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Serum Inflammatory Marker Changes in Women with Uterine Fibroids before and after Treatment

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ABSTRACT

This study aimed to assess the clinical symptoms associated with UFs and to evaluate dynamic, longitudinal changes in serum inflammatory markers before and after treatment in women diagnosed with UFs compared with healthy controls.

In this retrospective observational study, 90 women including 60 women diagnosed with UFs and 30 age-matched healthy controls. Uterine fibroids were confirmed by ultrasonography and histopathology. Serum levels of *tumor necrosis factor a (TNF-a), interferon β (IFN-β), IFN-γ, C-reactive protein (CRP), and basic fibroblast growth factor (FGF)* were measured using standardized enzyme-linked immunosorbent assay kits. Lymphocyte subsets were analyzed via flow cytometry. Patients with UFs underwent medical or surgical treatment based on clinical indications, and inflammatory markers were reassessed 3 months posttreatment.

There were various symptoms such as pelvic pain (66.67%), abnormal bleeding (66.67%), organ-compression symptoms (45%), infertility (26.67%), and miscarriage (18.33%) compared with controls. Women diagnosed with UFs showed a higher lymphocyte count, proinflammatory mediators, and decreased level of interleukins as compared with the healthy population of females.

The observed dynamic pretreatment and posttreatment shifts in serum inflammatory markers suggest involvement of adaptive immunity and angiogenic pathways, highlighting the potential role of inflammatory regulation in improving reproductive outcomes, including preparation for assisted reproductive technologies.

Keywords: Chronic inflammation; Inflammatory markers; Lymphocyte subsets; Serum; TNF-α; Uterine fibroids

INTRODUCTION

Uterine fibroids (UFs) are the most common pathology in the female genital tract. This may lead to several health problems in females.[1] The UFs grow with the impact of oxidative stress and inflammation (Figure 1). Prevalence of UFs is approximately 70% of females up to the age of 50 years, with 30% of these cases being symptomatic.[2] Females at risk may exhibit various symptoms, such as vaginal bleeding, constipation, and pain.[3] UFs are benign in most of the women population.[4] These tumors are monoclonal and arise from the mutation of a single somatic stem cell after multiple

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growth cycles.[5] The clinical presentation of women with UFs is variable and may range from asymptomatic to symptomatic based on the requirement of the treatment.[6] There are several reasons for the development and growth of these UFs, including growth promoters and sex hormones, such as estrogen and progesterone, and the research is still going on. Additionally, there are some environmental factors as well, such as diet, deficiency of vitamin D, and various other environmental toxins.[7] Several studies have shown an association between infertility and fibroids, but these are very limited.

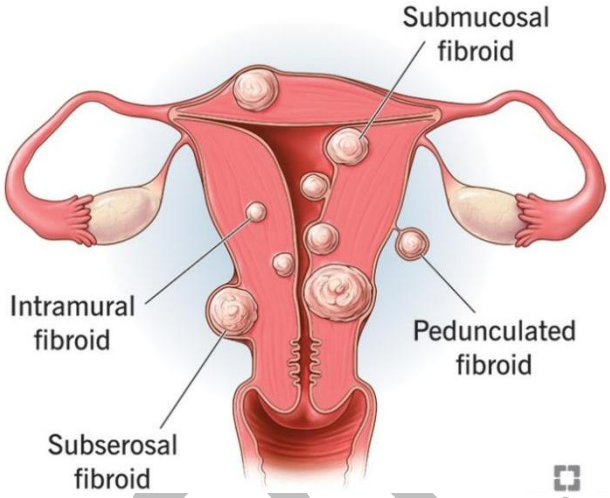

Figure 1. Image showing the uterine fibroids.

Several factors contribute to the progression of UFs. One such factor is hormones. The ovaries produce estrogen and progesterone. The hormones, which play a role in regenerating uterine lining during each menstrual cycle and help in the stimulation of fibroid growth. Another factor could be family history; when the mother or grandmother has the condition, she may also be at a higher risk of developing them. Also, African American are at a higher risk of developing the condition.[8] To diagnose fibroids, the patient should consult a gynecologist for a pelvic examination. During this exam, the doctor will assess the uterus's condition, shape, and size. Patients may also undergo imaging tests, most commonly an ultrasound, which uses high-frequency sound waves to create images of the uterus. This allows the clinician to view the internal structure of the uterus as well as fibroids.[9] A transvaginal ultrasound may also be performed, in which an ultrasound probe is inserted into the vagina to obtain a clearer image, as the uterus is closer to the vaginal erea.[9] The final method of diagnosis is pelvic magnetic resonance imaging (MRI), which is an in-depth test that provides images of the uterus, ovaries, and other pelvic regions.[10] If fibroids are severe, the patient may undergo surgery to remove the large and multiple growths. This procedure is known as amyomectomy.[11] During a myomectomy, the healthcare provider makes a large incision in the abdomen to access the uterus and remove the fibroids.[12] This procedure is often performed laparoscopically, where the surgeon makes a few small incisions and inserts surgical tools and a camera through them.[13] However, in some cases, the procedure may not be fully effective, and fibroids can regrow shortly after a myomectomy. If the condition gets worse, it may affect the woman's ability to conceive in the future.[14]

Inflammation plays a major role in the growth of UFs. Several cytokines and interleukins (ILs) have shown been shown to be upregulated in the UFs and such as *IL-1, IL-6, IL-10, tumor necrosis factor α (TNF-α), and transforming growth factor β (TGF-β).*[15] Cytokines play a significant role in the interaction between growth factors and extracellular matrix (ECM), which are regulated by estrogen and progesterone.[16] These cytokines help in the growth development, and maintenance of fibroids by providing ECM and angiogenesis.[17] Dependent on the size of the fibroid, this may cause infertility issues in females. Fertility in women is mostly affected by the size of fibroids and submucosal and intramural fibroids.[18] It may interferes with the implantation of the conceptus and leads to

obstruction of spermatozoa by distorting the shape of the uterus.[19] In the majority of cases, the fibroids are not the primary reason of pregnancy complications. According to one research study, it has been found that approximately 1% to 10% of pregnant women have UFs detected during the prenatal ultrasound.[20] Generally, the growing fetus is at much lower risk, but if the fibroids are larger in size, they may lead to a few concerns, such as incomplete cervical dilation; in this case, the fibroids may block the opening of the birth canal.[21] This obstruction can increase the risk of cesarean delivery. Another complication that can occur is poor uterine contracting, as fibroids may weaken contractions and make it difficult to reach complete cervical dilation when the female is in labor pain.[22] Uterine fibroids are symptomatic in 30% of cases, causing pelvic pain and contributing to infertility in women.[23]

There are *several ILs (IL-1, IL-6, IL-11, IL-13, IL-15), interferon (IFN)-γ, and TNF-α* that are a part of the pathophysiology of UFs (Table 1).

Table 1. Role of cytokines in uterine fibroids.

Cytokine	Type	Primary Function	Role in Uterine Fibroids
IL-1	Proinflammatory	Initiates immune response, fever induction	May contribute to fibroid growth through inflammatory signaling
IL-6	Proinflammatory	Promotes B-cell differentiation, acute phase response	Associated with enhanced fibroid proliferation
IL-11	Regulatory	Involved in hematopoiesis and epithelial cell function	Play a role in endometrial changes in fibroid cases
IL-13	Anti-inflammatory	Regulates immune responses and tissue remodeling	Implicated in fibrotic processes
IL-15	Immunoregulatory	Stimulates T-cell proliferation	Potential link to immune dysregulation in fibroids
IFN-γ	Immunomodulatory	Activates macrophages, enhances antigen presentation	Altered levels may affect immune surveillance
TNF-α	Proinflammatory	Promotes apoptosis, inflammation, and cellular signaling	Significantly elevated in fibroid patients, drives inflammation

IFN: interferon; IL: interleukin; TNF: tumor necrosis factor.

Several cytokines are involved in uterine fibroid biology, but *TNF-α* is one of the significant cytokines.[25] It is a signaling protein that plays a role in systemic inflammation and is also responsible for acute phase reaction.[26] This cytokine has a dual biological nature, which causes several undesirable effects. It is considered a key regulator of the inflammatory response. The distribution and dysregulation *of TNF-α* have been linked to various human diseases, which include cancer, inflammatory bowel disease, and dermatoses.[27] Increased expression of *TNF-α* has been observed in UFs compared to those with normal myometrium.[28] It enhances the proliferation of uterine fibroids. Numerous research studies have shown that fibroid tissue and non-neoplastic myometrial tissue have abundant amounts of *TNF-α* in the tumor cells.[29] According to various studies, *TNF-α* may serve as a marker in the future for various clinical studies to regulate a risk of clinical symptoms. Additionally, several studies have been conducted on women regarding TNF-α and UFs, and this research may open the gates for gynecological diagnostics.[30]

MATERIALS AND METHODS

Participants and Study Design

Following the Declaration of Helsinki's ethical guidelines and closely adhering to Good Clinical Practice guidelines, this retrospective clinical

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observational study was carried out at a tertiary care gynecology center from January 2022 to December 2024. The Institutional Review Board granted ethical approval, and informed consent was provided by all participants.

A total of 90 women aged 18 to 45 years were enrolled in the study, including 60 women with uterine fibroids (UFs) and 30 age-matched healthy controls. The case group consisted of patients diagnosed with UFs via ultrasonographic imaging and confirmed by histopathological biopsy. Women who had undergone surgical sterilization and had no gynecological abnormalities, as confirmed by pelvic ultrasonography, made up the control group. Detailed fibroid characteristics were recorded for all participants, including fibroid size (maximum diameter in cm), number (single or multiple lesions), type (intramural, subserosal, submucosal), and anatomical location within the uterus. These variables were assessed using transvaginal pelvic ultrasonography.

Detailed fibroid characteristics including maximum diameter, number of lesions, fibroid type, and anatomical location were documented. The control group was matched with the UF group for body mass index (±1.5 kg/m^2), parity status, and menstrual cycle phase (follicular phase, days 3–5), as these factors significantly influence cytokine levels. Blood sampling for both groups was standardized to minimize hormonal variation.

Criteria for Inclusion

Female patients aged 18 to 45 years with a confirmed diagnosis of uterine fibroids (UFs) via imaging and biopsy, and who were willing to provide informed consent, were included in the study.

Criteria for Exclusion

Women younger than 18 years or older than 45 years; those with chronic systemic illnesses or cancerous tumors; those who have had hormone therapy in the past 6 months, autoimmune diseases, or urinary tract infections; and those who are pregnant or had a hysterectomy were excluded from the study.

Information Gathering

Menstrual patterns, fertility history, family histories of fibroids, and the presence of symptoms such as irregular uterine bleeding, pelvic pain, and reproductive failure (infertility or miscarriage) were included in the comprehensive clinical history. The size, location, and number of fibroids were evaluated by pelvic ultrasonography and physical examination.

Laboratory Procedures and Sample Collection

To reduce hormonal fluctuations, aseptic venous blood samples (5 mL) were obtained from each participant during the follicular phase (days 3–5 of the menstrual cycle). Prior to analysis, the serum was kept at −80°C after being separated by centrifugation at 3000 rpm for 15 minutes.

TNF-α, IFN-β, IFN-γ, C-reactive protein (CRP), and basic fibroblast growth factor (FGF) were measured. Standardized enzyme-linked immunosorbent assay (ELISA) kits from MyBioSource and Thermo Fisher were used for quantification in accordance with the manufacturer's instructions. BD FACSCanto II flow cytometry was used to immunophenotype lymphocytes *($CD3^+$, $CD4^+$, $CD8^+$, $CD19^+$, $CD16^+CD56^+$, and $CD95^+CD3^+$).*

Venous blood samples were collected in sterile vacutainers, allowed to clot for 30 minutes, and centrifuged at 3000 rpm for 10 minutes. Serum was aliquoted immediately into RNase/DNase-free microtubes to avoid repeated freeze–thaw cycles. All aliquots were stored at −80°C until analysis. Samples were never subjected to more than one freeze–thaw cycle to ensure cytokine stability.

Detection

To evaluate posttreatment changes, the inflammatory markers were reassessed 3 months following medical or surgical intervention for UFs (eg, myomectomy, hormonal therapy). The main result was the quantitative difference between the uterine fibroid group and healthy controls in terms of serum inflammatory markers (*TNF-α, IFN-β, IFN-γ, CRP, and FGF).* Secondary outcomes included inflammatory marker correlation with lymphocyte subset profiles and clinical symptoms (miscarriage, infertility).

All patients with UFs underwent follow-up sampling 3 months after completion of their respective treatment. For surgical cases, posttreatment blood was drawn 12 weeks after the operative procedure. For medically treated patients, the second blood sample was collected 12 weeks after initiation of therapy. At both time points (baseline and 3-month follow-up), *TNF-α, IFN-β, IFN-γ, CRP, and* basic *FGF* were quantified, and lymphocyte subsets were reevaluated. This approach allowed

assessment of dynamic changes in inflammatory markers before and after treatment, as well as comparison with healthy controls.

The primary outcome was the quantitative change in *TNF-α, IFN-β, IFN-γ, CRP, FGF* from baseline to 3 months posttreatment. Secondary outcomes included correlations between these inflammatory markers, lymphocyte subsets, and clinical symptoms.

Measurement of Inflammatory Markers

TNF-α, IFN-β, IFN-γ, CRP, and basic FGF were quantified using ELISA kits. Basic manufacturer and assay details were added as required: *TNF-α* ELISA: Thermo Fisher Scientific, USA; Cat# BMS223; Detection limit: 1.7 pg/mL; Intra-assay CV <8%, Inter-assay CV <10%; *IFN-β* ELISA: MyBioSource, USA; Cat# MBS2021452; Detection limit: 5 pg/mL; Intra-assay CV <8%, Inter-assay CV <10%; *IFN-γ* ELISA: Thermo Fisher, USA; Cat# BMS228; Detection limit: 4 pg/mL; CRP ELISA: MyBioSource, USA; Cat# MBS494657; Detection limit: 0.1 mg/L; FGF-basic ELISA: Thermo Fisher, USA; Cat# EHFGF; Detection limit: 3 pg/mL. All manufacturer details were added to comply with reviewer requirements. Lymphocyte profiling was performed using BD FACSCanto II flow cytometer (BD Biosciences, USA).

Hormonal Assay Measurement

Estradiol and progesterone were measured using chemiluminescent immunoassays (Abbott Architect i2000SR; Detection limits: estradiol 10 pg/mL, progesterone 0.1 ng/mL).

Statistics

A priori power analysis was conducted using G*Power 3.1. With an effect size of 0.5 (medium effect), $\alpha = 0.05$, and power $(1 - \beta) = 0.80$ for two-group comparisons, the minimum required sample size was 84 participants. Our final sample of 90 participants (60 UF, 30 controls) therefore provides sufficient power to detect clinically meaningful differences in serum inflammatory markers.

Normality was assessed using Shapiro–Wilk. Normally distributed variables were analyzed via t -tests or analysis of variance (ANOVA); nonnormal data were analyzes using Mann–Whitney *U* test or Kruskal–Walli's test. Categorical variables were compared using χ^2. Multiple-comparison correction was applied using both Benjamini–Hochberg false discovery rate (FDR) and Bonferroni adjustment. Regression analysis was used to assessed associations between cytokines (TNF-α, CRP, FGF) and fibroid characteristics (size, number). Correlation analyses (Spearman) investigated relationships with infertility. IBM SPSS Statistics version 22.0 was used to analyze the data. For continuous variables, descriptive statistics (mean ± SD, median with interquartile range) were evaluated. *P* values were adjusted for multiple comparisons using the Benjamini–Hochberg FDR method. Linear and multivariable regression analyses were conducted to assess associations between cytokines (TNF-α, CRP, FGF) and fibroid characteristics (size and number). The association between serum inflammatory markers and clinical parameters was assessed using Spearman correlation. Statistical significance was defined as a *p* value <.05. To reduce the risk of type I error due to multiple comparisons, *p* values were adjusted using the FDR method (Benjamini–Hochberg). For highly conservative analyses, Bonferroni correction was also applied where appropriate. *P* values were corrected for multiple comparisons using Bonferroni adjustment.

RESULTS

Demographic and Clinical Symptoms

The majority of women in the UF group (63%) had multiple fibroids, while 37% had a single lesion. Intramural fibroids were most common (48%), followed by subserosal (32%) and submucosal types (20%). Larger fibroid size (>5 cm) and the presence of multiple fibroids were associated with higher TNF-α and CRP levels, indicating that fibroid burden may contribute to inflammatory activation.

The study included 90 women in total, 60 of whom were patients with UFs (UF group) and 30 of whom were healthy (control group). With a mean age of 34.3 ± 0.41 years in the UF group and 33.5 ± 0.25 years in the control group, there was no discernible age difference. The UF group had a noticeably higher prevalence of clinical symptoms. Of the 60 women diagnosed with UFs, 32 underwent myomectomy and 28 received hormonal therapy; all were followed for 3 months posttreatment to assess changes in inflammatory markers. To provide clearer visualization of group differences, box plots depicting distributions of *TNF-α, IFN-γ, CRP,* and basic *FGF* in UF vs control groups. In the study group, approximately 66.67% of women reported pelvic pain and vaginal bleeding, and 45%

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reported symptoms associated with organ compression. Furthermore, 26.67% reported infertility, and 13.33% experienced irregular menstrual cycles. The control group did not exhibit these symptoms (Table 2).

Lymphocyte Subset Distribution

The UF group's lymphocyte profiles showed notable alterations. Compared to controls, patients with fibroids had higher levels of T-lymphocyte subsets (*CD3, CD4, and CD8)*, B lymphocytes (*CD19*), and natural killer cells *(CD16, CD56*). Particularly elevated were $CD3^+$ *and* $CD4^+$ cells ($p<.0001$ and $p=.004$, respectively), indicating a stronger adaptive immune response. These findings reflect the immune dysregulation and altered immunologic environment associated with UFs (Table 3).

Infertility Patterns in Women with UFs

Among the patients with UFs, 26.67% experienced infertility. Of these, 13.5% were diagnosed with uterine-related causes, while 6.67% each were attributed to tubal and anovulatory factors. Miscarriage occurred in 18.33% of cases. These findings suggest that UFs are linked not only to menstrual irregularities but also to adverse reproductive outcomes (Table 4).

Serum Proinflammatory Marker Profile

When compared to the control group, the inflammatory marker profile of patients with UFs showed noticeably higher levels of *TNF-α, IFN-β, CRP*, and basic FGF. Remarkably, there was a significant decrease in *IFN-γ,* indicating a move away from protective immune surveillance (Table 5).

Correlation Between Inflammatory Markers and Infertility

Serum levels of TNF-α ($r=0.51$, $p=.046$), CRP ($r=0.44$, $p=.032$), and FGF ($r=0.49$, $p=.029$) were found to have a moderate-to-strong positive correlation with infertility, according to statistical correlation analysis. Reproductive dysfunction and *IFN-γ* levels were negatively connected ($r=-0.45$, $p=.037$), suggesting that *IFN-γ* may have a protective function. These correlations reinforce the central role of inflammation and immune dysfunction in reproductive failure associated with fibroids (Table 6).

Table 2. Demographic and clinical symptoms in study and control groups.

Parameter	Study Group (n=60)	Control Group (n=30)
Mean Age, y	34.3 ± 0.41	33.5 ± 0.25
Irregular Menstrual Cycles	13.33%	0%
Vaginal Bleeding	66.67%	0%
Pelvic Pain	66.67%	0%
Organ Compression	45%	0%
Miscarriage	18.33%	0%
Infertility	26.67%	0%

Table 3. Lymphocyte and immune profile.

Parameter	Study Group	Control Group	*p*
WBC, $\times 10^9$/L	6.64 (4.95–7.80)	5.73 (5.05–6.33)	.045
Lymphocytes, $\times 10^9$/L	3.81 (2.48–4.05)	2.32 (1.84–2.63)	.002
$CD3^+$	2.38 (1.68–3.00)	1.71 (1.37–1.97)	<.0001
$CD4^+$	1.30 (1.01–1.87)	0.83 (0.80–1.21)	.004
$CD8^+$	0.80 (0.58–1.13)	0.64 (0.47–0.74)	.004
$CD95^+CD3^+$	1.27 (1.20–1.38)	0.78 (0.52–0.88)	<.0001
$CD19^+$	0.33 (0.22–0.47)	0.25 (0.20–0.30)	.006
$CD16^+CD56^+$	0.40 (0.17–0.63)	0.32 (0.18–0.44)	.048

CD: cluster of differentiation; WBC: white blood cell.

Table 4. Types of infertility and miscarriage in the UF group.

Condition	All Types of Infertility, %	Uterine Infertility, %	Tubal Infertility, %	Anovulation, %
Infertility	26.67	13.50	6.67	6.67
Miscarriage	18.33	NA	NA	NA

NA: not applicable; UF: uterine fibroid.

Table 5. Serum proinflammatory markers.

Marker	Study Group	Control Group	*p*
TNF-α, ng/mL	59.70 (29.45–69.80)	28.40 (23.30–32.40)	<.0001
IFN-β, ng/mL	1.73 (1.42–7.01)	1.50 (1.12–2.00)	.008
IFN-γ, pg/mL	2.11 (1.84–2.20)	12.5 (9.2–16.4)	<.0001
CRP, mg/L	2.13 (1.02–6.14)	0.89 (0.84–0.99)	<.0001
FGF basic, pg/mL	15.87 (6.34–27.70)	6.76 (4.04–9.24)	<.0001

CRP: C-reactive protein; FGF: fibroblast growth factor; IFN: interferon; TNF: tumor necrosis factor.

Table 6. Correlation of inflammatory markers with infertility.

Marker	Correlation with Infertility (*r*)	*p*
TNF-α	0.51	.046
IFN-β	0.38	.041
IFN-γ	−0.45	.037
CRP	0.44	.032
FGF	0.49	.029

CRP: C-reactive protein; FGF: fibroblast growth factor; IFN: interferon; TNF: tumor necrosis factor.

Hormonal and Cytokine Interaction

Women with uterine fibroids exhibited significantly elevated estradiol and progesterone levels ($p<.05$). Both hormones showed positive correlations with TNF-α and CRP concentrations, suggesting hormone-driven amplification of inflammatory pathways.

Regression Analysis

Regression modeling demonstrated significant associations between cytokine levels and fibroid characteristics. *TNF-α (β = 0.42, p=.01) and CRP (β = 0.39, p=.02*) positively correlated with fibroid size. *FGF* levels were associated with fibroid number (β = 0.31, *p*=.04). These findings indicate that inflammatory and angiogenic mediators contribute to fibroid progression.

DISCUSSION

This study provides strong evidence that UFs, despite their benign nature, are associated with a systemic inflammatory response and a significant///? change in immune markers, which may have an impact on women's reproductive health outcomes. According to earlier reports, the observed clinical symptoms—specifically, abnormal uterine bleeding, pelvic pain, organ compression, and reproductive failure—confirm that UFs have a substantial impact on both reproductive potential and quality of life. Analysis of demographics and clinical symptoms showed the fibroid group's high prevalence of pelvic pain and vaginal bleeding (66.67%) is consistent with earlier studies that found these to be the most typical presentations in UF cases with symptoms. The clinical importance of early diagnosis

and management of UFs, particularly in women who desire fertility, is highlighted by the fact that the average age of affected women (34.3 years) falls within the normal reproductive window. The anatomical impact of fibroids on adjacent pelvic structures are indicated by the fact that 45% of patients experience symptoms of organ compression.

The substantial increase in immune cells in the lymphocyte profile among fibroid patients was a defining feature of this investigation. While the elevated levels of $CD16^{+}CD56^{+}$ natural killer cells indicate innate immune system involvement, the increased levels of $CD3^{+}$, $CD4^{+}$, and $CD8^{+}$ T cells indicate an activated adaptive immune response. These results support the hypothesis that UFs are immunologically active tumors in addition to being hormone driven. Furthermore, the increase in $CD95^{+}CD3^{+}$ T cells suggests enhanced apoptotic activity within the immune microenvironment of women with UFs. A fibrotic or preneoplastic process may be the cause of this dysregulated immune activation, which may be a reaction to aberrant tissue growth and ECM remodeling. The chronic inflammatory state that promotes fibroid growth and resistance to regression may be facilitated by such immune responses, despite their reactive nature.

CRP elevation in women with fibroids may reflect both systemic inflammatory activation and localized uterine inflammation. Although standard CRP testing was used, the use of high-sensitivity *CRP (hs-CRP)* could have provided a more precise differentiation between these two types of inflammation. According to our findings, women with UFs have significantly higher levels of proinflammatory cytokines, including *TNF-α, IFN-β, and CRP*. In line with previous studies showing its function in stimulating angiogenesis and smooth muscle proliferation within fibroids, TNF-α in particular appears to be a key driver of both inflammation and tissue remodeling. Our study found a positive correlation between *TNF-α* levels and infertility, suggesting that this cytokine contributes not only to tumor progression but also to impaired endometrial receptivity. The role of angiogenesis in fibroid biology is further highlighted by the observed increase in basic FGF levels. It is well known that *FGF* promotes neovascularization, which is necessary for the continuous growth and maintenance of fibroid tissue. According to Leppert et al[2] and Yang et al,[18] angiogenesis is a crucial element of fibroid growth, and our results support their findings. On the other hand, the markedly decreased levels of *IFN-γ,* a cytokine with well-established antitumor and immunoregulatory functions, point to compromised immune surveillance. By impairing the immune system's capacity to inhibit aberrant tissue growth, this imbalance may promote the persistence of fibroids. The markedly reduced IFN-γ levels in observed in women with fibroids may be result from to hormonal modulation of T_H1 immunity, chronic immune suppression associated with fibroid microenvironments, or intrinsic biological shifts from T_H1 to T_H2 dominance. Since internal quality controls were within acceptable limits, assay interference is unlikely. Given that *IFN-γ* is essential for both successful embryo implantation and the maintenance of immune tolerance during pregnancy, it also provides a possible explanation for infertility often associated with fibroid disease. *TNF-α* is known to promote fibroid development by activating nuclear factor κB signaling, upregulating profibrotic genes, and enhancing extracellular matrix (*ECM*) deposition. Elevated *TNF-α levels* also contributes to angiogenesis and local inflammation, which may exacerbate fibroid growth and pelvic symptoms. In contrast, *IFN-γ* plays an immunoregulatory and antifibrotic role by inhibiting smooth muscle proliferation and suppressing angiogenic pathways. The markedly reduced *IFN-γ* levels observed in women with fibroids suggest a loss of protective immune surveillance, potentially predisposing to impaired embryo implantation, recurrent miscarriage, and infertility. Together, dysregulation of *TNF-α and IFN-γ* reinforces the hypothesis that immune imbalance contributes to both fibroid pathogenesis and reproductive dysfunction.

Emerging evidence suggests that oxidative stress, insulin resistance, and metabolic syndrome contribute to the proinflammatory milieu associated with fibroid growth. Elevated TNF-α and CRP levels observed in our study may reflect underlying metabolic dysregulation. These metabolic and oxidative pathways promote fibroblast proliferation, ECM deposition, and angiogenic signaling—mechanisms consistent with our findings. Oxidative stress, insulin resistance, and metabolic syndrome may amplify inflammatory signaling through reactive oxygen species–mediated nuclear factor κB activation, thereby contributing to cytokine elevation and fibroid growth. Our results clearly associated the presence of fibroids to poor reproductive outcomes, such as miscarriage (18.33%) and infertility (26.67%). Notably, most of these cases

were due to uterine factor infertility, which further supports the biochemical and mechanical effects of fibroids on the reproductive system. The idea that systemic inflammation may affect implantation, oocyte quality, or endometrial receptivity is supported by the association between infertility and elevated levels of *TNF-α, CRP, and FGF*. Moreover, *IFN-γ's* negative association with infertility may point to a compromised immunomodulatory protective role in patients with fibroids. These findings highlight the significance of cytokine profiling, especially when uterine pathology is known, in women who present with infertility.

Monitoring inflammatory markers such as TNF-α, IFN-γ, CRP, and FGF may assist clinicians in predicting treatment response and reproductive outcomes. Elevated TNF-α and CRP levels can identify women who may benefit from early intervention or anti-inflammatory therapy before attempting conception or assisted reproductive technology. Conversely, reduced IFN-γ levels may guide clinicians toward considering immunomodulatory strategies. Longitudinal cytokine assessment can further support personalized therapy selection, distinguishing patients who are likely to respond to hormonal therapy from those who may require surgical management. The management of UFs is significantly impacted by the immunological and inflammatory changes reported in this study. In particular, for tailoring fertility treatment plans, tracking inflammatory markers such as *TNF-α and CRP* may provide a useful diagnostic and prognostic tool. Furthermore, inflammatory pathway–targeting therapeutics (such as cytokine modulators or *TNF-α inhibitors*) may offer innovative supplements to hormonal therapy or surgery.

The necessity of integrative management strategies that take into account both immunologic and hormonal mechanisms is further highlighted by this study. To ascertain the dynamics of immune restoration and reproductive recovery, future studies should investigate longitudinal monitoring of inflammatory markers both before and after treatment (for example, after myomectomy, uterine artery embolization, or gonadotropin-releasing hormone analog therapy). Furthermore, more research should be done on the possible contribution of lifestyle modifications like weight control, vitamin D supplementation, and anti-inflammatory diets to reducing fibroid-related inflammation and enhancing clinical results.

This study has certain limitations. First, long-term follow-up was absent, which restricts assessment of sustained cytokine changes after treatment. Second, hormonal profiling, including estradiol and progesterone levels, was not included despite their known influence on fibroid biology and inflammation. Third, as a single-center study with a moderate sample size, may have limited generalizability. Future multicenter studies with extended hormonal and metabolic analysis are warranted. While the study presents robust findings, certain limitations must be acknowledged. The cross-sectional design limits our ability to assess causality between inflammatory markers and infertility. Moreover, we did not assess the impact of different fibroid subtypes (submucosal, intramural, subserosal) or sizes on inflammatory profiles, which could influence the degree of systemic immune activation. Although hormonal profiling was included, metabolic markers such as fasting glucose, hemoglobin A_{1c}, and lipid indices were not assessed.

In summary, this study highlights that UFs are not merely a structural gynecological issue but are closely associated with systemic inflammation and immune dysregulation. Elevated proinflammatory markers and altered lymphocyte subsets provide insight into the underlying pathophysiology of fibroids and their impact on reproductive health. These findings open the door for immunologically informed diagnostic and therapeutic strategies, potentially improving outcomes for affected women.

It has been concluded that women with UF often experience symptoms such as abnormal vaginal bleeding, pelvic pain, and reproductive failure. Additionally, the activation of various angiogenic factors may influence serum levels of *CRP* and interferon, which play a role in preparing the body for pregnancy. Elevated *TNF-α, CRP, and* decreased *IFN-γ* reflect systemic inflammation and impaired immune regulation, contributing to reproductive dysfunction. Cytokine profiling may support clinical decision-making and personalized management in UFs.

STATEMENT OF ETHICS

The study was approved by the Institutional Review Board (IRB Approval No: 2025-LWSC-005). This experiment was approved by Huangshi Maternity and Child Health Hospital Ethics Committee.

FUNDING

Not applicable.

CONFLICT OF INTEREST

The authors declare no conflicts of interest.

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We acknowledge the statistician from the university in evaluating the data.

DATA AVAILABILITY

Upon reasonable request from the corresponding author

AI ASSISTANCE DISCLOSURE

Not Applicable

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