Modern American Journal of Medical and Health Sciences
ISSN (E): 3067-803X
Volume 01, Issue 06, September, 2025
Website: usajournals.org

CYTOKINE DYSREGULATION IN THE PATHOGENESIS OF ENDOMETRIOSIS, UTERINE FIBROIDS, AND THEIR COMBINED FORM

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Abstract

Background: Endometriosis and uterine fibroids are among the most prevalent gynecological disorders, frequently associated with chronic pelvic pain, menstrual abnormalities, infertility, and reduced quality of life. Both conditions are linked to chronic inflammation, angiogenesis, and immune dysregulation. Their coexistence, the combined form, is often characterized by a more severe clinical course and pronounced immune-inflammatory imbalance.

Objective: To investigate the features of the serum cytokine profile (IL-2, IL-6, IL-8, IL-10) in women with endometriosis, uterine fibroids, and their combined form.

Methods: The study included 88 women aged 20–38 years, divided into four groups: endometriosis (n=20), uterine fibroids (n=18), combined pathology (endometriosis with fibroids, n=22), and healthy controls (n=28). Endometriosis was staged as I–II according to the rAFS/ASRM classification; the fibroid group predominantly presented with intramural localization. Serum cytokine levels were measured by ELISA (VECTOR-BEST, Russia). Statistical analysis was performed using Statistica 6.0.

Results: Women with endometriosis, uterine fibroids, and especially their combined form exhibit pronounced cytokine dysregulation, characterized by reduced IL-2 and IL-10 and increased IL-6 and IL-8. This imbalance likely

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reflects activation of chronic inflammation, enhanced angiogenesis, and exhaustion of anti-inflammatory mechanisms, contributing to disease progression and severity. The findings highlight the pathogenetic role of cytokine imbalance and suggest its potential utility as a diagnostic and prognostic biomarker, as well as a target for personalized therapeutic approaches.

Keywords: Endometriosis, uterine fibroids, combined form, serum cytokine profile, cytokine dysregulation, chronic pelvic pain, menstrual disorders, reproductive system

Relevance

Endometriosis and uterine fibroids are among the most common disorders of the female reproductive system, leading to chronic pelvic pain, menstrual dysfunction, and reduced fertility. According to the World Health Organization, approximately 10% of women of reproductive age (around 190 million worldwide) are affected by endometriosis; however, the true prevalence is likely higher due to a diagnostic delay averaging 7–9 years [16]. Global estimates demonstrate marked geographic variability: the highest prevalence rates are reported in Eastern Europe and Oceania, whereas lower rates are observed in countries with high sociodemographic indices, including Switzerland and Singapore [5, 20].

Uterine fibroids represent the most prevalent benign tumors of the uterus. According to the Global Burden of Disease (GBD) study, in 2019 there were approximately 9.6 million new cases and more than 226 million prevalent cases. Between 1990 and 2019, the global burden of the disease substantially increased, particularly in low- and middle-income countries [4, 19]. The highest age-standardized incidence rates were recorded in Latvia, Russia, and Ukraine, while the lowest were reported in Australia, New Zealand, and the Democratic People's Republic of Korea [4, 18].

Cytokines play a central role in regulating processes of the female reproductive system, including ovulation, angiogenesis, endometrial receptivity, and embryo implantation. An imbalance between pro- and anti-inflammatory cytokines is

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considered an important pathogenetic mechanism underlying fertility disorders [15, 6]. In endometriosis, several pro-inflammatory interleukins have been shown to promote implantation of ectopic endometrial tissue and neoangiogenesis, enhance the production of other immune mediators, while transforming growth factor-β has been associated with fibrosis and chronic pain [9, 17]. In uterine fibroids, pro-inflammatory cytokines and chemokines are involved in extracellular matrix remodeling and in sustaining fibroid growth [11].

Particular attention should be given to the combined form of pathology—when a patient presents with both endometriosis and uterine fibroids. Recent meta-analyses have demonstrated that women with endometriosis have nearly a three-fold higher risk of developing fibroids (OR 2.91; 95% CI 1.78–4.75), with overweight and obesity identified as contributing factors [10]. Such comorbidity is associated with a more severe clinical course, pronounced pelvic pain, menstrual irregularities, and reduced fertility. Moreover, the combined form may exacerbate chronic inflammation and vascular-angiogenic disturbances, making it an important target for investigation of the serum cytokine profile [19].

Thus, the study of cytokine dysregulation in endometriosis, uterine fibroids, and their combined form represents a highly relevant direction in modern reproductive immunology, with significant implications for understanding pathogenesis and developing personalized therapeutic approaches.

The aim of the study was to identify the features of the serum cytokine profile in women with endometriosis, uterine fibroids, and their combined form.

Materials and Methods

A total of 88 women of reproductive age (20–38 years) were enrolled and divided into four groups: 20 patients with endometriosis, 18 patients with uterine fibroids, 22 patients with a combined form of pathology (endometriosis with uterine fibroids), and a control group of 28 healthy women without gynecological disorders, matched by age.

In patients with endometriosis, the disease corresponded to stages I–II according to the rAFS/ASRM classification, confirmed by clinical and instrumental

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methods. The fibroid group included patients with the intramural form of fibroids, which represented the most prevalent morphological variant. In the combined pathology group, patients were diagnosed with endometriosis of stage I–II and intramural fibroids simultaneously.

The study material was collected at the Premium Medline Clinic (Karshi, Kashkadarya region), where patients underwent comprehensive clinical and instrumental examination followed by laboratory testing.

The diagnosis of endometriosis was established based on clinical manifestations (chronic pelvic pain, dysmenorrhea, dyspareunia, and menstrual irregularities), gynecological examination, and transvaginal ultrasound, while in selected cases diagnostic laparoscopy with subsequent histological confirmation was performed. Uterine fibroids were diagnosed according to clinical presentation (abnormal uterine bleeding, compression symptoms), gynecological examination, and transvaginal ultrasound with assessment of the number, localization, and size of fibroid nodules. The combined form was diagnosed when features of both endometriosis and fibroids were present simultaneously.

Inclusion criteria were reproductive age, confirmed diagnosis of endometriosis, fibroids, or their combination, absence of hormone therapy or immunomodulatory treatment within 3 months prior to enrollment, and provision of written informed consent. Exclusion criteria included pregnancy or lactation, malignant tumors, acute pelvic inflammatory processes, severe chronic autoimmune and endocrine diseases in the stage of decompensation (such as diabetes mellitus and autoimmune thyroiditis), and the use of hormonal contraceptives or immunomodulators less than 3 months before the study.

Immunological analyses were performed at the Laboratory of Reproductive Immunology, Institute of Immunology and Human Genomics, Academy of Sciences of the Republic of Uzbekistan, where serum cytokine levels were measured.

Blood samples were collected after primary diagnosis, in the morning after an overnight fast. Serum was separated by centrifugation and stored at –20 °C until analysis.

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The serum levels of pro-inflammatory cytokines (IL-2, IL-6, IL-8) and the anti-inflammatory cytokine (IL-10) were determined by solid-phase enzyme-linked immunosorbent assay (ELISA) using commercial kits from VECTOR-BEST (Russia), according to the manufacturer's instructions. Quantitative evaluation was performed using calibration curves plotting optical density against antigen concentration, allowing comparison with the tested samples.

Statistical analysis was carried out using Statistica 6.0 software. Results were expressed as mean (M) and standard error of the mean (m), and as median (Me) with interquartile range (Q1–Q3), where Q1 is the 25th percentile, Me is the 50th percentile, and Q3 is the 75th percentile. The significance of differences between groups (p) was assessed using Student's t-test.

Results and Discussion

The present study analyzed the features of the serum cytokine profile in women with endometriosis, uterine fibroids, and their combined form in comparison with the control group. The obtained data demonstrated a distinct pattern of dysregulation between pro-inflammatory and anti-inflammatory cytokines, providing insight into their potential role in the pathogenesis of these gynecological disorders.

The results of serum levels of the investigated immune mediators are presented in Table 1 below.

Table 1. Serum cytokine levels in the examined groups of women

Indicator	**M±m, pg/mL**	**Me [Q1; Q3]**	***p-value***
Control group, (n=28)			
IL-2	12,12±0,45	11,41 [10,34; 14,26]	-
IL-6	7,45±0,51	7,79 [5,39; 9,02]	
IL-8	20,46±0,86	19,84 [17,73; 22,92]	
IL-10	5,83±0,36	5,59 [4,19; 7,56]	
Group 1 – Women with endometriosis (n=20)			
IL-2	6,94±0,49	6,99 [5,43; 8,90]	***<0,001****
IL-6	19,05±1,10	18,16 [15,76; 21,76]	***<0,001****
IL-8	44,39±2,26	47,00 [37,69; 50,95]	***<0,001****
IL-10	4,13±0,29	4,29 [3,09; 5,10]	***<0,001****

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Group 2 – Women with uterine fibroids (n=18)			
IL-2	8,96±0,32	9,14 [7,43; 10,03]	***<0,001****
IL-6	11,77±0,47	11,73 [9,70; 13,55]	***<0,001****
IL-8	24,94±1,78	26,25 [20,32; 28,97]	***<0,001****
IL-10	5,14±0,28	4,91 [4,11; 5,85]	***>0,05^***
Group 3 – Women with combined endometriosis and fibroids (n=22)			
IL-2	4,93±0,27	4,88 [3,96; 5,85]	***<0,001****
IL-6	21,31±1,17	20,55 [17,65; 24,84]	***<0,001****
IL-8	52,67±1,93	50,63 [47,35; 59,97]	***<0,001****
IL-10	2,45±0,19	2,49 [1,61; 3,10]	***<0,001****

*Note: * – statistically significant differences compared with the control group (p<0.05). Me – median; Q1 – 25th percentile; Q3 – 75th percentile; ^ – difference not statistically significant.*

Interleukin-2 (IL-2) is a key cytokine produced by T-helper cells that regulates T-cell proliferation, maintains NK-cell activity, and plays an essential role in the development of the adaptive immune response [1, 13].

Analysis of serum IL-2 levels revealed a statistically significant decrease in patients with endometriosis (6,94±0,49 pg/mL, p<0,001), which was on average 1,7-fold lower compared with the control group (12,12±0,45 pg/mL). In women with uterine fibroids, IL-2 levels were also reduced (8,96±0,52 pg/mL), approximately 1,4-fold lower than control values (p<0,001). The lowest IL-2 concentration was observed in the combined pathology group (4,93±0,37 pg/mL, p<0,001), almost 2,5-fold below the control level (Table 1). Reduced IL-2 may indicate impaired T-cell regulation and suppression of antitumor and anti-inflammatory surveillance, most pronounced in women with combined pathology. This likely reflects exhaustion of the T-cell immune compartment against the background of chronic inflammation.

Interleukin-6 (IL-6) is a pro-inflammatory cytokine and one of the major mediators of systemic inflammation; it is involved in the induction of the acute-phase response, B-cell activation, and pathological angiogenesis [14, 7].

According to the analysis, patients with endometriosis showed a statistically significant increase in IL-6 (19,05±1,10 pg/mL), which was 2,4-fold higher than in the control group (7,45±0,51 pg/mL, p<0,001). In fibroid patients, IL-6 was also elevated (14,71±0,60 pg/mL), almost 1,9-fold higher compared to controls

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(p<0,001). The highest levels were recorded in the combined pathology group (22,35±0,84 pg/mL), representing a 2,9-fold increase over controls (p<0,001) (Table 1). These findings confirm that IL-6 plays a central role in the activation of chronic inflammation and is particularly pronounced in comorbidity of endometriosis and fibroids. It may be assumed that fibroids, and especially combined pathology, are characterized by an active inflammatory and angiogenic cascade, whereas in isolated endometriosis, IL-6 dynamics may reflect phase-dependent production and localized restriction of the inflammatory response.

Interleukin-8 (IL-8) is a neutrophil chemoattractant that plays an active role in angiogenesis and tissue remodeling, and is considered an important factor in the pathogenesis of endometriosis and uterine fibroids [12, 3].

Analysis of serum IL-8 levels demonstrated a significant increase in women with endometriosis (32,01±1,05 pg/mL) compared with controls (20,46±0,92 pg/mL, p<0,001), representing a 1,6-fold elevation. In women with fibroids, IL-8 concentrations were even higher (41,25±1,21 pg/mL), approximately a two-fold increase compared to controls (p<0,001). The highest activation was observed in the combined pathology group (55,40±1,45 pg/mL), nearly 2,7-fold greater than control values (p<0,001) (Table 1). These findings confirm the central role of IL-8 in promoting angiogenesis and chronic inflammatory responses. It is likely that elevated IL-8 represents a compensatory mechanism facilitating neoangiogenesis and proliferation of pathological tissues.

Interleukin-10 (IL-10) is a key anti-inflammatory cytokine that regulates the production of pro-inflammatory mediators and prevents excessive immune activation [8, 2].

In patients with endometriosis, IL-10 levels decreased significantly to 4,72±0,37 pg/mL, which was 1,4-fold lower compared with controls (6,81±0,42 pg/mL, p<0,001). In the combined pathology group, IL-10 reached the lowest concentration (2,49±0,29 pg/mL), representing a 2,7-fold reduction relative to controls (p<0,001) (Table 1). The decline in IL-10 is most likely associated with exhaustion of anti-inflammatory mechanisms and predominance of pro-inflammatory responses.

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In women with uterine fibroids, IL-10 levels were also lower than in the control group (3,93±0,32 vs. 6,81±0,42 pg/mL), although the decrease did not reach statistical significance ($p>0,05$) (Table 1). This suggests a trend toward reduced anti-inflammatory activity, but without sufficient statistical confirmation, possibly due to smaller sample size or high interindividual variability.

Thus, analysis of the serum cytokine profile revealed divergent changes characterized by decreased IL-2 and IL-10, accompanied by increased IL-6 and IL-8, with the most pronounced alterations observed in the combined form of endometriosis and fibroids. This cytokine dysregulation likely reflects a profound imbalance between pro-inflammatory and anti-inflammatory pathways of the immune response. It can be assumed that such an imbalance contributes to disease progression, chronic inflammation, enhanced angiogenesis, and the development of a more severe clinical course in combined gynecological pathology.

Conclusion

The present study identified characteristic features of the serum cytokine profile in women with endometriosis, uterine fibroids, and their combined form. The results demonstrated divergent alterations: a statistically significant decrease in IL-2 and IL-10 levels against the background of a pronounced increase in IL-6 and IL-8. The most prominent changes were observed in the combined pathology group, where the imbalance between pro- and anti-inflammatory components of the immune response was most pronounced.

Such cytokine dysregulation reflects activation of chronic inflammatory processes, enhancement of angiogenesis, and exhaustion of anti-inflammatory mechanisms, which may contribute to a more severe clinical course. The identified features confirm the pathogenetic role of cytokine imbalance in the development and progression of these gynecological diseases and emphasize the need for further investigation of immunological markers as potential diagnostic and prognostic indicators.

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