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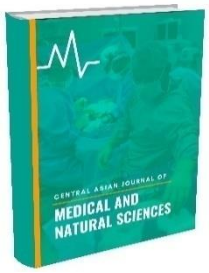

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Diagnosis of Assymptom Uterine Leuomyoma in Premenopausal Women

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Abstract: The article presents the evaluation of the effectiveness of immunomodulatory therapy in women with asymptomatic uterine leiomyoma. In this article, we was studied 67 women who were treated with asymptomatic uterine leiomyoma. By age, all patients were identical, the average age was 29.6 +_1,2 years. As the main method of investigation, IFA was used, diagnostic test systems were used to determine serum lymphocytes with an activation marker in women with asymptomatic uterine leiomyoma CD25, CD71, CD95, lactoferrin, proinflammatory cytokines IL-6, IL-8, IL-18, IL-10, TNF. Complex treatment with an immunomodulator for asymptomatic uterine leiomyoma normalized the level of lactoferrin in the composition of lymphocytes. The use of the immunomodulatory drug Likopid in complex therapy contributed to the restoration of altered parameters of the immune system, which in turn made it possible to optimize reproductive health. After complex treatment, 60.0% of women diagnosed with asymptomatic uterine fibroids became pregnant and gave birth to healthy children.

Key words: uterine leiomyoma, lymphocytes with activation marker in CD25, CD71, CD95, lactoferrin, proinflammatory cytokines IL-6, IL-8, IL-18, IL-10, TNF immunomodulatory therapy, likopid.

The search for pathophysiological mechanisms for the development of uterine leiomyoma and the development of effective methods for treating the tumor process in the myometrium are due to two circumstances: the prevalence of the disease and the high frequency of surgical interventions for this benign tumor [1-6].Protection of the reproductive health of the female population remains one of the priorities of modern health care. Uterine leiomyoma affects 25-30% of women over 35 years of age, and in recent years the disease has been increasingly detected at a younger age [7,8]. The causes of uterine leiomyoma have not been definitively established. uterine leiomyoma is the most common cause of abnormal uterine bleeding, infertility, recurrent pregnancy loss, and pelvic organ dysfunction [10]. These symptoms significantly impair a woman's quality of life [9].

Leiomyomas of the uterus are benign (non-cancerous) growths that develop on the surface or inside the muscle tissue of the uterus. In many women, uterine leomyoma is completely asymptomatic. In others, the location and size of these benign tumors can significantly impair quality of life. The mechanisms of development and growth of this benign tumor have not been fully established and continue to cause controversy. The role of immune disorders in the pathogenesis of leomyoma is currently being discussed. It has been proven that the growth of leomyoma is accompanied by a weakening of the immune defense against the background of an increase in the level of pro-inflammatory cytokines, which are regulators of the processes of proliferation and apoptosis, mediators of the action of sex steroids.

Thus, determining the type of tumor growth is an important point in developing the optimal tactics for managing patients, which will help preserve their reproductive function. The data obtained to date indicate the direct involvement of immune system reactions in the mechanisms that determine the development and growth of uterine leomyoma, but the role of cells with cytotoxic activity in the pathogenesis of this disease has not yet been studied. Establishing the relationship between the features of the production of cytokines and growth factors by immunocompetent cells with the rate and morphological types of growth of uterine leiomyoma will allow us to identify new aspects of the pathogenesis of this tumor and develop new approaches to its conservative treatment.

Purpose of the study

Evaluation of the effectiveness of immunomodulatory therapy in women with asymptomatic uterine leiomyoma.

Material and methods

67 women with asymptomatic uterine leiomyoma were examined. The mean age was 29.6±1.2 years. Ultrasound mapping was used as the main research method before and after surgery for asymptomatic uterine leiomyoma, which makes it possible to identify a certain dependence of changes after immunomodulatory therapy. All patients were examined before treatment, i.e. before surgery immunomodulatory therapy. Current trends in the treatment of uterine fibroids are guided by ideas about the mechanisms of growth of the leiomyomatous node.

Despite a fairly large clinical experience in the treatment of uterine leiomyoma, the effect of treatment is often incomplete, the disease progresses, which requires radical surgical intervention.

The goal of medical treatment of uterine leiomyoma is to relieve or eliminate symptoms and, if possible, regression of leiomyomatous nodes. When choosing a drug therapy option, one should evaluate not only its effectiveness, but also its safety, tolerability, and also take into account its cost-effectiveness.

Results and discussion

67 women were divided into 2 groups: group 1 - 38 women who underwent basic therapy with the inclusion of ulipristal acetate for 8 months (3 months daily at 5 mg, a break of 2 months and then another 3 months at 5 mg daily), Group 2 - 29 women who, after basic therapy, additionally received the Likopid immunocorrector (10 mg, 1 tab., sublingually daily).

Likopid is a high-tech semi-synthetic preparation of a new generation of muramyl dipeptides, the active ingredient of which is glucosaminylmuramyl peptide (GMDP) - a synthetic analogue of the universal fragment - peptidoglycan - the cell wall of all known bacteria, including microorganisms of the normal microflora of the mucous membranes of the macroorganism [15,16]. As a result of the specific interaction of GIDP with intracellularly located NOD2 receptors, phagocyte activation occurs, followed by a balance in cytokine synthesis [16,19].

Immunological studies were performed 2 weeks after treatment.

Analysis of the obtained results showed that against the background of hormonal therapy of uterine fibroids, latent forms of urogenital infections are activated, as a result of the potentiating immunosuppressive effect of hormonal drugs that contribute to immune status disorders, the reduction of the functions of Th1- and Th2-lymphocytes, as well as a significant inhibition of apoptosis.

As can be seen from the table, the content of activated lymphocytes changed after hormone therapy, but not significantly; there was only a tendency to change. The inclusion of the immunocorrector Licopid in the complex therapy of women with asymptomatic uterine leomyoma contributed to the positive dynamics of the content of lymphocytes with activation markers. Thus, the level of CD25+- and CD71+-cells significantly decreased, averaging 21.8±1.3% ($p<0.05$) and 11.8±1.0% ($p<0.01$), respectively. The level of CD95+-lymphocytes after complex therapy averaged 24.6±1.2% ($p<0.05$).

Table 1. Dynamics of lymphocytes with an activation marker in women with asymptomatic, uterine leiomyoma M±m

Index	Counter. group	Experimental group		+ lycopid
		before treatment	after treatment	
CD25+, %	21,6±0,9	25,8±1,0[a]	26,8±1,1[a]	21,8±1,3[бв]
CD71+, %	18,7±0,8	34,6±1,2[a]	32,7±1,2[a]	18,8±1,0[бв]
CD95+, %	24,5±1,0	22,3±0,9	19,8±1,1[a]	24,6±1,2[в]

Note. $p<0.05$-0.001: a — compared with control; b — in comparison with the initial data; c - in relation to the data of women with hormone therapy.

The acute phase protein level of lactoferrin in women with asymptomatic uterine leiomyoma, reduced before treatment, after hormone therapy significantly increased to an average of 914±14.6 ng/ml ($p<0.05$), and after the inclusion of licopide reached control values - 1098±23 .8 ng/ml ($p<0.001$).

The content of IL-6, slightly increased before treatment, after hormone therapy became significantly higher than in women in the control group, averaging 25.5±1.3 pg/ml ($p<0.05$).

Table 2. Levels of pro-inflammatory cytokines in the dynamics of treatment in women with asymptomatic uterine leiomyoma, M±m

Index	Counter. group, n=30	Initial data, n=38	hormone therapy,, n=18	+ lycopid, n=20
ИЛ-6	20,8±1,3	23,7±1,1	25,5±1,3[a]	22,6±1,2[a]
ИЛ-8	28,7±1,4	35,4±1,5[a]	34,6±1,6[a]	29,6±1,3[бв]
ИЛ-18	68,6±4,7	70,3±3,9	78,7±4,1[a]	70,4±3,7[бв]
ИЛ-10	14,9±1,2	18,7±1,4[a]	17,5±1,0[a]	15,1±0,8[a]
ФНО	34,1±1,8	79,3±3,8[a]	76,3±3,4[a]	36,8±1,3[бв]

Note. $p<0.05$-0.001: a — compared with control; b — in comparison with the initial data; c - in relation to the data of women with hormone therapy.

The inclusion of Likopid in the complex treatment contributed to the decrease in the level of IL-6 to the values of the control group - 22.6±1.2 pg/ml. As can be seen from Table 2, the level of IL-8, significantly increased before treatment, showed a downward trend after hormone therapy. A significant decrease was observed after the immunocorrective drug licopid to 29.6±1.3 pg/ml ($p<0.05$).

The content of IL-18 in women with asymptomatic uterine leiomyoma initially did not differ significantly from the control. However, after hormone therapy, the level of this hormone significantly

increased, averaging 78.7±4.1 pg/ml ($p<0.05$). The inclusion of an immunomodulator in complex therapy contributed to a significant decrease in the level of this cytokine to 70.4±3.7 pg/ml ($p<0.01$).

In our studies, the level of IL-10 in women with asymptomatic uterine leiomyoma was increased by 1.25 times ($p<0.05$). After hormone therapy, the level of this cytokine did not change, averaging 17.5±1.0 pg/ml. When the licopid preparation was added, the level of this cytokine averaged 15.1±0.8 pg/ml ($p<0.05$).

Analysis of the obtained results showed that the level of TNF-α in women with asymptomatic uterine leiomyoma was increased by 2.3 times - up to 79.3±3.8 pg/ml ($p<0.01$). After hormone therapy, the level of TNF-α did not change, averaging 76.8±3.4 pg/ml, which is 2.2 times higher than the control ($p<0.05$). And in the group of women who were added to the complex therapy with the immunomodulatory drug licopid, the level of TNF-α decreased to control values and averaged 36.8±1.3 pg/ml ($p<0.01$). This value was lower not only compared with the baseline data, but also with the indicator of women who received hormone therapy.

Immunological studies in women with asymptomatic uterine leiomyoma and complaints of infertility with the inclusion of the immunomodulator lycopid in the complex treatment showed that a positive dynamics of the studied parameters was observed in the immune system. Thus, the content of lymphocytes with an activation marker was normalized, the level of lactoferrin was normalized, as well as the synthesis of the studied cytokines.

Conclusions

1. The treatment with the use of hormone therapy contributed to the positive dynamics of clinical parameters, but did not affect the parameters of the immune system. The inclusion of the immunomodulatory drug licopid in the complex therapy contributed to the restoration of altered parameters of the immune system, which, in turn, made it possible to optimize reproductive health.
2. Of the women with asymptomatic uterine leiomyoma after complex treatment, 60.0% became pregnant and gave birth to healthy children.
3. Therefore, the inclusion of immunomodulatory drugs in the complex treatment indicates the possibility of their use as one of the elements of the pathogenetic therapy of this disease.

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