American Journal of Medicine and Medical Sciences 2026, 16(5): 2655-2657
DOI: 10.5923/j.ajmms.20261605.81

Interleukin-6 and Interleukin-8 as Potential Biomarkers of Endometrial Instability in Ovulatory Abnormal Uterine Bleeding Associated with Undifferentiated Connective Tissue Dysplasia

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Abstract Background. Ovulatory abnormal uterine bleeding (AUB-O) remains one of the most common gynecological disorders affecting reproductive-aged women. Recent studies suggest that inflammatory cytokines may contribute to endometrial instability and impaired vascular regulation. However, the role of interleukin-6 (IL-6) and interleukin-8 (IL-8) in AUB-O associated with undifferentiated connective tissue dysplasia (UCTD) remains insufficiently investigated. Objective. To evaluate serum levels of IL-6 and IL-8 in women with AUB-O associated with UCTD and assess their potential role as biomarkers of endometrial dysfunction. Materials and Methods. The study included reproductive-aged women divided into three groups: patients with AUB-O associated with UCTD, patients with AUB-O associated with polycystic ovary syndrome (PCOS), and healthy controls. Clinical assessment, pelvic ultrasonography, and enzyme-linked immunosorbent assay (ELISA) for IL-6 and IL-8 were performed. Results. Women with AUB-O associated with UCTD demonstrated significantly elevated serum IL-6 and IL-8 levels compared with healthy controls. The increase in cytokine levels was associated with prolonged menstrual bleeding, signs of endometrial instability, and chronic inflammatory activation. Conclusion. Elevated IL-6 and IL-8 levels may reflect inflammatory and vascular disturbances in AUB-O associated with UCTD. These cytokines could be considered promising biomarkers for personalized diagnostic and therapeutic approaches.

Keywords Abnormal uterine bleeding, Ovulatory dysfunction, IL-6, IL-8, Cytokines, Inflammation, Angiogenesis, Endometrium, Connective tissue dysplasia, Biomarkers, Precision gynecology, UCTD

1. Introduction

Abnormal uterine bleeding (AUB) is one of the leading causes of gynecological consultations among reproductive-aged women and significantly affects quality of life, reproductive health, and psychosocial well-being [1,2]. According to the FIGO PALM-COEIN classification, ovulatory dysfunction-related abnormal uterine bleeding (AUB-O) belongs to the group of non-structural causes of menstrual disorders [1].

Recent evidence suggests that inflammatory pathways play an important role in the development of endometrial dysfunction in women with AUB-O [2,6]. Cytokines regulate immune responses, vascular permeability, angiogenesis, tissue remodeling, and endometrial repair [6,7]. Disturbances in these mechanisms may lead to prolonged or recurrent uterine bleeding [8].

Among numerous inflammatory mediators, interleukin-6 (IL-6) and interleukin-8 (IL-8) are considered particularly important due to their involvement in chronic inflammatory activation and vascular instability [6,7]. IL-6 participates in systemic inflammatory responses and modulation of endometrial immune activity, whereas IL-8 contributes to neutrophil chemotaxis and increased vascular permeability [7,10].

Undifferentiated connective tissue dysplasia (UCTD) is characterized by structural abnormalities of connective tissue, impaired collagen synthesis, vascular fragility, and microcirculatory disturbances. These changes may aggravate endometrial instability and influence the severity of uterine bleeding [8,10].

Despite growing interest in inflammatory mechanisms of AUB-O, the role of IL-6 and IL-8 in patients with AUB-O associated with UCTD remains insufficiently explored.

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Received: Apr. 20, 2026; Accepted: May 15, 2026; Published: May 27, 2026
Published online at http://journal.sapub.org/ajmms

The aim of the study was to evaluate serum IL-6 and IL-8 levels in women with AUB-O associated with UCTD and assess their significance as potential biomarkers of endometrial instability.

2. Materials and Methods

The study was conducted at the Department of Obstetrics and Gynecology No. 2 of Andijan State Medical Institute.

Women of reproductive age were enrolled in the study and divided into three groups. The main group included patients diagnosed with AUB-O associated with UCTD. The comparison group consisted of women with AUB-O associated with polycystic ovary syndrome without signs of connective tissue dysplasia. Healthy women without gynecological pathology formed the control group.

Clinical examination included assessment of menstrual history, gynecological status, and ultrasonographic evaluation of pelvic organs. Signs suggestive of UCTD were identified according to clinical phenotypic criteria.

Venous blood samples were collected under standard laboratory conditions. Serum levels of IL-6 and IL-8 were determined using enzyme-linked immunosorbent assay (ELISA). Blood serum samples were stored at −20 ℃ before analysis.

Statistical analysis was performed using SPSS and Statistica 6.0 software packages. Quantitative variables were expressed as mean values and standard errors. Statistical significance was considered at $p<0.05$.

3. Results

Women with AUB-O associated with UCTD more frequently reported prolonged menstrual bleeding, intermenstrual spotting, fatigue, and symptoms suggestive of chronic iron deficiency.

Clinical manifestations of connective tissue dysplasia included joint hypermobility, varicose veins, skin striae, and autonomic dysfunction.

Ultrasonographic examination demonstrated functional endometrial abnormalities without evidence of structural uterine pathology. In several patients, reduced endometrial thickness and heterogeneous endometrial structure were observed.

Serum IL-6 and IL-8 levels were significantly elevated in women with AUB-O associated with UCTD compared with healthy controls.

Increased IL-6 levels indicated activation of inflammatory pathways and persistent immune dysregulation within the endometrium. Elevated IL-8 levels reflected enhanced inflammatory cell recruitment and increased vascular permeability.

Patients with more severe and prolonged bleeding episodes demonstrated higher cytokine concentrations, suggesting a relationship between inflammatory activation and endometrial instability.

Women with AUB-O associated with PCOS also demonstrated elevated cytokine levels; however, these changes were less pronounced than in patients with UCTD.

The obtained findings support the hypothesis that inflammatory imbalance contributes to vascular dysfunction and impaired endometrial repair mechanisms in AUB-O associated with connective tissue dysplasia, which is consistent with previously published data [6,10]

4. Discussion

The results of the present study confirm the important role of inflammatory cytokines in the pathogenesis of ovulatory abnormal uterine bleeding [2,6].

Elevated IL-6 and IL-8 levels observed in women with AUB-O associated with UCTD indicate persistent inflammatory activation and vascular instability within the endometrium. Similar findings have been described in previous studies investigating inflammatory mechanisms of menstrual disorders and impaired endometrial repair [6,7,10].

IL-6 is known to regulate inflammatory signaling and endothelial function, whereas IL-8 contributes to leukocyte migration and increased vascular permeability [7]. Excessive expression of these cytokines may impair normal endometrial regeneration and promote abnormal bleeding [2,6].

The presence of connective tissue dysplasia may additionally aggravate vascular fragility and microcirculatory dysfunction, leading to a more severe clinical course of AUB-O [8].

The study findings suggest that IL-6 and IL-8 may serve as potential biomarkers of inflammatory endometrial instability and could be useful for the development of personalized diagnostic and therapeutic strategies.

5. Conclusions

Women with AUB-O associated with UCTD demonstrate significantly elevated serum IL-6 and IL-8 levels compared with healthy controls.

Increased cytokine expression reflects inflammatory activation, vascular instability, and impaired endometrial repair processes.

IL-6 and IL-8 may be considered promising biomarkers for evaluating inflammatory phenotypes of AUB-O and developing personalized management approaches in reproductive-aged women.

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