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PREDICTION OF UTERINE MYOMA GROWTH RATE: WHAT'S NEW? (LITERATURE REVIEW)

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Abstract

Uterine fibroid remains a relevant issue in modern gynecology and reproductive medicine as the most common benign tumor of the female reproductive organs. Comprehensive diagnosis of the condition of the myomatous nodule and its potential growth rate plays a significant role in the rational selection of treatment tactics for women of reproductive age with uterine fibroids.

Objective. To study and analyze existing methods of diagnosis and prediction the growth of uterine fibroids.

Matherials and methods. Information search was conducted in the scientific literature in domestic and foreign publications, 46 sources were studied and analyzed. In the course of the study, a meta-analysis of the information obtained was carried out as to the set goal.

Results and discussion. At present, at least three main mechanisms of activation of signal pathways stimulating leiomyocyte to pathological growth and division have been

elucidated: cytokines, growth factors, and hormone-dependent channels. All links in the activation of signal pathways affecting the cell, which subsequently lead to pathological proliferation and tumor transformation, are interconnected. In recent years, the pathogenesis of uterine fibroids has been actively studied not only at the tissue level but also at the genetic and epigenetic levels. It has been definitively proven that disturbances in microRNAs, both tissue-specific and stable, play a leading role in regulating the expression of key genes associated with the pathogenesis of uterine leiomyomas, both in tumor foci and in biological fluids. **Conclusions**. Study of the expression of microRNAs is a promising method for understanding the further development of the pathological process and for predicting the growth of uterine fibroids.

Keywords: **epigenetics; microRNAs; uterine fibroids; prognosis**

ПРОГНОЗУВАННЯ ТЕМПІВ РОСТУ МІОМИ МАТКИ: ЩО НОВОГО? (ОГЛЯД ЛІТЕРАТУРИ)

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Міома матки є найпоширенішим доброякісним пухлинним захворюванням жінок. Важливе значення для раціонального вибору лікувальної тактики у жінок репродуктивного віку з ММ має комплексна діагностика стану міоматозного вузла та можливого темпу росту.

На теперішній час з’ясовані три основні механізми активації сигнальних шляхів, що стимулюють лейоміоцит до патологічного росту та поділу: цитокіни, фактори росту та гормон-залежні канали, які пов’язані між собою.

В останні роки активно досліджується патогенез ММ на генетичному та епігенетичному рівнях. Провідну роль у регуляції експресії ключових генів, асоційованих з патогенезом лейоміоми матки, відіграють порушення мікроРНК, як у фокусі пухлини так і у біологічних рідинах, некодуючих молекул РНК. Дослідження експресії мікроРНК є перспективним методом для прогнозування росту міоми матки.

Ключові слова: епігенетика; мікроРНК; міома матки; прогнозування.

Introduction. Uterine fibroids are an urgent problem in current gynecology and reproductology, as well as the most widespread benign tumorous diseases of female organs [1, 2]. According to various literature data, the frequency of uterine fibroids in women of the reproductive age reaches 20 to 50%, although in hundreds of cases the incidence of the disease is significantly increasing, since this nosological form can be asymptomatic and therefore undiagnosed and episodes [3, 4] of UF is most frequently diagnosed during perimenopause. However, in older women, symptoms may begin much earlier [5, 6, 7].

The objective of the study was the development and analysis of existing methods for diagnosing and prognosis of the growth of uterine fibroids. Of importance for the rational choice of medical tactics in women of the reproductive age with uterine fibroids is a comprehensive diagnosis of the myomatous node, including assessment of its blood supply and possible growth rate [1].

A present, there is a lot of questions as for the development of uterine fibroids and one of them is “How to predict the growth of a myomatous node?” [3].

There is no such thing as a universal model that would create real dynamics of UF growth. Algorithms have been developed for predicting the receptor state of the myometrium, parameters of the hormonal profile, markers of cell proliferation and apoptosis, cytokine profile [7, 8]. As a rule, in models the real shape of the myomatous node is considered to be spherical or epileptoid, and the mechanical properties of the distant tissues is either not guaranteed, or is taken as a constant [9].

Materials and methods. Information search was carried out in the scientific literature in native and foreign literature, 46 providers of information with the problem of investigation were studied and analyzed. During the study, a meta-analysis was carried out on the information that was extracted.

The results and discussion. Today in practice, the most utilized approach to prognosis of the uterine fibroids growth is to determine the histotype of uterine fibroids, which is possible through microinvasive procedures or surgical resection.

Consistent with the histogenetic principle that underlies the WHO classification (1997), the smooth cell tumor is called leiomyoma. The term “leiomyoma” characterizes the morphogenesis of the disease and the histological structure of the tumor itself, which is indicated by the relationship of its muscular and tissue elements:

1. fibromyoma - the cellular tissue elements prevail (comparison between the muscular and connective tissue 1: 2–3);

2. fibroids - a mixture of the muscular and connective tissue 4–5: 1;

2.1. leiomyoma – a tumor of the smooth muscular cells of the myometrium;

2.2. rhabdomyoma is a tumor with striated cells.

The basis of the subsection of uterine fibroids by histotype is described in the monograph by Zaporozhan V.M., where the current classification of uterine fibroids of smooth muscles is presented: [10]

I. Smooth muscular tumors with primary differentiation - Primary leiomyoma, leiomyoma with a high mitotic index - Leiomyosarcoma

II. Smooth muscular tumors with an unusual histological structure:

- Atypical leiomyoma (symplastic leiomyoma)
- Epithelioid smooth muscular tumor
- Lipoleiomyoma
- Neurilemoma-like leiomyoma
- Leiomyoma with “tubules” or glands
- Leiomyoma with benign heterologous elements

III. Tumors with extraordinary height

- Infiltrative leiomyoma, including leiomyomatosis
- Disseminating peritoneal leiomyomatosis
- Benign metastatic leiomyoma
- Parasitic leiomyoma
- Leiomyoma with vascular invasion
- Intravascular leiomyomatosis

In addition, there are classifications that evaluate the stage of proliferative processes, on the basis of which clinical and morphological types are determined:

1. simple myoma, develops like benign myomatous hyperplasia – slow growth, proliferative processes are not significant;

2. proliferating myoma –real tumor with high mitotic activity;

3. presarcoma - characterized by the presence of multiple atypical elements, heterogeneity of cell nuclei with large hyperchromic nuclei [11].

Simple UFs are characterized by rapid growth, a tendency to fibrosis, spontaneous regression, and UFs of the proliferative type exhibit rapid growth, associated with hyperplastic, neoplastic processes of the endometrium, pathology of the cervix, uterine appendages [12]. According to the international morphological classification, the simple UF is considered to be the most important and most common. Proliferating UF, according to the

morphological classification, ranges from “cellular”, “mitotically active” (“chimeric”) [12]. According to the literature [11, 12, 13], UF of the simple type has:

- low proliferative and mitotic activity; — increased production of components of the post-occlusive matrix (laminin, fibronectin, collagen);

- low angiogenesis;

- low proliferative activity;

Leiomyoma of the uterus of the proliferative type is characterized by:

- high proliferative activity;

- enhanced production of components of the post-occlusive matrix (laminin, fibronectin, collagen), a high level of angiogenesis;

- numerous nodes, rapid growth, sometimes associated with adenomyosis;

- macroscopically – clear edges, of a red color on section, apparently empty with hemorrhagic content.

Yet, most of the classifications do not provide us with information about the possible prediction of the tumor growth, except the histotype options, which are based on the quality of this and other tissue and its proliferation activity. But it should be stressed that the determination of the tumor histotype still requires invasive procedures, which is a disadvantage of this method.

Taking into account everything that has been said, it becomes obvious that the need for methods for predicting the growth rate of uterine fibroids is urgent, and it will also be possible to reverse effective treatment tactics, which in turn will allow a shorter implementation of the reproductive function and patient’s life quality. It is also important to note rare types, which may not only rapidly grow, but also lead to a generalization of the process and internal vascular dissemination.

Internal vascular leiomyomatosis is a rare disease, in which the pathological process can extend to the cardio-pulmonary system, including the right atrium, right ventricle and pulmonary arteries [14].

Clinical case. *As an example of this rare uterine fibroid with a highly active level of proliferation and capable of the intravascular expansion is the clinical case, which we observed in our clinic. A patient of 35 years old with a diagnosis of benign metastatic leiomyoma, who underwent a conservative myomectomy with penetration into the empty uterus 8 years before the onset of symptoms of metastasis in the lung. Recurrence of the illness occurred in 2 years after the first operation with gradual progression. The patient refused surgical treatment. After the development of bronchial symptoms and coughing she*

referred to the doctor's office, a comprehensive procedure was carried out and a diagnosis was made: Primary benign leiomyoma of the uterus. Secondary affection of the lungs. The patients underwent surgical treatment followed by tamoxifen and dynamic follow-up. The illness progressed. The patient was consulted abroad, as a result of which she was advised and underwent secondary surgical intervention. The patient is under dynamic follow-up at the present time [15].

The growth of UF is primarily due to the process of proliferation, which is subsequently stimulated by the sexual hormones through growth factors by an autocrine-paracrine mechanism, with apparently low readiness of the tumor cells to undergo apoptosis.

Currently, three main mechanisms of activation of signal pathways have been identified that stimulate the leiomyocyte to pathological growth and division [16]. One of them contains cytokines that regulate the processes of proliferation, cell growth and apoptosis (interferon-alpha, interleukins, tumor necrosis factor, etc.) [16].

Another way of stimulating proliferation is closely related to growth factors, such as oncogenes and factors that stimulate the creation of blood vessels necessary for the growth of tumor. The most powerful stimulators of the cellular division are epidermal growth factor, insulin-like growth factor (type 1), epithelial and fibroblastic growth factors. The most powerful stimulator of neoangiogenesis is the endothelial growth factor.

The third route of the myocyte stimulation to pathological growth runs through the hormone-dependent channels. Sexual steroid hormones, namely the excessive estrogenic influence in women with insufficient progesterone, play one of the key positions [17]. Uterine leiomyoma nodes may have increased sensitivity to steroid hormones, which differs from the normal myometrial response to estrogen and progesterone [17, 18]. When normal myometrium is less responsive to estrogen and is insensitive in the luteal phase the uterine leiomyoma tissue demonstrates increased expression of estrogen-regulated genes in the luteal phase [17]. In addition to the loss of temporary/cyclical regulation by estrogen, uterine leiomyoma also increases its response to progesterone, which usually has a depressive effect on the myometrium [17]. However, it is still not clear if there are clear changes in sensitivity to the sexual steroid hormones.

Besides, there is an increase in the expression of the Ki-67 antigen in the myomatous tissue, which is indicative of cell proliferation, that in combination with the insufficient activity of the bcl-2 proteins, which control the stages of biological reactions leading to apoptosis, inhibit the growth of the tumor [18]. All sections of activation of signal pathways

influencing the cell, which subsequently lead to pathological proliferation and tumor transformation, are interconnected.

The growth of myomatous nodules directly depends on increased blood flow in the vascular system of the uterus [19, 20]. The Doppler ultrasound method is highly informative in diagnosing tumors of the female genital system, including uterine fibroids [20, 21]. Doppler ultrasound allows you to identify arterial vessels of two types:

- those that nourish myoma, they emerge from the myometrial vascular network and form an area of angiogenesis in the form of a regular ring at the periphery of the myomatous node;

- central internal tumor cells, which develop in response to the angiogenic activity of tumor cells [22].

At present, an obstetrician-gynecologist has a lot of laboratory, clinical and instrumental diagnostic methods in his arsenal. According to modern clinical protocols for the existing diagnosis of UF there are a variety of imaging methods (ultrasound, CT with and without contrast, MRI), as well as endoscopic methods [1, 2, 21-2 5]. Yet, there is an important question in diagnosis and clinical tactics necessary to predict the growth of tumor. In the midst of the great expansion of diagnostic methods for uterine leiomyoma, there are only a few ones that in varying degree can help in predicting the progression of the disease. Such methods include the monitoring of sexual hormones, Dopplerography/metry, epigenetic studies, using the method of microRNA expression. In addition, clinicians have a dynamic follow-up in their practice, which is based on bimanual examination and visualization methods, which allows assessing the growth rate of uterine fibroids for a short period of time (at least 6 months). However, there is a drawback in the dynamic follow-ups; it is duration and impossibility to use them in patients with symptomatic illness.

An increase in the frequency of UF detection after menarche, an increase in its size during pregnancy and regression after menopause indicate a clear connection with the increase in tumor and the level of sexual hormones [26]. Estrogens are considered to be stimulants of UF growth. The level of local estrogens in myomatous nodes can stimulate their growth independently of ovarian hormones [27]. The most clearly visible is the growth of the tumor due to the production of estrogens, steroid, and local concentrations of estradiol and aromatase in the tissue of the myomatous node and the expression of receptors to estrogen and progesterone in healthy myometrium vary [28]. All these changes are observed locally, and the monitoring of sexual hormones in this condition is invasive, so there is no need to select any other method for predicting the pathological process.

Dopplerography of the myoma artery was useful for monitoring the response of leiomyoma to drug treatment, differentiating leiomyoma from adenomyosis and assessing changes in the size of tumor as a response of the uterine artery to embolization (EMA) [29]. In addition, it is considered that the stage of vascularization reflects the possible character of tumor growth and the risk of increased bleeding during surgery.

Myoma tumor genesis associated with myometrial vascular anomalies, includes venular ectasia and enlarged venous plexus [30], arterial dilatation [31], localized dilation of the myometrial vessels and abnormal organization of vessels in the perifibrotic region [32]. These findings can be assessed using Doppler imaging [21]. Besides, this examination method makes it possible to assess the stage of vascularization of the tumor, and therefore the likelihood of its further growth.

It should not be forgotten that the tumor growth, associated with uterine leiomyomas, depends not only on vascularization and the intensity of the blood supply, but also on the proliferation and apoptosis of cells, and namely on prioritizing of one process over another. The regulation of metabolic processes, as well as many others, involves the products of microRNA target genes.

Uterine fibroid is a multifactorial disease of the female sexual system and today the role of the epigenetic factor in the pathogenesis of uterine fibroids is proved but insufficiently developed [33-35]. The pathogenesis of UF is still being actively studied not only at the tissue level, but also at the genetic and epigenetic levels [33-37, 38-41]. It is considered that cell proliferation and apoptosis may be of primary importance for the growth and progression of fibroids, and inhibition of transcription, translation, or degradation of microRNA (mRNA) is associated with a wide range of disorders, including new formations and tissue fibrosis [17, 18]. Epigenetic anomalies and associated transcriptional disturbances of genes can provoke the transformation of the normal tissue into trunk tumorous, which will then give rise to monoclonal uterine fibroids. In particular, it has been established that changes in the synchronic expression of microRNA, as a key factor in the regulation of gene expression, play an important role in the pathobiology of uterine fibroids [33, 36, 37]. MicroRNAs (mRNAs) are evolutionarily conservative, small non-coding RNA molecules (21–23 nucleotides), which play an important role in the transcriptional and post-transcriptional regulation of gene expression. To date, it has been proven that microRNA disruption plays a major role in regulating the expression of key genes associated with the pathogenesis of uterine leiomyomas, which indicates the prospects for their use in predicting relapses of this disease. MicroRNAs have substantial advantage to other byomarkers as they are tissue -specific and

stable both in the tumor focus and in the biological fluids (blood, lymph, urine, tears, breast milk and other secrets) [36, 37]. The main method for identifying miRNA levels is the polymerase chain reaction (PCR), which is apparently inexpensive, highly sensitive, and widely used in routine laboratory practice [42]. MicroRNA-29 and microRNA-146 are the most studied in the pathogenesis of UF [43, 44]. March et al. found that the level of micro-RNA expression in tumorous UF tissue is significantly lower than that in the normal myometrium, whereas a high level of expression is associated with decrease production of components of the intercellular matrix [45].

Concclusion. The study of microRNA expression provides a clear understanding of the further development of the pathological process. It can be especially informative when combined with Doppler measurements to identify the correlation of the data obtained using these two methods. Thus, in our opinion this direction of investigation is promising and will require detailed study in order to improve the effectiveness of diagnosis, prediction, and therefore treatment of uterine leiomyoma.

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