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FEATURES OF CYTOKINE PROFILE DYNAMICS IN WOMEN WITH UTERINE FIBROIDS AFTER RADIOFREQUENCY ABLATION IN ORGAN-PRESERVING TREATMENT

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Abstract

Uterine fibroids are one of the most common benign tumors in women of reproductive and perimenopausal age and are accompanied by activation of inflammatory, angiogenic, and fibrotic mechanisms. With the development of minimally invasive organ-preserving technologies, there is a growing interest in assessing the molecular effects of radiofrequency ablation (RF) on the microenvironment of the myometrial tissue.

The aim of the study was to evaluate the dynamics of the cytokine profile (TNF-α, VEGF-A, TGF-β2) in women with uterine fibroids after radiofrequency ablation in comparison with uterine artery embolization (UAE).

Material and methods. The study included 45 women with uterine fibroids and 28 healthy women in the control group. Patients were divided into two groups depending on the treatment method used: uterine artery embolization (19 patients) and radiofrequency ablation (26 patients). Serum levels of TNF-α, VEGF-A, and TGF-β2 were determined using ELISA; a follow-up study was performed 3 months after treatment.

Results. Before the treatment, patients with uterine fibroids showed significantly elevated levels of TNF-α, VEGF-A, and TGF-β2 compared to the control group, reflecting increased inflammation, angiogenesis, and fibrogenesis. After UAE, cytokine levels decreased but remained above normal. After radiofrequency

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ablation, a statistically significant reduction in the concentrations of all three markers was observed, indicating effective suppression of key pathogenetic mechanisms of fibroid growth.
Key words: Uterine fibroids, radiofrequency ablation, cytokines, treatment, inflammation, angiogenesis.

Introduction

Relevance

Uterine fibroids (leiomyoma) are the most common benign tumor of the female reproductive system, arising from the smooth muscle cells of the myometrium. According to epidemiological studies, signs of fibroids are detected in 70–80% of women by the age of 50 [1–7, 11, 12], and in 25–30% of cases, the disease is accompanied by clinically significant symptoms that significantly affect the quality of life, ability to work, and reproductive function [16]. The main manifestations include chronic pelvic pain, dysmenorrhea, heavy uterine bleeding, and compression syndrome, which, if not treated promptly, can lead to iron deficiency anemia and impaired fertility [5].

Traditional treatment methods include drug therapy, surgical removal of nodes (myomectomy), and radical intervention—hysterectomy. Despite the high efficacy of myomectomy, the recurrence rate after organ-preserving surgery reaches 15–30% over 5 years [9,10]. Uterine artery embolization is also an effective option; however, its use is limited by the risk of affecting ovarian reserve and the possible development of post-embolization syndrome [8].

Over the past two decades, minimally invasive, uterine-preserving technologies have been rapidly developing, including high-intensity focused ultrasound (HIFU) and radiofrequency ablation (RFA). HIFU has been shown to reduce fibroid volume and symptom severity [3], but limitations remain related to the type and location of fibroids, procedure duration, and heterogeneity in long-term results [11].

Against this background, radiofrequency ablation represents a promising alternative, allowing for the destruction of myomatous tissue under imaging control without damaging the surrounding myometrium [1]. This method can be

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performed laparoscopically, transcervically, or percutaneously in an outpatient setting, ensuring rapid recovery, minimal blood loss, and preservation of the anatomical integrity of the uterus [6]. Clinical observations have also shown an improvement in quality of life, normalization of the menstrual cycle, and a reduction in the volume of myomatous nodes within the first few months following the procedure [2].

However, despite the growing evidence base regarding the clinical efficacy of RFA, its impact on the immune-inflammatory component of myoma pathogenesis remains poorly understood. It is currently known that uterine myoma is associated with an imbalance in cytokine regulation, increased levels of proinflammatory mediators, activation of tissue macrophages, and impaired extracellular matrix remodeling mechanisms [7; 12; 10]. Studying cytokine status before and after radiofrequency ablation allows not only to assess the immunological reactivity of the myometrium but also to identify biomarkers of treatment efficacy and prognosis [12].

Thus, the study of the dynamics of the cytokine profile in women with uterine fibroids after radiofrequency ablation is a relevant and clinically significant area that contributes to the improvement of personalized treatment tactics for patients of reproductive and premenopausal age.

The aim of the study was to determine the dynamics of serum levels of the proinflammatory cytokine TNF-α, angiogenic factors VEGF-A and TGF-β2 in women with uterine fibroids before and after treatment, comparing their changes with the use of radiofrequency ablation and traditional methods of therapy, in order to evaluate the immunoinflammatory and angiogenic mechanisms of the effectiveness of various therapeutic approaches.

Materials and Methods

This study was conducted at the Tashkent State Medical University Clinic. The study included 45 women of reproductive age and premenopause with clinically and instrumentally confirmed uterine fibroids undergoing treatment, as well as 28 somatically healthy women who formed a control group. The diagnosis of uterine

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fibroids was established based on a gynecological examination, transvaginal ultrasound, and, when necessary, magnetic resonance imaging. Inclusion criteria complied with current clinical guidelines and took into account the severity of symptoms, the size and location of fibroids, the desire to preserve the uterus, and the absence of signs of tumor transformation.

Of the examined patients, 26 underwent organ-preserving, minimally invasive ultrasound-guided radiofrequency ablation performed on an outpatient basis. The procedure provided localized thermal stimulation of the fibroid tissue while preserving the surrounding myometrium and minimizing the recovery period. Clinical and instrumental follow-up and ultrasound examinations were performed post-treatment to assess changes in the size and vascularity of the fibroid nodes.

Immunological studies were conducted at the Institute of Human Immunology and Genomics of the Academy of Sciences of the Republic of Uzbekistan, in the Laboratory of Reproductive Immunology. To assess immune-inflammatory and angiogenic processes, serum levels of TNF-α, VEGF-A, and TGF-β2 were measured. Venous blood was collected on an empty stomach. Serum was isolated by centrifugation and stored at –80°C until analysis. Cytokine concentrations were determined by ELISA using certified Vector-Best and BiokhimMak kits (Russia) according to the manufacturer's instructions, with optical density recorded on a spectrophotometer at 450 nm and calibration curves plotted.

Statistical data processing was performed using the Statistica 6.0 software package (StatSoft Inc., USA). For quantitative indicators, the mean (M) and standard error (m) were calculated. Comparison of mean values between groups was performed using Student's t-test. When analyzing intergroup differences, the median (Me) and interquartile range (Q1–Q3) values were additionally used. Differences were considered statistically significant at $p < 0.05$.

Results and Discussion

The data obtained were analyzed to assess the impact of radiofrequency ablation on the myometrium, with a focus on changes in TNF-α, VEGF-A, and TGF-β2, which reflect the activity of inflammatory, angiogenic, and fibrotic processes in myoma tissue. Comparison of serum levels of these markers before treatment and

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3 months after uterine artery embolization allowed us to evaluate the severity of tissue remodeling and the nature of the myometrial biological response to the intervention.

The results obtained are presented in Table 1. TNF-α (tumor necrosis factor-α) is a key proinflammatory cytokine that regulates macrophage activation, smooth muscle cell proliferation, and extracellular matrix remodeling in the myometrium. Its increased expression is considered one of the leading mechanisms in the formation of the pathological inflammatory microenvironment of the myomatous node [4; 7].

Data analysis revealed that before treatment, elevated serum TNF-α levels were observed, reflecting active inflammatory micromolecular activity in the myometrial tissue. The mean value was 82.97 ± 2.68 pg/ml, and the Me was 82.75 [75.02–95.50], versus 23.84 ± 1.19 pg/ml ($p < 0.001$).

Three months after uterine artery embolization, TNF-α decreased to 61.63 ± 4.87 pg/ml, Me 61.30 [52.73–71.44], and this decrease was statistically significant compared to the baseline value ($p<0.001$). However, the indicator remained above the normal level, which means that residual inflammatory activity remained. After radiofrequency ablation, the average TNF-α level was 38.91 ± 3.09 pg/ml, Me 38.15 [32.57–42.24], which was significantly lower than the baseline values ($p<0.001$). It is likely that the obtained result reflects the direct elimination of the intratissue source of the proinflammatory signal, since RFA leads to the destruction of the structures of the myomatous node and interruption of the mechanism of maintaining the inflammatory microclimate. Uterine artery embolization reduces inflammation indirectly without eliminating its morphological basis.

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Table 1. Serum levels of the studied immunological markers.

Indicator	M±m, pg/ml	Me [Q1:Q3]	*p-value*
Control group, n=28			
TNF-α	23,84 ± 1,19	19,51 [13,72:28,34]	-
VEGF-A	55,21 ± 2,16	51,36 [39,85:62,97]	
TGF-β2	82,44 ± 2,81	78,65 [65,48:87,09]	
Women with UF before treatment, n=45			
TNF-α	82,97±2,68	82,75 [75,04:92,50]	*<0,001**
VEGF-A	238,64±25,08	233,59 [172,25:310,03]	*<0,001**
TGF-β2	132,30±6,39	129,51 [124,79:131,92]	*<0,001**
Women with UF after UAE, n=19			
TNF-α	61,63±4,78	61,30 [52,83:71,44]	*<0,001⁑*
VEGF-A	112,50±6,85	105,01 [96,30:134,88]	*<0,001⁑*
TGF-β2	104,72±3,89	111,13 [92,77:114,12]	*<0,001⁑*
Women with UF after RFA, n=26			
TNF-α	38,91±3,09	38,15 [32,57:42,24]	*<0,001⁑*
VEGF-A	80,88±6,59	78,19 [63,75:84,70]	*<0,001⁑*
TGF-β2	94,05±3,01	90,63 [89,03:99,56]	*<0,001⁑*

*Note: * - differences are significant compared to the control group. ⁑ - differences are significant compared to the main group data before treatment. Me – median, Q1 (percentile) – 25%, Q3 (percentile) – 75%.*

VEGF-A (vascular endothelial growth factor A) is a key regulator of angiogenesis—the process of forming new blood vessels from existing vascular network. Its synthesis is activated by hypoxia, mechanical tissue stretching, and the action of proinflammatory cytokines, including TNF-α and IL-6. In myoma tissue, VEGF-A is produced by myometrial smooth muscle cells, fibroblasts, and resident macrophages, forming a local proangiogenic microenvironment [10; 11]. The obtained data revealed that before treatment, serum VEGF-A was significantly elevated, indicating pronounced neoangiogenesis necessary for trophic of myomatous nodes. The values were 238.64±25.02 pg/ml, Me 235.79 [152.90–310.03], versus the normal values of the control group 55.21±2.16 pg/ml ($p<0.001$).

After uterine artery embolization, the VEGF-A level decreased to 112.50 ± 6.85 pg/ml, Me 105.91 [96.10–138.84], which was significantly lower than the

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baseline level ($p < 0.001$), but the indicator still exceeded the physiological level. This means that the vascular supply of the node was partially preserved. After RFA, the VEGF-A level was 80.88 ± 6.59 pg/ml, Me 78.19 [63.75–84.70], which was significantly lower than the baseline level ($p < 0.001$).

The established result is consistent with a likely direct interruption of the node's blood supply due to localized thermal destruction of vascularized tissue. Uterine artery embolization reduces VEGF-A production but does not alter vascular architecture, whereas RFA leads to vascular regression.

TGF-β2 (transforming growth factor beta 2) is a key regulator of tissue remodeling and fibrogenesis. It controls smooth muscle cell proliferation, stimulates fibroblast differentiation into myofibroblasts, and enhances the synthesis of collagen types I and III, proteoglycans, and other components of the extracellular matrix. In uterine fibroids, TGF-β2 promotes the compaction and maturation of the stromal framework of the node, thereby increasing the rigidity, density, and mechanical stability of the myomatous tissue [8; 10].

Initially, the level of TGF-β2 was 132.30 ± 6.39 pg/ml, Me 129.51 [124.79–131.92], while in the control it was 82.44 ± 2.21 pg/ml ($p<0.001$), which corresponded to an active fibrotic process in the structure of the myomatous node. After uterine artery embolization, the indicator decreased to 104.72 ± 3.89 pg/ml, Me 111.13 [92.77–114.12], which was significantly lower than the initial values ($p<0.001$), but still indicated the preservation of fibrosis processes. After RFA, the TGF-β2 level was 94.05 ± 3.01 pg/ml, Me 90.63 [89.09–96.91], which was significantly lower than the initial data ($p<0.001$).

It is likely that the obtained data reflect the initiation of processes of controlled resorption of fibrous tissue and a decrease in the synthetic activity of fibroblasts in the ablation zone, which leads to a decrease in the density and rigidity of the node.

Conclusion

The study confirmed that UF is accompanied by significant disturbances in the immune-inflammatory, angiogenic, and fibrotic balance, manifested by a significant increase in serum levels of TNF-α, VEGF-A, and TGF-β2. After 3

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months, it was found that uterine artery embolization only partially reduced the activity of these pathogenic factors, whereas RFA provided a more pronounced reduction in the inflammatory response, suppression of pathological angiogenesis, and attenuation of fibrogenesis.

The obtained results indicate that RFA not only reduces the size of the node and the severity of clinical manifestations, but also promotes the normalization of key biological processes in the myometrium, which confirms its advantage as an organ-preserving treatment method in women of reproductive and premenopausal age.

Conclusions

1. In women with uterine fibroids, pre-treatment levels of TNF-α, VEGF-A, and TGF-β2 were significantly elevated compared to physiological values, reflecting the activation of inflammatory, angiogenic, and fibrotic processes in the myometrium.
2. Uterine artery embolization leads to a decrease in the concentrations of the studied markers, but their level remains above the physiological range, which indicates incomplete suppression of the pathogenetic mechanisms of fibroid growth.
3. Radiofrequency ablation provides a more pronounced and statistically significant reduction in the levels of TNF-α, VEGF-A and TGF-β2 compared to traditional treatment, which indicates effective suppression of inflammation, pathological angiogenesis and fibrosis in the tissue of the myomatous node and confirms its advantage as a promising organ-preserving therapy method.

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