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MODERN ASPECTS OF THE ETIOLOGY AND PATHOGENESIS OF UTERINE MYOMA

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Abstract:

This article outlines various theories of the pathogenesis of uterine leiomyoma, and bases on these theories, it still refers to benign smooth muscle monoclonal tumors.

Keywords:

Uterine myoma (leiomyoma) is consistently considered the most common benign tumor of the female reproductive system. According to the summary data, its frequency fluctuates within a fairly wide range (20-50%) and has a stable tendency to increase. Despite various theories of the pathogenesis of uterine leiomyoma, it still refers to benign smooth muscle monoclonal tumors.

Morphogenesis and further growth of uterine leiomyoma includes the following stages of development:

• Stage 1 – formation of an active growth zone in the myometrium; active zones are located near microvessels and are characterized by a high level of metabolism and vascular-tissue permeability, which favors tumor development;
• Stage 2 – tumor growth without signs of differentiation (microscopically detectable node);
• Stage 3 – tumor growth with its differentiation and maturation (microscopically detectable node).

There are two theories of the origin of the uterine fibroid precursor cell: one implies the appearance of a cell defect during the ontogenetic development of the uterus due to a long unstable period of embryonic smooth muscle cells; the second suggests the possibility of cell damage in a mature uterus. The latter theory seems more obvious, since the prevalence of uterine fibroids, according to ultrasound and pathological studies, can reach 85%.

The mechanism of formation of the rudiment of growth of the myomatous node, most likely, occurs as follows. During each ovulatory menstrual cycle, in its first phase, receptors for progesterone and various growth factors (transforming, epidermal, fibroblast growth factor, etc.) accumulate on the surface of the myometrium cells. After ovulation, the processes of hyperplasia and hypertrophy of the myometrium occur under the influence of progesterone produced by the corpus luteum. Progesterone has both a direct effect on the myometrium cells, binding to its specific receptors, and an indirect effect due to the expression of various growth factors. Hyperplasia and hypertrophy of the myometrium develop uniformly, mainly due to the balanced expression of two types of progesterone receptors (A and B). The A-type of receptors is blocking, and the B-type is effector. Uniform distribution of these receptors ensures a measured increase in the mass of the myometrium tissue. In the absence of conception, the concentration of progesterone in the woman's blood drops, and the process of apoptosis is activated in the myometrium tissue, due to which the elimination of excess smooth muscle cells occurs. It is due to this mechanism that the uterus does not increase in size from cycle to cycle.

Probably, during the course of repeated cycles of myometrial hyperplasia, followed by apoptosis, there is an accumulation of smooth muscle cells in which the apoptosis process is disrupted, and these proliferating cells are exposed to various damaging factors. The damaging factor may be ischemia caused by spasm of the spiral arteries during menstruation, an inflammatory process, traumatic impact due to surgical interventions, or a focus of endometriosis. With each menstrual cycle, the number of damaged cells accumulates, but their fate may be different. Some of the cells are sooner or later eliminated from the myometrium, while others begin to form the rudiments of myomatous nodes with different growth potential.

An active growth rudiment in the early stages develops due to physiological fluctuations in hormones during the menstrual cycle. Subsequently, the resulting cell cooperation activates autocrine-paracrine mechanisms caused by growth factors, forms local autonomous mechanisms for maintaining growth (local production of estrogens from androgens and formation of connective tissue), and the significance of physiological concentrations of sex hormones for the formation of a myomatous node ceases to be the main one. The hypothesis of the stimulating effect of progesterone on the growth of uterine myoma is confirmed by clinical studies, which noted tumor growth

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against the background of taking estrogen-gestagen agents with a high level of progesterone for the purpose of hormone replacement therapy in the premenopausal period. There is an opinion that the significance of the hormonal background for the growth of a myomatous node up to a certain stage is critical. With an increase in the size of the tumor, local autonomous mechanisms are formed, which makes the growth of the myoma relatively independent. It is necessary to clarify that we are not talking about the ability of a myoma node to autonomously increase in size in the complete absence of hormonal influence, but about the impossibility of significant regression of the tumor size when deprived of its hormonal stimuli. In this regard, it is logical to assume that each myomatous node conditionally consists of two parts: a stable core and a regressing part.

The stable core is the volume of the node that remains after the complete cessation of its blood supply, and the regressing part is, accordingly, the volume of the node by which it decreases in the absence of blood supply to the tumor. Its minimum size is determined by the stable core. To establish the tactics of treating patients with uterine myoma, it is necessary to understand what size of the myomatous node will not have clinical significance (clinically inactive (insignificant) tumor).

Provoking factors in the development of uterine myoma are chronic inflammatory foci in the myometrium, mechanical damage, adenomyosis. In comparison with the surrounding tissues of the uterus, the amount of associated microbial flora, including pathogens of genital infections, is increased in myomatous nodes. The conducted morphological and immunohistochemical studies indicate the formation of "growth zones" of uterine myoma in the form of bundle proliferation of smooth muscle cells around inflammatory infiltrates and endometrioid explants in the myometrium. Today, it has been absolutely proven that the development and growth of uterine myoma is largely due to the state of the receptor apparatus of the uterus. Specific receptors, interacting with hormones, form estrogen-receptor or gestagen-receptor complexes.

Currently, clinicians in many countries around the world use the classification of uterine myoma recommended by the International Federation of Obstetrics and Gynecology.

This classification presents eight types of uterine myoma, including a hybrid class (the presence of two types of myomas at the same time);

• SM (submucosal), submucosal:

Type 0 - tumor on a "pedicle" (thin base)

Type 1 - at least 50% of the node volume is in the thickness of the uterine muscle;

Type 2 - no more than 50% of the node volume is in the thickness of the uterine muscle;

• O (other), others:

Type 3 - tumor contacts the endometrium; 100% intermuscular;

Type 4 - intermuscular;

Type 5 - subperitoneal; more than 50% of the node volume is in the uterine muscle;

Type 6 - subperitoneal; less than 50% of the node volume is in the uterine muscle;

Type 7 - subperitoneal on a "pedicle" (thin base);

Type 8 - other localization (requires specification, for example, cervical);

• Hybrid - for example, types 2-5 indicate the localization of the tumor, which on one side deforms the uterine mucosa, on the other - its serous cover.

The choice of treatment method for patients with uterine fibroids, despite the long history of the issue, still causes a lot of discussion. The essence of the disagreement lies in the choice of indications for the use of one or another method of treating this disease - medication or surgery. According to the classical canons, the indications for surgical treatment of patients with uterine fibroids are:

1) Large tumor size (over 12 weeks of pregnancy);
2) Submucous localization of fibroids, accompanied by prolonged and heavy menstruation, anemia;
3) Rapid tumor growth (over 4 weeks of pregnancy within one year);
4) Subperitoneal fibroids on a thin base (on a "pedicle"); these tumors are associated with a high risk of torsion of the base of the node and the subsequent development of its necrosis;
5) Necrosis of the fibroid node;
6) Dysfunction of neighboring organs;
7) Cervical uterine myoma localized in the vagina;
8) Combination of uterine myoma with other diseases of the genital organs requiring surgical intervention;
9) Infertility (in those cases where it is convincingly proven that the cause of infertility is uterine myoma).

The extent of surgical intervention depends on the age of the patient, concomitant gynecological diseases (condition of the endometrium, cervix, ovaries, fallopian tubes), reproductive function. Women interested in preserving the generative and menstrual function, if conditions are available, undergo organ-preserving surgery - myomectomy - enucleation (excision) of myomatous nodes.

Currently, two main directions of treatment of patients with uterine myoma are being developed and improved:

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conservative and surgical; and in some situations they are mutually complementary.

For many years, drug therapy for patients with uterine myoma was based on suppression of estrogen synthesis. Accordingly, for these purposes, agents with an antiestrogenic effect were used - progestogens, antigonadotropins, gonadotropin-releasing hormone agonists. With the emergence of new data on the pathogenesis of leiomyoma and, in particular, the determining role of progesterone in stimulating the growth of myometrial tumors, approaches to drug therapy for patients with uterine myoma have changed fundamentally. According to modern concepts of uterine myoma morphogenesis, progesterone receptor blockers are able to suppress the growth of uterine myoma, as well as stimulate its regression. Progesterone receptor ligands include both progesterone itself or its analogs (progestogens), which make up a group of pure agonists, and pure progesterone receptor antagonists. It is quite logical that the greatest efficiency in the treatment of patients with uterine myoma can be achieved by using a symbiosis of these substances. Today, agents have been developed that have mixed agonist-antagonist properties in relation to progesterone receptors. As a class, they are called "selective progesterone receptor modulators" (SPRMs). SPRMs inhibit the expression of epidermal growth factor, insulin-like growth factor type 1, transforming growth factor p3 and their receptors in cultured leiomyoma cells, without affecting their expression in myometrial cells. SPRMs have an antiproliferative, proapoptotic and antifibrotic effect on leiomyoma cell culture, without having a similar effect on normal myometrial cells. SPRMs modulate the ratio of progesterone receptor isoforms (PR-A and PR-B) in cultured leiomyoma cells, which ensures cell viability; suppression of expression of growth factors, angiogenic factors and their receptors in these cells; induction of apoptosis by activation of mitochondrial ligand associated with tumor necrosis factor, causing apoptosis and destruction of the endoplasmic reticulum. In addition, SPRMs suppress collagen synthesis by modulating extracellular matrix enzymes in cultured leiomyoma cells, without affecting similar processes in cultured normal myometrium cells.

CONCLUSION: Today, SPRMs are actively used as preoperative (medicinal) preparation of patients who are scheduled for myomectomy. Moreover, a number of authors speak out in favor of the mandatory use of SPRMs for preoperative preparation of patients with uterine myoma in reproductive age.

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