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PROINFLAMMATORY CYTOKINES IN THE PATHOGENESIS AND STROMAL REMODELING OF UTERINE LEIOMYOMAS (A LITERATURE REVIEW)

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Introduction

Uterine leiomyomas/fibroids (leiomyomas, UFs) represent the most prevalent benign tumors of the female reproductive system and constitute a major cause of menorrhagia, pelvic pain, anemia, reduced quality of life, and infertility among women of reproductive age. According to recent reviews, by the age of 50, ultrasound or histological evidence of fibroids is found in approximately 70% of women, with a prevalence exceeding 80% in African American women at the time of menopause [43]. The incidence of uterine fibroids increases with age, particularly in the 35–49-year age group [49, 24].

At the population level, this translates into a significant healthcare burden, encompassing conservative, minimally invasive, and surgical treatment options, and is accompanied by substantial economic costs. Fibroids account for a considerable proportion of abnormal uterine bleeding (AUB) cases [4, 36]. On an individual level, between 25% and 50% of women with fibroids experience symptoms such as heavy menstrual bleeding, pelvic pain, and pressure-related complaints. Approximately 30% of working-age women miss work due to fibroid-related symptoms or surgical interventions [29, 43]. A national survey revealed that 28% of employed women with symptomatic fibroids reported absenteeism from work, while 66% expressed concern that the disease limited their career potential [43, 5].

According to data from the Global Burden of Disease (GBD) study, the global incidence of uterine fibroids has been steadily increasing over the past decades. In 2019 alone, an estimated 9.64 million new cases were registered across 204 countries and territories. Rates of incidence, prevalence, and years lived with disability (YLDs) continue to rise, whereas mortality remains low. The most rapid increases are observed in regions with low and low-middle Socio-Demographic Index (SDI), while high-SDI countries show stabilization or slower growth trends. The greatest burden

in terms of prevalence and disability-adjusted life years (DALYs) is observed in the 35–49 age group [11, 25, 9]. These findings underscore the persistent relevance of uterine fibroids as a global public health challenge, particularly in resource-limited settings across all WHO regions.

In recent years, scientific attention has increasingly shifted toward the immuno-inflammatory mechanisms underlying the development of uterine leiomyomas. Chronic low-grade inflammation, along with an imbalance of proinflammatory cytokines, chemokines, and growth factors, is now regarded as a pivotal component of pathogenesis that shapes the clinical course of the disease and provides a rationale for personalized diagnostic and therapeutic strategies [49, 36]. However, the absence of standardized biomarker panels and a lack of consensus on diagnostic criteria currently limit the integration of immune and cytokine markers into routine clinical practice.

Therefore, the investigation of immune and cytokine profiles in patients with uterine fibroids is of critical importance for the development of novel approaches to early diagnosis, risk stratification, and personalized therapy.

The aim of this review article is to synthesize and systematize current evidence on the role of key proinflammatory cytokines in the pathogenesis and tissue remodeling processes associated with uterine leiomyomas.

Methodology for Literature Search and Selection. To achieve this objective, a targeted literature search and analytical review of scientific publications were conducted, focusing on the immunological aspects of uterine fibroid pathogenesis, clinical manifestations, and diagnostic approaches. The review includes data from peer-reviewed international and national journals indexed in PubMed, Scopus, Web of Science, eLibrary, and CyberLeninka.

Keywords and their combinations in both English and Russian were used: “uterine fibroids”, “uterine myomas”, “myomatous tumors”, “leiomyoma”, “immune markers”, “cytokines”, “interleukins”, “interferons”, “tumor necrosis factor”, “proinflammatory cytokines”, as well as «миома матки», «лейомиома», «иммунные маркеры», «цитокины», «интерлейкины», «интерфероны», «фактор некроза опухолей», «провоспалительные цитокины».

Priority was given to publications from the last 10 years, with special attention paid to systematic reviews, meta-analyses, large-scale cohort studies, and original articles with high levels of evidence. In addition, up-to-date clinical guidelines and consensus statements from major professional societies (e.g., ESHRE, ASRM, Endocrine Society, Russian Association of Human Reproduction – RAHR) were reviewed. This

comprehensive approach enabled the integration of basic and clinical data into a unified pathogenetic framework and facilitated a holistic understanding of the immunological mechanisms involved in the development of uterine leiomyomas in the context of personalized medicine.

Cytokines and Proinflammatory Signaling in Gynecological Disorders

Cytokines constitute a heterogeneous group of low-molecular-weight protein mediators that regulate intercellular communication, cell growth, differentiation, and the functional activity of immune cells and target tissues. This group includes interleukins (ILs), interferons (IFNs), tumor necrosis factors (TNFs), chemokines, and growth factors. Cytokines exert their effects through binding to specific receptors and activating intracellular signaling cascades—such as JAK/STAT, NF-κB, and MAPK—forming complex networks that integrate innate and adaptive immune responses [15, 47].

Under physiological conditions, cytokines are essential for maintaining homeostasis, antimicrobial defense, tissue repair, and regulation of reproductive function. However, dysregulation of cytokine production or signaling can result in chronic inflammation, imbalanced cellular and humoral immunity, angiogenesis, and fibrosis, thereby contributing to the pathogenesis of various gynecological disorders, including uterine fibroids, endometriosis, and ovarian dysfunction [48, 41].

Recent research highlights that distinct cytokine profiles—involving proinflammatory, anti-inflammatory, and Th1/Th2/Th17-associated cytokines—not only reflect the underlying immunopathogenesis but also serve as potential diagnostic and prognostic biomarkers for disease activity and therapeutic response [49, 31].

Proinflammatory cytokines represent a class of mediators that initiate and sustain inflammatory responses, regulate activation of both innate and adaptive immunity, and influence proliferation, migration, and differentiation of target cells. They are predominantly synthesized by macrophages, dendritic cells, T lymphocytes, natural killer (NK) cells, and stromal cells in response to microbial products, stress signals, or tissue injury. Through engagement with specific receptors, these cytokines activate intracellular cascades—NF-κB, MAPK, JAK/STAT—which in turn upregulate the expression of acute phase proteins, chemokines, adhesion molecules, matrix metalloproteinases (MMPs), and growth factors [15, 47].

Functionally, proinflammatory cytokines mediate leukocyte recruitment, increased vascular permeability, endothelial activation, and remodeling of the extracellular matrix. In the context of chronic or dysregulated release, they drive persistent low-grade inflammation, angiogenesis, and fibrosis, processes that are critical in the

pathogenesis of gynecological conditions such as leiomyoma, endometriosis, and ovarian dysfunction [48, 40].

Interleukin-1β (IL-1β) is a key proinflammatory cytokine of the IL-1 family, produced by monocytes, macrophages, dendritic cells, as well as endometrial and myometrial cells. It plays a pivotal role in cellular infiltration, angiogenesis, and tissue remodeling [15, 33].

In the context of uterine fibroids, IL-1β is regarded as a central mediator of chronic inflammation. According to de Mezer et al. (2025), the median IL-1β concentration in the fibroid core was 912,6 vs. 1957,1 arbitrary units in control myometrium (approximately 0,47×, a ~53% decrease; p=0,001). In the fibroid periphery, IL-1β levels were 1477,8 vs. 1957,1, with the difference being statistically non-significant (~0,76×). IL-1β levels showed a positive correlation with NF-κB expression (r=0,32; p=0,022), indicating its involvement in local proinflammatory activity and extracellular matrix (ECM) remodeling [26].

This localized attenuation of IL-1β expression in the fibroid core may reflect the unique characteristics of the microenvironment, such as hypoxia or immune exhaustion, while proinflammatory activity is shifted toward the fibroid periphery—where active growth and remodeling are more prominent. Systemic alterations in IL-1β are generally modest, emphasizing the primarily localized dysregulation of this cytokine. Clinically, this aligns with the observation that fibroid-related symptoms (e.g., heavy menstrual bleeding, pelvic pain, infertility) are primarily driven by local trophic changes and inflammation in the myometrium and endometrium, rather than persistent systemic cytokinemia [33, 45].

Studies of the fibroid microenvironment also highlight the ability of IL-1β to stimulate the production of vascular endothelial growth factor (VEGF) and activate matrix metalloproteinases (MMPs), thereby promoting angiogenesis and ECM accumulation [38]. Moreover, IL-1β has been implicated in the upregulation of prostaglandins and cyclooxygenase-2 (COX-2), which may underlie the pathophysiological mechanisms of menorrhagia and pelvic pain in women with fibroids [45].

Interleukin-2 (IL-2) is a key Th1-type cytokine, secreted predominantly by activated $CD4^+$ and $CD8^+$ T lymphocytes. Through engagement with the IL-2 receptor (IL-2Rα/β/γc), it activates JAK1/3–STAT5 signaling pathways, promotes T cell proliferation, maintains regulatory T cell (Treg) homeostasis, enhances natural killer (NK) cell activity, and stimulates IFN-γ synthesis, thereby orchestrating the balance of Th1/Th2 responses. IL-2 deficiency impairs cytotoxic immunity and increases tissue tolerance [27, 6].

A targeted literature search yielded only one quantitative study reporting IL-2 levels in the context of uterine fibroids. In the study by Demir et al. (2019), IL-2 concentration in endometrial splash fluid was significantly lower in women with fibroids (282,9 ± 70,2 ng/mL) compared to controls (416,0 ± 123,4 ng/mL), reflecting a ~1.47-fold decrease (~0,68×; p=0,0002). Clinically, this reduction may be associated with reduced endometrial receptivity, which may negatively impact fertility outcomes [13]. Notably, few studies in the past decade have reported IL-2 dynamics in fibroid pathology with clear fold-changes, underscoring a major gap in current data and the need for further quantitative investigations linked to clinical scoring systems.
Interleukin-6 (IL-6) is a multifunctional cytokine produced by macrophages, T lymphocytes, endothelial, and stromal cells. Upon binding to the IL-6R/gp130 receptor complex, it activates JAK/STAT-3 and MAPK/ERK pathways, driving acute phase protein synthesis, B-cell differentiation, angiogenesis, and ECM remodeling. Chronic overproduction of IL-6 is associated with inflammation, fibrosis, and tumorigenesis [22, 46].
In uterine fibroids, IL-6 is considered a major proinflammatory mediator. In vitro models have demonstrated that IL-6 exposure leads to activation of the JAK/STAT-3 pathway in leiomyoma cells, resulting in over two-fold increases in collagen-1 and fibronectin expression, thereby highlighting its profibrotic role in fibroid growth [19]. In a clinical study by Adediji et al. (2019), serum IL-6 levels were significantly elevated in fibroid patients (352,6 ± 39,7 pg/mL) compared to healthy controls (233,5 ± 43,6 pg/mL), representing a ~1,5-fold increase ($p < 0,05$). This elevation was associated with dyslipidemia and increased obesity indices, suggesting that systemic IL-6 levels may reflect low-grade chronic inflammation linked to metabolic risk factors in women with fibroids [1].
This supports the hypothesis that elevated systemic IL-6 may reflect metabolic-inflammatory comorbidities (e.g., obesity, dyslipidemia) rather than fibroid-specific microenvironmental activity. The functional role of IL-6 in the fibroid microenvironment remains potentially indirect or mediated by downstream effectors. In support of this, Malik et al. (2019) demonstrated that IL-6 exposure in cultured fibroid cells increased collagen-1 expression by ~1,9-fold after 3 hours of stimulation, implicating IL-6 as a driver of fibrotic remodeling via STAT3 activation [28]. Conversely, in the study by de Mezer et al. (2025), IL-6 levels in fibroid tissue (both core and periphery) did not differ significantly from those in control myometrium ($p > 0,05$), suggesting that local IL-6 upregulation may not be a consistent feature of leiomyoma pathophysiology [12].

Interleukin-17 (IL-17, primarily IL-17A) is a pro-inflammatory cytokine associated with Th17-type immune responses. It is predominantly secreted by Th17 cells, γδ-T cells, and innate lymphoid cells. Upon binding to the IL-17RA/RC receptor complex, IL-17A activates downstream NF-κB, MAPK, and ACT1 signaling pathways, inducing the expression of IL-6, TNF-α, G-CSF, CXCL1, CXCL8/IL-8, matrix metalloproteinases, and VEGF. These mediators collectively contribute to neutrophil recruitment, angiogenesis, extracellular matrix (ECM) remodeling, and chronic inflammation [23, 3].

In a study by Mohamed et al., seasonal variability of the cytokine profile was observed in women with uterine fibroids, with higher levels of IL-17 and IL-13 in winter compared to controls, alongside a reduction in IP-10. This pattern reflects a pro-angiogenic and pro-inflammatory shift, potentially contributing to the severity of menorrhagia and fibroid growth during colder months [30, 32].

In a comprehensive review by Saad et al., the IL-17/Th17 axis was described as a key driver of chronic inflammation and stromal remodeling in uterine fibroids. This axis has been linked to angiogenesis and the clinical manifestations of leiomyomas (bleeding, pain); however, precise fold-changes in IL-17A levels (either systemic or tissue-based) remain poorly standardized across studies [39].

Additionally, a genetic study by Konenkov et al. demonstrated that carriage of the homozygous –197A/A variant of the IL17A gene is associated with an increased risk of uterine fibroids (OR ≈ 4.33), indirectly implicating IL-17 signaling in fibroid pathogenesis and possibly in the modulation of clinical outcomes such as fibroid size and symptom severity [21]. Nevertheless, this association is genetic and not equivalent to direct measurement of IL-17A protein levels. Taken together, current evidence supports that IL-17A/Th17 signaling in uterine fibroids is linked to angiogenesis, local inflammation, and disease burden, yet quantitative data on its expression dynamics in fibroid tissue versus control myometrium remain insufficient for meta-analytical conclusions.

Interleukin-18 (IL-18) is a pro-inflammatory cytokine from the IL-1 family, primarily produced by macrophages, dendritic cells, and epithelial cells. Upon cleavage by caspase-1 within the NLRP3 inflammasome, active IL-18 binds to its receptor complex (IL-18Rα/β), initiating MyD88–NF-κB and MAPK signaling cascades. It promotes IFN-γ synthesis and enhances cellular immune responses. Depending on the cytokine milieu, IL-18 may support Th1 immunity (with IL-12) or favor Th2 responses (in the absence of IL-12), thereby participating in angiogenesis, tissue remodeling, and sustained inflammation [14, 34].

Available studies investigating IL-18 in the context of uterine fibroids are sparse, and quantitative fold-change data remain largely unreported, thereby limiting the potential for integrative meta-analyses. In a recent review on NLRP3 inflammasome activation, caspase-1-dependent release of IL-18 was implicated in a pro-fibrotic cascade relevant to myometrial fibrosis, although the authors did not provide direct quantitative evidence of IL-18 changes in fibroid tissue [50].

In the review by Ihim et al. (2022), IL-18 is described as a regulator of innate and adaptive immunity, contributing to tissue inflammation and remodeling via the IFN-γ/STAT pathway. Associations were noted with abnormal uterine bleeding and implantation failure, but specific data regarding IL-18 concentrations in fibroid patients were not disclosed [18].

One animal model study on pregnancy suggested a protective role of IL-18 against LPS-induced miscarriage, indicating its involvement in maternal-fetal immune interactions, but offering no direct insight into its behavior in fibroid pathophysiology [17]. In patients with adenomyosis, altered expression of IL-18 signaling components at the endometrial–myometrial interface has been reported, correlating with heavy menstrual bleeding and subfertility. However, these findings do not substitute for fibroid-specific studies with reported fold-changes in IL-18 expression [8].

Tumor necrosis factor alpha (TNF-α) is a key proinflammatory cytokine of innate immunity produced by activated macrophages, T lymphocytes, NK cells, and other immune cells. Through TNFR1/2 signaling, it activates NF-κB, MAPK, and JNK pathways, enhancing the expression of inflammatory genes, adhesion molecules, matrix metalloproteinases, and growth factors [2]. TNF-α promotes immune cell migration, angiogenesis, and tissue remodeling, while chronic overproduction is associated with fibrosis and persistent inflammation.

The level of TNF-α in ULs has been studied both in serum and in fibroid tissues. In the study by Ciebiera et al. (2018), the mean serum concentration of TNF-α in women with symptomatic fibroids was 0.34 ± 0.14 pg/mL, whereas in the control group it was 0.17 ± 0.09 pg/mL, approximately 2-fold higher and statistically significant ($p < 0.05$). TNF-α levels positively correlated with fibroid size and the severity of heavy menstrual bleeding (HMB) [10]. In another study by Gao et al. (2020), TNF-α was increased in fibroid tissues compared to normal myometrium, although no specific fold-change was reported. Clinically, TNF-α expression was associated with pain intensity and prevalence of submucosal fibroids [16]. These findings suggest TNF-α as a potential biomarker of symptom severity, but further studies are needed to define its fold-change and correlations with validated clinical scales.

Interferon gamma (IFN-γ) is a central Th1-type cytokine produced by activated $CD4^+$ Th1 cells, $CD8^+$ cytotoxic lymphocytes, and NK cells. Upon binding to IFNGR1/IFNGR2, it activates the JAK1/JAK2–STAT1 signaling axis, leading to enhanced MHC-II expression, ROS production, and cytotoxic activity of macrophages and NK cells, while suppressing Th2 differentiation. IFN-γ plays critical roles in maintaining the balance between cellular and humoral immunity and exhibits antiproliferative and antifibrotic effects in tissues [42, 7].

Recent studies on IFN-γ in uterine fibroids report limited quantitative fold-change data, which should be taken into account in data interpretation. In the study by Konenkov et al., a significant decrease in serum IFN-γ was observed in fibroid patients compared to healthy controls, although the authors reported only directionality and statistical significance without fold-change values [21]. Similarly, Sevostyanova et al. found reduced IFN-γ in fibroid patients presenting with abnormal uterine bleeding and pelvic pain, alongside elevated TNF-α and CRP. Clinically, this was associated with adverse reproductive outcomes, including miscarriage and infertility, suggesting a potential prognostic value of IFN-γ in preconception screening and ART planning [44].

Review studies indicate that a reduced IFN-γ profile, coupled with Th2/M2 immune polarization, is associated with angiogenesis, fibrosis, and more severe clinical symptoms in leiomyoma. However, standardized data on IFN-γ fold-changes and associations with quantitative symptom scales remain lacking [40].

Interferon alpha (IFN-α) is the major type I interferon, predominantly produced by plasmacytoid dendritic cells and macrophages. Via IFNAR1/IFNAR2, it activates the JAK1/TYK2–STAT1/STAT2 pathway, inducing interferon-stimulated genes (ISGs) responsible for antiviral defense and antiproliferative effects. IFN-α enhances antigen presentation, T cell differentiation, modulates cytokine signaling, influences angiogenesis, and supports antitumor immunity [37, 20].

Over the past decade, studies with quantitative IFN-α measurements in leiomyoma patients are virtually absent, highlighting a critical gap in the evidence base. In the review by Saad et al. (2023), the type I IFN axis, including IFN-α, was implicated in inflammation and angiogenesis within fibroid nodules, but no clinical data on IFN-α levels or fold-change were provided [38]. In a study by Park et al. (2022), type I interferons were associated with endometrial receptivity, vascular remodeling, and immune tolerance, but again, no IFN-α fold-changes were reported in fibroid patients [35]. Clinical biomarker studies indicate dysregulation of the interferon axis (e.g., reduced IFN-γ), but IFN-α is either not measured or not expressed as fold-change,

limiting interpretation of its relationship to symptoms, fibroid volume, or fertility outcomes [44].

Conclusion

In summary, current literature demonstrates consistent alterations in the proinflammatory cytokine profile in women with uterine leiomyoma. Increased levels of IL-6, TNF-α, and IL-17A, as well as reduced IFN-γ and localized downregulation of IL-1β in fibroid cores, reflect a complex immune microenvironment promoting cellular proliferation, fibrosis, and impaired apoptosis. These immune shifts are clinically associated with menorrhagia, pelvic pain, and impaired fertility, and may potentially serve as molecular markers of fibroid activity and progression.

However, the heterogeneity of quantitative data, lack of standardized clinical correlation tools (e.g., PBAC, UFS-QOL, VAS), and methodological inconsistencies hinder meta-analysis and call for further prospective studies. Identification of reproducible cytokine signatures with clinical relevance could serve as the foundation for a personalized diagnostic and therapeutic approach to uterine leiomyoma.

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