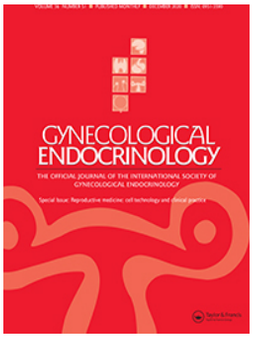

Gynecological Endocrinology

ISSN: (Print) (Online) Journal homepage: https://www.tandfonline.com/loi/igye20

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To cite this article: Olga Sevostyanova, Tatiana Lisovskaya, Gusel Chistyakova, Marina Kiseleva, Natalia Sevostyanova, Irina Remizova & Yuri Buev (2020) Proinflammatory mediators and reproductive failure in women with uterine fibroids, Gynecological Endocrinology, 36:sup1, 33-35, DOI: 10.1080/09513590.2020.1816726

To link to this article: https://doi.org/10.1080/09513590.2020.1816726

Published online: 11 Dec 2020.

GYNECOLOGICAL ENDOCRINOLOGY
2020, VOL. 36, NO. S1, S33–S35
https://doi.org/10.1080/09513590.2020.1816726

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ORIGINAL ARTICLE

Proinflammatory mediators and reproductive failure in women with uterine fibroids

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ABSTRACT

Objective: study the levels of proinflammatory mediators and their correlation with reproductivefailure in women with uterine fibroids (UF).

Materials and methods: 90 women aged 18 – 45 years (mean age – 33.9 ± 0.31) were recruited in the study: 60 women with UF were included in the study group and 30 healthy women were included in the control group. The lymphocyte count was performed with laser-based flow cytofluorimetry. The levels of C-reactive protein (CRP), interferon IFN-β (IFN-β), interferon-γ (IFN-γ), tumor necrotizing factor α (TNF-α) and basic fibroblast growth factor (FGF basic) were detected with ELISA test. The diagnosis of UF was confirmed with histological examination of biopsy specimen.

Results: Typical clinical features of UF (abnormal uterine bleeding, pelvic pains, symptoms of adjacent organs compression) were found in 66.67% women in the study group while 18.33% of them had miscarriages and 26.67% had infertility. Women with UF had significantly higher absolute count of lymphocytes: $CD3^+$, $CD19^+$, $CD16^+CD56^+$, $CD4^+$, $CD8^+$, $CD95^+CD3^+$, proinflammatory mediators: TNF-α, IFN-β, CRP, FGF basic and decreased levels of IFN-γ compared with the control group.

Conclusion: In women of reproductive age, typical symptoms of UF are associated with reproductive failure with activation of adaptive immunity, angiogenic factors, inflammatory cell reactions, deficit of human antitumor factors, that is why detection of TNF-α, СРБ, IFN-γ in serum is necessary to perform in pregravid preparation of women, including IVF program.

ARTICLE HISTORY
Received 24 July 2020
Revised 19 August 2020
Accepted 26 August 2020
Published online 11 December 2020

KEYWORDS
Uterine fibroids; proinflammatory mediators; reproductive failure

Background

Uterine fibroids (UF) is a common benign tumor. The incidence of UF increases with women's age. The number of women suffering from UF in the reproductive age is high and accounts for 40% [1,2]. UF is found in 5–10% women with infertility [3]. Some types of UF localization and size are considered to be independent factors affecting fertility, such as intramural UF with nodule size over 4 cm and submucous UF. It was shown that such types of UF had a negative impact on IVF success rate [1,4]. Despite many studies devoted to the role of steroid hormones, progesterone and estrogen receptors in the uterine and fibroid tissue, our knowledge about the reasons of UF has still been limited [5]. It is thought that proliferative effects of estrogens and progesterone could be shown through proinflammatory mediators: tumor necrotizing factor α (TNFα), growth factors: transforming growth factor β (TGF-β), basic fibroblast growth factor (FGF basic), as well as apoptosis inhibitors: cellular tumor antigen p53 (p53), apoptosis regulator bcl-2 (bcl-2) [6–8]. Scientific and practical interest to study pathogenesis of UF have been supported by the relevance of organ preservation treatment to restore and preserve reproductive function, as well as an increase in IVF success rate [1].

Materials and methods

The study enrolled 90 women aged 18–45 years (mean age 33.9 ± 0.35): 60 women with UF were included in the study group and 30 healthy women of the same age who visited the clinic for surgical sterilization–in the control group. The study was conducted in accordance with GCP criteria.

Inclusion criteria

Women aged 18–45 years, simple fibroids (benign tumor) and proliferative uterine fibroids on histological examination of biopsy specimen according to WHO classification [1].

Exclusion criteria

women's age younger than 18 years and older than 45 years, malignant tumors of any localization, infectious diseases, active stage of urogenital tract infections, endometriosis, other histological types of uterine fibroids.

Mean women's age in the study group was 34.3 ± 0.41 years and in the control group – 33.5 ± 0.25 years ($p > .05$). Patients

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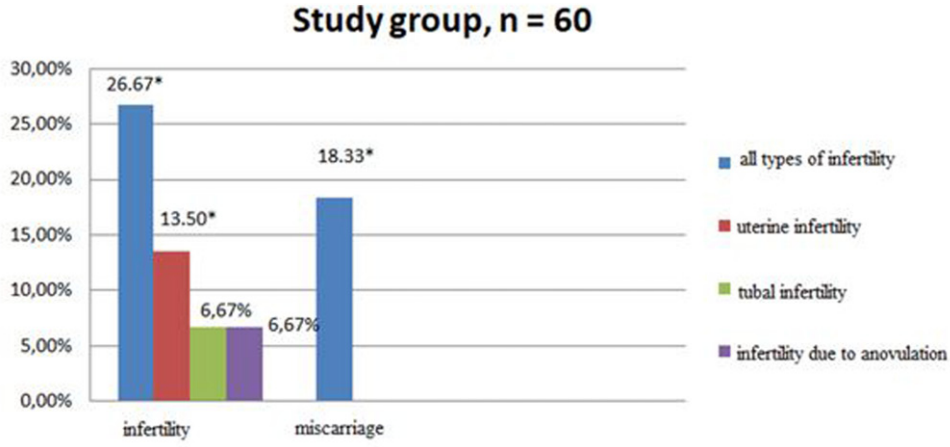

Figure 1. Reproductive failure in women with uterine fibroids. *Significant differences compared with the control group.

were examined with national clinical protocol of the Russian Federation [1]. Clinical manifestations of UF were assessed and characterized in accordance with International Classification of Diseases, 10th revision and FIGO classification [9,10].

The lymphocyte count in venous blood: $CD3^+$, $CD4^+$, $CD8^+$, $CD19^+$, $CD16^+CD56^+$, $CD95^+CD3^+$ was performed with laser-based flow cytofluorimetry. The levels of serum C-reactive protein, IFN-β, IFN-γ, TNF-α and FGF basic were detected with ELISA (an Enzyme-Linked Immunosorbent Assay) test.

All women with UF had surgical treatment with diagnosis verification after histological examination of biopsy specimen.

The statistical analysis was done with IBM SPSS Statistics 22. The Mann-Whitney U test was used to compare quantitative variables while Chi-square (χ^2) was used to compare qualitative variables. The correlation analysis was done with Spearman rank correlation.

Results

Age at menarche in women with UF was 12.9 ± 0.10 years and did not differ from the control group – 13.3 ± 0.31 years ($p > .05$). In 13.33% women of the study group, menstrual irregularities were registered before the onset of the disease ($p = .035$). The time from diagnosis verification of UF to surgical treatment was 2.79 ± 0.20 years. Clinical symptoms were found in 66.67% women of the study group and included abnormal uterine bleeding (N92.0, N92.1)–in 66.67% ($p = .0001$), pelvic pains–in 33.33% ($p = .002$), symptoms of adjacent organs compression–in 6.67% ($p > .05$). The women of the control group did not have clinical symptoms mentioned above.

Reproductive failure such as miscarriage and infertility were registered in 45.0% women with UF (of the study group) while women in the control group had no abnormalities ($p = .001$) (Figure 1). Herewith, 18.33% women of the study group had a history of miscarriages ($p = .012$), 26.67% women with UF had infertility ($p = .002$). Uterine infertility (N97.2) prevailed and was revealed in 13.33% women of the study group ($p = .035$). Tubal infertility (N97.1) was revealed in 6.67% patients with UF ($p > .05$); infertility due to anovulation (N97.0)–in 6.67% ($p > .05$).

The women of the control group had no abnormal symptoms, any reproductive diseases or infertility.

One myoma nodule was found in 58.33% women of the study group. Multiple myoma nodules were revealed in 41.67% women. The nodules were different in the size: from 2 to 17 cm. The nodules of 2–5 cm were found in 46.67% women, 5 cm to 10 cm–in 53.33%, over 10 cm–in 18.33%.

48.33% women had proliferative tumor while 51.67% had simple fibroids (benign tumor) ($p > .05$).

The levels of lymphocyte population and subpopulations in women with UF are shown in Table 1.

Phenotypic spectrum of lymphocytes in women with UF was characterized by an increase in absolute count of T-cell populations: $CD3^+$ and $CD19^+$, T-cell subpopulations: $CD4^+$ and $CD8^+$ (Table 1). Patients with UF had an increased absolute count of T-lymphocytes with apoptosis markers ($CD95^+CD3^+$) that were 1.6 higher than in the control group (Table 1). The absolute count of natural killers ($CD16^+CD56^+$) also was higher than in the control group ($p < .05$).

The levels of proinflammatory mediators in women of reproductive age with UF are given Table 2.

Women with UF had higher levels of serum proinflammatory mediators: TNF-α, C-reactive protein, interferon-β and decreased levels of interferon-γ (Table 2). The levels of serum FGF basic in women with UF were higher than in the control group ($p = .0001$).

A correlation between clinical-morphological characteristics of UF and the levels of serum proinflammatory mediators: FGF basic, C-reactive protein, interferon-γ was found. Thus, the following correlations were revealed: between FGF basic levels and the size of the myoma nodule ($r = 0.40$, $p = .04$), FGF basic levels and the presence of nodule necrosis ($r = 0.35$, $p = .04$), FGF basic levels and the presence of multiple myoma ($r = 0.56$, $p = .01$), as well as C-reactive protein levels and atypical nodule localization ($r = 0.56$, $p = .01$), IFN-γ levels and nodule edema ($r = -0.51$, $p = .03$).

In women with UF, a correlation between the levels of proinflammatory mediators and reproductive failure: the presence of infertility and C-reactive protein levels ($r = 0.52$, $p = .03$), also between infertility and FGF basic levels ($r = 0.51$, $p = .046$) was found.

In women of the study group there was a close correlation between the presence of reproductive failure and multiple UF, particularly between miscarriages and multiple UF ($r = 0.98$, $p = .0001$), as well as between infertility and multiple UF ($r = 0.98$, $p = .0001$). There was no significant correlation between the size of UF and reproductive failure. Thus, the correlation between the size of UFs and the presence of infertility was ($r = 0.05$, $p = .47$), between the size of UFs and miscarriages ($r = 0.12$, $p = .09$).

Table 1. Phenotypic characteristics of lymphocyte populations in women of reproductive age with UF (25–75).

Parameters	Study group ($n = 60$)	Control group ($n = 30$)	p
WBC, 10^9/L	6.64 (4.95–7.80)	5.73 (5.05–6.33)	.045
Lymphocytes, 10^9/L	3.81 (2.48–4.05)	2.32 (1.84–2.63)	.002
$CD3^+$, 10^9/L	2.38 (1.68–3.0)	1.71 (1.37–1.97)	.0001
$CD4^+$, 10^9/L	1.30 (1.01–1.87)	0.83 (0.80–1.21)	.004
$CD8^+$, 10^9/L	0.80 (0.58–1.13)	0.64 (0.47–0.74)	.004
$CD95^+CD3^+$, 10^9/L	1.27 (1.20–1.38)	0.78 (0.52–0.88)	.0001
$CD19^+$, 10^9/L	0.33 (0.22–0.47)	0.25 (0.20–0.30)	.006
$CD16^+CD56^+$, 10^9/L	0.40 (0.17–0.63)	0.32 (0.18–0.44)	.048

Table 2. Proinflammatory mediators in women of reproductive age with UF, Me (25–75).

Parameters	Study group ($n = 60$)	Control group ($n = 30$)	p
TNF-α, ng/ml	59.70 (29.45–69.80)	28.4 (23.30–32.40)	.0001
IFN-β, ng/ml	1.73 (1.42–7.01)	1.5 (1.12–2.0)	.008
IFN-γ, ng/ml	2.11 (1.84–2.20)	21.3 (2.81–30.90)	.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

In the study group there was a correlation between FGF basic levels and absolute count of CD3+ lymphocytes with Fas-receptors ($r = 0.55$, $p = .03$), FGF basic levels and C-reactive protein ($r = 0.52$, $p = .03$), C-reactive protein and absolute count of $CD95^+CD3^+$-lymphocytes ($r = 0.81$, $p = .005$).

Discussion

Impaired immunity has played a certain role in uterine fibroids and could lead to some types of infertility. The results of our study evidenced of abnormal absolute count of lymphocytes with activation of systemic adaptive immunity and preservation of cytotoxic potential in women of reproductive age with UF.

As cytokines are thought to be the factors regulating apoptosis and inflammation, and TNF-α often plays the role of signaling molecules of cell apoptosis, an increase in the levels of proinflammatory mediators (TNF-α, C-reactive protein, interferon-β) can be considered as Th1 dependent immune response in UF. Elevated TNF-α levels, probably, trigger such reaction being an inflammation marker, and participate in neoangiogenesis and uterine tissue remodeling [10].

It should be mentioned that interferon-γ levels in women with UF was low. Taking into account the role of that cytokine in the mechanisms of antiproliferative, antitumor, antiinfectious resistance and proapoptotic activity [11], the significance of that cytokine deficiency in benign uterine fibroids in reproductive age becomes clear. Decreased levels of interferon-γ found in our research was also determined by other authors [12].

The development and growth of UF is closely related to activation of neoangiogenesis, with a certain role of vascular epithelial growth factor and basic fibroblast growth factor [13], that was confirmed by elevated FGF basic levels in the study group. The received results can suggest that factors to participate in the development of UF in women of reproductive age.

We also suggest that increased levels of apoptosis markers (TNF-α, $CD95^+CD3^+$-lymphocytes) in women with UF depended on the intensiveness of programmed cell death due to increased proliferative activity. However, the level of apoptosis in patients was probably not enough for overcoming proliferation process as there were revealed elevated FGF basic levels and the presence of benign tumor.

There was found a correlation between the levels of proinflammatory mediators (basic fibroblast growth factor, C-reactive protein, interferon-γ) and clinical features of UF (size, necrosis, atypical localization, nodule edema), as well as correlation between FGF basic levels and C-reactive protein, FGF basic levels and absolute count of $CD3^+$-lymphocytes with Fas-receptor, that indirectly evidenced of the role of proinflammatory mediators in the development of tumor. The correlations between infertility and such proinflammatory mediators as C-reactive protein, basic fibroblast growth factor emphasize their role in the development of reproductive failure in women with UF.

Conclusion

Women of reproductive age with UF more often had abnormal uterine bleeding, pelvic pains and reproductive failure (infertility, and miscarriage) with activation of adaptive immunity and angiogenic factors, inflammatory cellular reactions and human antitumor factor deficit that made it reasonable to determine the levels of serum TNF-α, C-reactive protein, IFN-γ during pregravid preparation, including IVF programs.

Disclosure statement

No potential conflict of interest was reported by the author(s).

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