ORIGINAL ARTICLE

Hormonal therapy and peritoneal cytokine profiles in stage III–IV endometriosis: A comparative study of combined oral contraceptives, dienogest, and leuprolide acetate

IRWANTO THENGKANO, SRI RATNA DWININGSIH, RELLY YANUARI PRIMARIAWAN, YETTI HERNANINGSIH

Department of Obstetrics and Gynecology, Dr. Soetomo General Academic Hospital, Faculty of Medicine, Universitas Airlangga, Surabaya, East Java, Indonesia.

ABSTRACT

Background and aim: Endometriosis is a chronic inflammatory disease characterized by ectopic endometrial tissue growth and persistent pelvic inflammation. Hormonal therapy is widely used in advanced disease; however, evidence regarding its differential effects on local peritoneal inflammatory cytokines remains limited. This study aimed to compare the effects of combined oral contraceptives (COCs), dienogest, and leuprolide acetate on peritoneal cytokine profiles in women with stage III–IV endometriosis.

Methods: This non-randomized comparative study included women with surgically confirmed stage III–IV endometriosis who received COCs, dienogest, or leuprolide acetate for 3–8 months prior to surgery, along with a control group without hormonal therapy. Peritoneal fluid samples were collected intraoperatively. Levels of tumor necrosis factor-alpha (TNF-α), interleukin-1β (IL-1β), and interleukin-6 (IL-6) were measured using enzyme-linked immunosorbent assay. Group comparisons were performed using the Kruskal–Wallis test with post hoc analysis.

Results: Significant differences in peritoneal TNF-α levels were observed among groups ($p = 0.023$). Post hoc analysis showed significantly lower TNF-α levels in the COC and dienogest groups compared with controls ($p = 0.004$ and $p = 0.041$, respectively). No significant differences were found in peritoneal IL-1β or IL-6 levels.

Received: 28 December 2025 | Accepted: 28 January 2026

Correspondence: Irwanto Thengkano / Affiliation of author: Department of Obstetrics and Gynecology, Dr. Soetomo General Academic Hospital, Faculty of Medicine, Universitas Airlangga, Surabaya, East Java, Indonesia. Street Jl. Mayjen Prof. Dr. Moestopo number: 6-8. Postal code: 60286, Surabaya, Indonesia / E-mail: irwantothengkano@gmail.com
ORCID: 0009-0006-5635-2306

Conclusions: Hormonal therapy was associated with differences in peritoneal TNF-α levels in women with advanced endometriosis, suggesting a modulatory effect on local inflammatory activity. COCs and dienogest were associated with lower peritoneal TNF-α concentrations compared with no hormonal treatment. These findings should be interpreted cautiously, as causal inference and clinical implications cannot be established from this study. (www.actabiomedica.it)

Key words: endometriosis, hormonal therapy, peritoneal fluid, inflammatory cytokines, TNF-α, dienogest, leuprolide acetate

Introduction

Endometriosis is a chronic gynecological disease that has a profound impact on women's quality of life, including physical, psychological, and social aspects. This disease causes chronic pelvic pain, dysmenorrhea, dyspareunia, indigestion, and pain when urinating, which can interfere with daily activities, work or study performance, and marital relationships. In addition, endometriosis contributes significantly to infertility, up to 20–40% (1,2) through the distortion of the pelvic anatomy and a decrease in oocyte quality, which can lead to emotional distress, family conflicts, and even divorce. In some instances, the disease is also at risk of progressing to malignant tumors of the ovaries. Overall, endometriosis triggers chronic fatigue, immune impairment, and profound anxiety, making it a medical and social challenge that requires comprehensive and ongoing treatment. So far, the approach to endometriosis therapy has been adjusted to the severity of symptoms, the patient's desire to have children, and the response to previous therapy. Medical therapy is generally the first-line choice, especially in mild to moderate cases. The use of non-steroidal anti-inflammatory drugs (NSAIDs) is recommended to manage menstrual pain and pelvic pain(3) and hormonal (4–8). Hormonal therapy aims to suppress estrogen activity, which plays a role in the proliferation of ectopic endometrial tissue (9,10). Available hormonal options include combination oral contraceptives, progestins (such as medroxyprogesterone acetate and dienogest), GnRH agonists with add-back therapy, and aromatase inhibitors for refractory cases. Hormonal therapy aims to suppress estrogen production, reduce stimulation of lesions, and relieve inflammation, reducing pain and slowing down the progression of the disease (9,10). In addition, hormonal therapy is often more accessible and accepted by patients as an effective alternative to non-surgical therapy for symptom management and long-term recurrence prevention. Hormonal therapy is cheap and easy, so it is necessary to research its impact further. The type of therapy used is a combination of oral contraceptives (COC) with two new generation hormonal therapies, namely Dienogest oral 2 mg and Leuprolide acetate injection 3.75 mg. The goal of treatment is to reduce inflammation in endometriosis patients. Focus on reducing inflammation because endometriosis is a chronic inflammatory disease characterized by the activation of the immune system, an increase in immune cells in the peritoneal fluid, and the production of pro-inflammatory cytokines such as TNF-α, IL-1β, and IL-6. This inflammatory process is the primary pathophysiological basis of the symptoms and progression of the disease, including pelvic pain, dysmenorrhea, dyspareunia, and infertility. Chronic inflammation leads to growth and invasion of ectopic endometrial tissue, adhesion formation, and damage to surrounding tissues(11,12). Therefore, lowering inflammation is a key therapeutic strategy in managing endometriosis. Various hormonal therapies, such as COC, Dienogest, and GnRH agonists such as Leuprolide, not only aim to suppress ovulation and estrogen production which fuels the growth of endometriotic tissue but also directly or indirectly decrease the expression of proinflammatory cytokines and inhibit local and systemic inflammatory

processes (9,10). Thus, measuring the decrease in levels of inflammatory cytokines such as IL-1β, IL-6, and TNF-α is a relevant and objective indicator to assess the effectiveness of hormonal therapy against the underlying disease mechanisms. This approach confirms clinical symptom improvement and strengthens the evidence for treatment success. Some key cytokines in endometriosis are IL-1β and TNF-α, which initiate a cascade of cytokines and inflammatory responses. TNF-α, whose concentration increases in the peritoneal fluid of women with endometriosis, plays a role in mediating chronic inflammation as well as immune response, and contributes to disease progression (13–17). IL-6 also contributes to the adhesion process of endometrial cells to the peritoneal cavity and can inhibit the proliferation of endometrial stromal cells. However, in endometriotic lesions, these cells resist the inhibitory effects of IL-6. These cytokines also induce T cell activation and differentiation of B lymphocytes into antibody-producing plasma cells (12,18). Therefore, IL-1β, IL-6, and TNF-α measurements were performed to provide a more comprehensive picture of the dynamics of the local (in peritoneal fluid) and systemic (in serum) inflammatory responses. The selection of these three cytokines represents a major inflammatory pathway relevant to the pathophysiology of endometriosis and is a potential target of hormonal therapy. Thus, although the primary focus of the study was TNF-α, this approach integrates measurements of IL-1β and IL-6 to reinforce the clinical outcomes of the effectiveness of all three types of therapy. This study aimed to evaluate the efficacy of combination oral contraceptive (COC) hormonal therapy, oral Dienogest 2 mg and Leuprolide acetate injection 3.75 mg given to endometriosis patients in lowering levels of the proinflammatory cytokines IL-1β, IL-6, and TNF-α, both systemically (through serum measurement) and locally in the peritoneal fluid.

Method

Study design and participants

This study employed a non-randomized comparative design. Women aged 18–45 years with surgically confirmed stage III–IV endometriosis according to the revised American Society for Reproductive Medicine (rASRM) classification were consecutively recruited. Participants underwent elective surgery at a tertiary referral hospital between October 2023 and runs through July 2024. Eligible participants were allocated into three treatment groups based on the hormonal therapy received prior to surgery, combined oral contraceptives (COCs), dienogest, or leuprolide acetate and a control group that did not receive hormonal therapy. Allocation was determined by clinical indication and patient preference. Patients with autoimmune disease, malignancy, acute infection, pregnancy, or prior hormonal treatment within three months before enrollment were excluded.

Hormonal therapy regimens

Participants received hormonal therapy for 3–8 months prior to surgery. The COC group received a monophasic combined oral contraceptive, the dienogest group received oral dienogest 2 mg daily, and the leuprolide acetate group received depot leuprolide acetate according to standard clinical protocols. No add-back therapy was administered during the treatment period.

Peritoneal fluid collection

Peritoneal fluid samples were collected intraoperatively at the beginning of surgery, prior to extensive manipulation of pelvic organs, to minimize procedural contamination. Samples were aspirated under sterile conditions, centrifuged to remove cellular debris, and stored at −80°C until analysis.

Cytokine measurement

Peritoneal concentrations of tumor necrosis factor-alpha (TNF-α), interleukin-1β (IL-1β), and interleukin-6 (IL-6) were quantified using commercially available enzyme-linked immunosorbent assay (ELISA) kits according to the manufacturers' instructions. All samples were analyzed in duplicate, and mean values were used for statistical analysis.

Statistical analysis

Data distribution was assessed using the Shapiro–Wilk test. Continuous variables were expressed as median (range) or mean ± standard deviation, as appropriate. Differences in cytokine levels among groups were analyzed using the Kruskal–Wallis test, followed by post hoc pairwise comparisons when significant. A p-value < 0.05 was considered statistically significant. Statistical analyses were performed using IBM SPSS Windows version 26.

Result

Baseline demographic and clinical characteristics were generally comparable across the study groups, including age, body mass index, disease stage, pain severity, and laboratory parameters. Although numerical differences in symptom duration were observed, the between-group comparison did not reach statistical significance (Table 1). Therefore, symptom duration was considered descriptively in the interpretation of cytokine findings.

All baseline characteristics were comparable across groups; however, a difference in symptom duration was observed. This variable was considered in the interpretation of cytokine outcomes.

Overall, no statistically significant differences were observed for most cytokines (Table 2), except for peritoneal tumor necrosis factor-alpha (TNF-α). For interleukin-1β (IL-1β), Kruskal–Wallis analysis demonstrated no significant differences among groups in either serum (p = 0.457) or peritoneal fluid (p = 0.509). Consequently, post hoc pairwise comparisons were not performed for IL-1β. Similarly, interleukin-6 (IL-6) levels did not differ significantly between groups in serum (p = 0.834) or peritoneal fluid (p = 0.176), indicating comparable IL-6 profiles across the COC, dienogest, leuprolide acetate, and control groups. In contrast, a significant difference was observed in peritoneal TNF-α levels among groups (Kruskal–Wallis p = 0.023), whereas serum TNF-α levels showed no significant difference (p = 0.457). Post hoc Mann–Whitney analysis revealed significantly lower peritoneal TNF-α levels in the COC group and the dienogest group compared with the control group (p = 0.004 and p = 0.041, respectively). No significant differences were observed

Table 1. Sample Characteristics and Between-Group Homogeneity Test After Data Normality Test in All Groups

Characteristic	COC (N = 10)	Dienogest (N = 10)	Leuprolide acetate (N = 10)	Control (N = 10)	P value
Age (years)	35 (24 - 47)	32 (23 - 41)	31 (25 - 43)	35.5 (25 - 49)	0.506
	34.3 + 6.634	31.7 + 5.417	32.9 + 5.724	36.1 + 8.634	
BMI (kg/m²)	23.55 (18.7 - 28.5)	24.85 (19.1 - 30.8)	22.3 (18.2 - 23.1)	23.8 (20.8 - 31.3)	0.141
	23.67 + 3.419	24.7 + 3.841	21.65 + 1.583	24.16 + 2.954	
VAS Score	7 (5 - 9)	7 (6 - 8)	6.5 (4 - 9)	6 (5 - 8)	0.177
	7.2 + 1.135	7 + 0.816	6.5 + 1.581	6.2 + 0.919	
Duration of Therapy (months)	4 (3 - 6)	4.5 (3 - 7)	4 (3 - 5)	0 (0 - 0)	0.154
	3.9 + 0.994	4.9 + 1.37	4 + 0.816	0 + 0	
Leukosit	8055 (5700 - 10100)	7390 (5910 - 10210)	7250 (5000 - 9830)	8025 (5580 - 18380)	0.777
	7986 + 1292.991	7759 + 1539.917	7392 + 1719.786	8728 + 3709.294	
Paritas 0	9 (90%)	9 (90%)	8 (80%)	7 (70%)	0.592
(n, %) 1	1 (10%)	1 (10%)	2 20%)	3 (30 %)	
Stagging III	4 (40%)	3 (30%)	4 (40%)	5 (50%)	0.841
(n, %) IV	6 (60%)	7 (70%)	6 (60%)	5 (50%)	

Table 2. Recapitulation of cytokine statistical test results

Test Cytokines	Sample Origin	*p–value* (Kruskal-Wallis)	Conclusion	Comparison Between Groups	*p-value* (Mann-Whitney)
IL-1β	Serum	0,457	No difference	_	_
	Peritoneum	0,509	No difference	_	_
IL-6	Serum	0,834	No difference	_	_
	Peritoneum	0,176	No difference	_	_
TNF-α	Serum	0,457	No difference	_	_
	Peritoneum	0,023	There is a Difference	1 *vs* 4	0,004
				2 vs 4	0,041

between the leuprolide acetate group and the control group, nor among the hormonal therapy groups. These findings indicate that differences in inflammatory response associated with hormonal therapy were evident at the local peritoneal level, particularly for TNF-α, while systemic cytokine levels remained comparable across treatment and control groups.

Discussion

Given the complex and heterogeneous nature of endometriosis, biomarker-based findings should be interpreted within a biological framework rather than as direct surrogates of symptom severity or treatment efficacy. This study evaluated the effects of different hormonal therapies on inflammatory cytokine levels in both serum and peritoneal fluid among women with advanced endometriosis. Overall, the results demonstrated that significant differences were limited to peritoneal TNF-α levels, whereas systemic cytokine concentrations and other peritoneal cytokines remained comparable across groups. These findings provide a basis for further discussion regarding the localized inflammatory mechanisms of endometriosis and the potential modulatory effects of hormonal therapy at the peritoneal level. Combined oral contraceptives (COCs) have long been used in clinical practice for the management of endometriosis-related symptoms, particularly dysmenorrhea, due to their relatively favorable tolerability and wide availability compared with other hormonal preparations. Nevertheless, robust evidence supporting the long-term efficacy of COCs in endometriosis remains controversial, as previous studies have reported heterogeneous outcomes and inconsistent symptom control (19,20). The proposed mechanisms of COCs include reduction of menstrual flow, decidualization of endometriotic implants, and suppression of endometriotic cell proliferation, which may indirectly reduce inflammatory stimuli and pain intensity (4,7,21). For these reasons, COCs are often considered a first-line therapeutic option for symptom management rather than a definitive disease-modifying treatment (4,5,7,21,22). The analysis demonstrated that IL-1β and IL-6 levels did not differ significantly among the four groups in either serum or peritoneal fluid. Several factors may explain these findings. Although all three hormonal therapies suppress estrogen activity, their mechanisms do not directly target the complex regulatory pathways responsible for IL-1β and IL-6 production. The synthesis of these cytokines is multifactorial and influenced by the local peritoneal microenvironment, genetic predisposition, immune cell activation, and chronic inflammatory stimuli beyond estrogen dependence. Consequently, IL-1β and IL-6 levels may remain relatively stable despite hormonal suppression. In addition, resistance of endometriotic lesions to hormonal therapy may contribute to persistent cytokine production. Alterations in hormone receptor expression, increased local aromatase activity, and chronic inflammatory signaling within endometriotic tissue may sustain IL-1β and IL-6 synthesis even under estrogen-suppressive conditions. The duration of preoperative hormonal therapy

may also influence cytokine modulation, as insufficient exposure time may limit measurable anti-inflammatory effects. These observations suggest that while hormonal therapy is effective in controlling clinical symptoms, it may not uniformly suppress all proinflammatory cytokines, particularly IL-1β and IL-6. Progestin-based therapy is generally effective in alleviating endometriosis symptoms through ovarian estradiol suppression; however, treatment failure has been reported in a subset of patients. One proposed mechanism is progesterone resistance, characterized by altered progesterone receptor expression, particularly the predominance of progesterone receptor A (PR-A) over progesterone receptor B (PR-B) (23). PR-B normally mediates transcription of anti-inflammatory and antiestrogenic genes, including glycodelin, N-acetylglucosamine-6-O-sulfotransferase, and 17β-hydroxysteroid dehydrogenase type 2 (17βHSD2). Epigenetic modifications such as hypermethylation may suppress PR-B activity, thereby reducing the anti-inflammatory effects of progesterone and allowing continued cytokine production by immune cells within endometriotic lesions (11). Furthermore, serum progestin levels may not accurately reflect drug accumulation or receptor engagement within the peritoneal cavity, limiting their ability to predict local inflammatory responses (24). Among the cytokines evaluated, a significant difference was observed only for peritoneal TNF-α levels. TNF-α is predominantly produced by activated macrophages, natural killer cells, and Th1 lymphocytes and plays a central role in the inflammatory pathophysiology of endometriosis. Elevated TNF-α concentrations in peritoneal fluid have been consistently reported, highlighting its importance in angiogenesis, immune cell recruitment, and lesion survival. Previous studies have suggested an inverse relationship between disease severity and peritoneal TNF-α levels, with higher concentrations observed in earlier stages and relatively lower levels in advanced disease (25). TNF-α also regulates apoptosis and immune homeostasis, contributing to the persistence and progression of endometriotic implants (26). Experimental studies by Kim and colleagues demonstrated that dienogest suppresses endometriotic cell proliferation and viability by inhibiting estradiol-, TNF-α-, IL-1β-, and IL-32–mediated signaling pathways, as well as reducing proliferating cell nuclear antigen (PCNA) expression (27). These findings support the observed reduction in peritoneal TNF-α levels in the dienogest group in the present study after 4–6 months of treatment, reinforcing the potential role of dienogest in modulating local inflammatory activity rather than systemic cytokine concentrations. Interleukin-6 exhibits both proinflammatory and anti-inflammatory properties, making its role in endometriosis complex and difficult to interpret linearly (28). Although elevated peritoneal IL-6 levels have been reported in patients with endometriosis compared with controls (26), no significant differences were observed between treatment groups in this study. The broad biological functions of IL-6 and its involvement in multiple organ systems may contribute to its relative stability despite hormonal intervention. Regulation of apoptosis represents an important therapeutic target in endometriosis. Gonadotropin-releasing hormone analogues have been shown to increase proapoptotic Bax expression and decrease antiapoptotic Bcl-2 expression, leading to regression of endometriotic lesions and reduced inflammatory cytokine production (29). However, in the present study, leuprolide acetate was not associated with significantly lower cytokine levels compared with controls. This finding may reflect differences in treatment duration, timing of cytokine assessment, or variability in individual inflammatory responses (19). Cytokine production in endometriosis is not limited to endometriotic lesions but also involves mesothelial cells and immune cells within the peritoneal cavity. Previous studies have demonstrated a higher CD4/CD8 T-lymphocyte ratio in peritoneal fluid compared with peripheral blood, indicating enhanced local Th1-mediated cytokine production. These findings support the concept that the peritoneal environment in endometriosis favors localized inflammatory activity. These results suggest that hormonal therapies may exert differential effects on local inflammatory pathways in endometriosis, particularly reflected by changes in peritoneal TNF-α levels. However, interindividual variability, hormone receptor expression, and immune regulatory mechanisms should be considered when interpreting treatment response. Further immunological studies are needed to clarify the complex interactions between hormonal modulation, cytokine signaling,

and lesion biology, which may inform the development of more targeted therapeutic strategies (12,30). Several limitations of this study should be acknowledged. First, the non-randomized design with treatment allocation based on clinical indication and patient preference introduces a potential risk of confounding related to symptom severity, disease phenotype, and clinician-driven therapeutic decisions. Consequently, the observed associations between hormonal therapy and cytokine levels cannot be interpreted as causal. Nevertheless, this design reflects routine clinical practice and provides exploratory insights into local inflammatory responses under commonly used hormonal regimens. Second, rASRM stage III–IV endometriosis represents a heterogeneous disease spectrum, including ovarian endometrioma, deep infiltrating lesions, and extensive adhesions; the inability to stratify cytokine profiles according to lesion phenotype may have influenced the observed inflammatory patterns. Third, cytokine measurements were obtained at a single intraoperative time point, precluding assessment of temporal changes and dynamic responses to hormonal therapy. Fourth, the menstrual cycle phase was not standardized in the control group, which may have contributed to cytokine variability; however, all hormonally treated patients were in pharmacologic amenorrhea, partially reducing hormonal fluctuation–related bias in the treatment groups. Fifth, variability in treatment duration prior to surgery may have influenced cytokine modulation, although this reflects real-world clinical practice. Finally, the analysis focused on selected inflammatory cytokines and did not include other immune mediators or hormonal receptor expression, limiting comprehensive immunological interpretation. These limitations warrant cautious interpretation of the findings and underscore the need for larger, prospective studies with longitudinal sampling further to elucidate the immunological effects of hormonal therapy in endometriosis. The absence of add-back therapy in the leuprolide acetate group may limit generalizability to longer treatment durations; however, all patients received short-term preoperative therapy of less than six months, during which add-back therapy is not routinely required. Detailed stratification according to disease phenotype (ovarian endometrioma, deep infiltrating endometriosis, or extensive adhesions), prior surgical history, and infertility or reproductive intent was not performed, as these variables were not systematically recorded for all participants. Exploratory analyses linking cytokine levels with clinically meaningful outcomes, such as pain severity or lesion phenotype, were not performed because the study was not designed or powered to evaluate clinical outcome associations. Accordingly, causal inferences and direct clinical implications cannot be drawn based solely on cytokine measurements.

Conclusion

In women with stage III–IV endometriosis, hormonal therapy was associated with differences in local inflammatory activity, as reflected by peritoneal TNF-α levels, while systemic cytokine concentrations remained comparable across treatment and control groups. Combined oral contraceptives and dienogest were associated with lower peritoneal TNF-α levels compared with no hormonal therapy, whereas leuprolide acetate did not demonstrate a significant difference. These findings support the concept that inflammatory modulation in endometriosis is predominantly localized to the peritoneal environment and may vary according to hormonal regimen. Accordingly, causal inferences and direct clinical implications cannot be drawn based solely on cytokine measurements, and further longitudinal studies integrating clinical outcomes are warranted.

Ethic approval: This study has obtained ethical clearance from the Health Research Ethics Committee (KEPK) of Dr. Soetomo General Hospital, Surabaya, with approval number 0802/KEPK/X/2023.

Conflict of interest: Each author declares that he or she has no commercial associations (e.g. consultancies, stock ownership, equity interest, patent/licensing arrangement etc.) that might pose a conflict of interest in connection with the submitted article.

Authors contribution: All authors contributed equally to the conceptualization, design, analysis, and preparation of this manuscript. IT prepared the initial draft and coordinated data collection. SRD, RYP and YH provided academic supervision, critical review, and final approval of the manuscript. All authors have read and agreed to the final version of the manuscript.

Declaration on the use of AI: None.

Acknowledgments: We extend our gratitude to the Obgyn Polyclinic team at FER, the Gynecology Outpatient Clinic team, the Gynecologic Operating Room team at RSUD Dr. Soetomo, the Clinical Pathology Immunology Laboratory team at RSUD Dr. Soetomo, Surabaya, Indonesia.

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