severity.[24]

The multicenter design improved the representation of women receiving care in different tertiary hospitals. Consecutive recruitment reduced the likelihood of selective enrolment, while histopathological confirmation improved diagnostic validity. Preoperative sampling prevented surgical manipulation from affecting biomarker values. Blinding of laboratory personnel and duplicate measurements further strengthened the reliability of the findings.

## CONCLUSION

Women with endometriosis had significantly increased hs-CRP, IL-6, TNF-α and MDA and reduced SOD and TAC. The disturbance became more pronounced in stage III–IV disease. IL-6, MDA and TAC were independently associated with advanced endometriosis, and their combined model showed better discriminatory ability than individual biomarkers. This affordable panel may support severity assessment and clinical triage in resource-constrained settings; however, it should not replace clinical evaluation, imaging, laparoscopy or histopathological confirmation.

## REFERENCES


1. Zondervan KT, Becker CM, Missmer SA. Endometriosis. N Engl J Med. 2020;382(13):1244–1256.
2. Taylor HS, Kotlyar AM, Flores VA. Endometriosis is a chronic systemic disease: clinical challenges and novel innovations. Lancet. 2021;397(10276):839–852.
3. Becker CM, Bokor A, Heikinheimo O, et al. ESHRE guideline: endometriosis. Hum Reprod Open. 2022;2022(2):hoac009.
4. Saunders PTK, Horne AW. Endometriosis: etiology, pathobiology, and therapeutic prospects. Cell. 2021;184(11):2807–2824.
5. Chapron C, Marcellin L, Borghese B, Santulli P. Rethinking mechanisms, diagnosis and management of endometriosis. Nat Rev Endocrinol. 2019;15(11):666–682.
6. Villanacci R, Bandini V, Ottolina J, Pagliardini L, Candiani M, Viganò P. The pathogenesis of endometriosis: clues from the immunological evidence. Minerva Obstet Gynecol. 2021;73(3):275–282.
7. Arafah M, Rashid S, Akhtar M. Endometriosis: a comprehensive review. Adv Anat Pathol. 2021;28(1):30–43.
8. Kapoor R, Stratopoulou CA, Dolmans MM. Pathogenesis of endometriosis: new insights into prospective therapies. Int J Mol Sci. 2021;22(21):11700.
9. Clower L, Fleshman T, Geldenhuys WJ, Santanam N. Targeting oxidative stress involved in endometriosis and its pain. Biomolecules. 2022;12(8):1055.
10. Nassif J, Abbasi SA, Khan A, et al. Role of AMPK/mTOR, mitochondria, and reactive oxygen species in the pathogenesis of endometriosis. Life Sci. 2022;306:120805.
11. Encalada Soto D, Rassier S, Green IC, Burnett T, Khan Z, Cope A. Endometriosis biomarkers of the disease: an update. Curr Opin Obstet Gynecol. 2022;34(4):210–219.
12. Pant A, Moar K, Arora TK, Maurya PK. Biomarkers of endometriosis. Clin Chim Acta. 2023;549:117563.
13. Swift B, Taneri B, Becker CM, et al. Prevalence, diagnostic delay and economic burden of endometriosis and its impact on quality of life: results from an Eastern Mediterranean population. Eur J Public Health. 2024;34(2):244–252.

14. Zafari N, Bahramy A, Majidi Zolbin M, et al. MicroRNAs as novel diagnostic biomarkers in endometriosis patients: a systematic review and meta-analysis. Expert Rev Mol Diagn. 2022;22(4):479–495.
15. Mao X, Luo Q, Zhang H, et al. Oxidative stress in endometriosis: sources, mechanisms and therapeutic potential of antioxidants. Exp Ther Med. 2025;29(5):95.
16. Vallvé-Juanico J, Houshdaran S, Giudice LC. The endometrial immune environment of women with endometriosis. Hum Reprod Update. 2019;25(5):564–591.
17. Abramiuk M, Grywalska E, Małkowska P, Sierawska O, Hrynkiewicz R, Niedźwiedzka-Rystwej P. The role of the immune system in the development of endometriosis. Cells. 2022;11(13):2028.
18. Anastasiu CV, Moga MA, Neculau AE, et al. Biomarkers for the noninvasive diagnosis of endometriosis: state of the art and future perspectives. Int J Mol Sci. 2020;21(5):1750.
19. Janša V, Klančič T, Rižner TL, et al. Oxidative stress markers cannot be used as endometriosis biomarkers in infertile patients. Gynecol Endocrinol. 2023;39(1):2242965.
20. Taye M, Horne AW, Saunders PTK, et al. An integrated multi-tissue approach for endometriosis candidate biomarkers: a systematic review. Reprod Biol Endocrinol. 2024;22(1):13.
21. Egashira EM, Trovó-Marqui AB, Tanaka SCSV, Cintra MTR. Investigation of biomarkers in endometriosis-associated infertility: systematic review. An Acad Bras Cienc. 2022;94(suppl 3):e20211572.
22. Tabatabaei F, Tahernia H, Ghaedi A, Bazrgar A, Khanzadeh S. Diagnostic significance of neutrophil-to-lymphocyte ratio in endometriosis: a systematic review and meta-analysis. BMC Womens Health. 2023;23(1):576.
23. Maddern J, Grundy L, Castro J, Brierley SM. Pain in endometriosis. Front Cell Neurosci. 2020;14:590823.
24. Giudice LC, As-Sanie S, Arjona Ferreira JC, et al. Once-daily oral relugolix combination therapy versus placebo in patients with endometriosis-associated pain: two replicate phase 3 randomized studies. Lancet. 2022;399(10343):2267–2279.