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MODERN ASPECTS OF DIAGNOSTICS AND TREATMENT OF UTERINE FIBROIDS

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Abstract:

Uterine fibroids are still the most common cause of surgical interventions in gynecology, often leading to the loss of the reproductive organ. The reason for this is the late appeal of women to the doctor after the occurrence of complications, an increase in the size of the uterus and the number of nodes. Numerous studies have shown that today a differentiated approach to the treatment of each woman is necessary, since the widespread use of modern high-resolution ultrasound devices and Doppler sonography allow not only to describe the topography and size of the nodes, but also to determine the nature of the fibroid nodes, their proliferative activity. Uterine fibroids (MF) are formed from smooth muscle cells and affect up to 29% of women aged 15-54 years worldwide. Given the current demographic situation and the increasing trend of pregnancy planning at an older reproductive age every year, an organ-preserving approach to the treatment of MF is becoming a priority.

Keywords: Uterine fibroids, sex hormones, growth factors, proliferation, apoptosis, gene mutations.

Uterine myoma (UM) is a benign monoclonal hormone-sensitive formation formed from smooth myocytes of the cervix and body of the uterus [1]. The incidence of leiomyomas is up to 29% [2], the prevalence of UM in Eastern Siberia according to the results of a non-selective sample of 2389 women was 26.4% [3], and according to autopsy methods of research it can reach 70-80% [4]. In most cases, the disease is asymptomatic, while 25% of women have abnormal uterine bleeding (AUB), chronic pelvic pain, dysfunction of adjacent organs, concomitant symptoms of iron deficiency anemia (IDA), dyshormonal diseases of the mammary glands, infertility, complications of gestation and its course [5]. MM ranks second among gynecological pathologies and, despite the introduction of minimally invasive organ-preserving treatment methods, remains the cause of every third hysterectomy in the world [5]. In recent years, MM has also been "rejuvenated" due to the improvement of visualization methods of examination, so the diagnosis of the formation in patients under 25 years of age is no longer casuistry. This aspect, coupled with the tendency to plan pregnancy in the late reproductive period, makes the problem of preserving women's health especially relevant. The etiology and pathogenesis of MM currently remain controversial and ambiguous issues [5]. Leiomyoma is a progesterone-dependent formation, which is confirmed by the predominant increase in the size of the nodes in the secretory phase of the menstrual cycle [5]. The hypothesis about the leading role of estrogens is considered obsolete by most authors, since the local hyperestrogenic environment created by tumor cells only contributes to an increase in the density of progesterone receptors in the MM tissues in the follicular phase of the menstrual cycle, while progesterone is the most important mitogen for its growth and development [4]. The role of this hormone is realized through stimulation of the expression of endothelial and vascular growth factors. Today, the role of the genetic factor in the development of neoplasms is also actively studied. Thus, cytogenetic studies have shown that about 40-50% of myomatous nodes have chromosomal and gene abnormalities, including changes in the genes MED12, HMGA2, COL4A5/COL4A6, etc. [6], which may be of a secondary somatic mutation nature. At the same time, these studies are potentially capable of predicting the risk of MM relapses and contributing to a more thorough differentiated approach to choosing treatment for this group of patients. The following factors predispose to the development of leiomyomas: early menarche and late childbearing, low reproductive rates, excessive therapy with body-identical gestagens, a history of chronic inflammatory diseases of the pelvic organs and intestines, as well as the Negroid race, obesity, and an aggravated family history [4, 7]. In particular, in chronic inflammatory diseases of the genitals and intestines, infectious agents, through various mechanisms, potentially entering the uterus, can initiate an immune-inflammatory reaction accompanied by the production of a large number of growth factors by mononuclear cells - epidermal growth factor (EGF), insulin-like

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growth factor (IGF), vascular endothelial growth factor (VEGF) - the main triggers of leiomyoma, as well as increased synthesis of the intercellular matrix by activated myofibroblasts [8]. All this leads to the activation of the formation and acceleration of the growth rate of myomatous nodes. At the same time, signs of chronic inflammation of the pelvic organs and intestines in women with MM are associated with the ineffectiveness of hormonal therapy, which emphasizes the importance of eradication of pathogens and restoration of the normocenosis of the genital tract and intestines as an important stage of drug treatment [8]. Given the current demographic situation, an organ-preserving approach to the treatment of MM is a priority. A single algorithm has not yet been developed, and it is hardly possible given the diversity of the clinical picture and the characteristics of the course of the pathology in each specific case of the disease. Therefore, MM therapy involves a strictly personalized approach. Today, it is becoming obvious that various options for drug therapy and surgical treatment should not be opposed and exclude each other, because it is the possibility of combining surgical and therapeutic approaches that ensures the best clinical outcomes. It is important to understand that when even small, clinically insignificant myomatous nodes are detected, a long-term passive-expectant tactic can contribute to the loss of therapeutic opportunities. Only clinically insignificant avascular subserous MM can be subject to dynamic observation, mainly during the perimenopause and provided that the patient visits the obstetrician-gynecologist regularly. The main indication for drug treatment remains "symptomatic" MM [4, 5]. The therapeutic strategy, depending on the clinical situation, can pursue 3 main goals: reducing the severity of disease symptoms and improving the quality of life, stabilizing hemostatic parameters as a stage of preoperative preparation in women with severe IDA, and regression of myomatous nodes. The "gold standard" of treatment in our country to date is considered to be gonadotropin-releasing hormone agonists (GnRH agonists), which are able to stop bleeding within 7-14 days after the start of administration and cause regression of myomatous nodes with sufficiently long-term use. However, their use is limited due to undesirable side effects due to ovarian hypofunction, which is accompanied by menopausal symptoms and necessitates add-back therapy with estrogens [4]. Another disadvantage of the treatment is the lack of a lasting effect - after discontinuation of the drug in fairly young patients, the size of myomatous nodes returns to the original parameters. Therefore, GnRH agonists are increasingly used as a means of short-term preoperative preparation in patients with severe AUB or as an independent therapy option in women with MM and adenomyosis, who are approaching the age of menopause and have contraindications to surgery or refuse surgical treatment. For the same purposes, a group of selective progesterone receptor modulators (SPRMs), in particular, ulipristal acetate (UPA), can also be used in clinical practice. It has been proven that the drug helps to reduce intraoperative blood loss, shorten the length of hospital stay for patients after myomectomy and ensure stable regression of myomatous nodes, which in some clinical cases makes it possible to avoid surgical intervention altogether and consider the use of UPA as an independent method of MM therapy [9]. With this approach, treatment with long intermittent courses is recommended [10]. The indication may be MM types 3–5 according to the 2011 classification of the International Federation of Gynecology and Obstetrics (FIGO) [11]. Selective progesterone receptor modulators, unlike GnRH agonists, do not cause undesirable side effects in the form of concomitant symptoms of hypoestrogenism and are well tolerated by patients. However, the use of UPA may be limited in women with concomitant hyperplastic processes in the endometrium. Numerous studies have shown that changes in the uterine mucosa associated with the drug, the so-called progesterone receptor modulators Associated Endometrial Changes (PAEC), are exclusively benign and completely reversible [9]. Nevertheless, according to a number of sources, it is recommended to perform a pipelle biopsy of the endometrium in women with concomitant hyperplastic processes in order to reduce the risk of worsening the course of the disease [9]. A similar study may be prescribed by the attending physician 6 months after discontinuation of the drug [9]. A direct indication for discontinuation of the drug is a threefold increase in the level of transaminases, as well as a more than twofold increase in bilirubin relative to the upper limit of normal [11]. In 2020, the European Medicines Agency (EMA) Committee of the European Commission considered that the benefits of using UPA outweigh the possible risks, especially in patients for whom alternative treatments are unavailable or ineffective for various reasons [12]. Thus, UPA has an impressive evidence base, studied clinical efficacy, good tolerability by patients, promotes stabilization of hemodynamic parameters and regression of myomatous nodes, which persists even after drug withdrawal, which in some cases makes it possible to avoid surgical treatment [9–11]. Speaking about organ-preserving tactics for managing patients with MM, one cannot fail to mention the well-proven minimally

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invasive, stable-regressive method of uterine artery embolization (UAE). It is the operation of choice for women with established reproductive function, whose myomatous nodes do not exceed 6 cm in diameter, especially if extensive surgery or hormonal treatment methods may be contraindicated for them for various reasons. The embolization technique may differ slightly in different countries, but the essence of this microinvasive operation remains unchanged - to achieve complete bilateral selective catheterization of the uterine arteries and coaxial occlusion of the distal arterioles [13]. The expected outcome of the intervention is complete cessation of arterial blood flow (during UAE, the cessation of contrast flow to the myoma nodes is recorded on the X-ray monitor screen, after UAE - based on color Doppler mapping data [13]), dehydration of the nodes, formation of their calcified capsule, as well as aseptic necrosis, hyalinosis and calcification of the nodes. Control ultrasound examinations (US) of the treatment effectiveness are carried out 3, 6, 12 months after UAE. An undesirable side effect may be post-embolization pain syndrome of varying severity. Non-specific postoperative symptoms also include a possible increase in body temperature and a feeling of general malaise [13]. Pathogenetically, the occurrence of "severe" and "unbearable" pain can be explained by the difficulty of venous outflow from involutional MM nodes in patients with varicose veins [13]. This problem can be solved by using flavonoids and other groups of venoprotectors in the early postoperative period. By acting systemically on the venous wall, the drugs reduce the severity of the hyperdynamic reaction of blood circulation, promote better outflow of venous blood from ischemic nodes and alleviate pain [13]. The most controversial issue regarding EMA has long been the hypothesis of its negative effect on the ovarian reserve. The decrease in the number of antral follicles is likely to be a consequence of insufficient collateral blood flow in the ovaries. Therefore, most countries do not recommend the use of UAE in women with reproductive plans, and especially those who use assisted reproductive technologies (ART) [1]. However, in 2019, a meta-analysis of 353 patients showed that the decrease in the number of antral follicles on control ultrasound scans in women who underwent UAE, recorded 3–4 months after the intervention, is completely eliminated within 1 year, and in some cases the technique even provokes a rebound effect [9]. Hemodynamic shifts in the ovarian artery basin can compensate for the insufficient blood flow in the collaterals of the ascending uterine artery, which can hypothetically be affected by embolization, which explains the subsequent restoration of the number of follicles [10]. An equally serious complication of UAE, which limits the use of the technique in women of reproductive age, is subsequent miscarriages in early pregnancy, which is presumably associated with changes in the morphofunctional properties of healthy myometrium, which has undergone short-term ischemia during surgery [6]. However, there is convincing evidence that artificially created ischemia usually resolves within 48-72 hours after UAE due to the highly developed network of collaterals of the branches of the uterine, ovarian and iliac arteries in the healthy myometrium, while leiomyoma nodes, which often have a single source of blood supply, infarct [13]. Conclusion. In recent years, a pronounced transition to an organ-preserving treatment strategy has been observed in domestic and foreign approaches to the treatment of leiomyomas. Understanding the pathogenetic mechanisms of MM indicates the need for a personalized approach in each specific case of the disease. Today, conservative and surgical methods of treating leiomyomas should not be opposed, but, on the contrary, complement each other in order to achieve the best clinical results. Modern ideas about the etiology and pathogenesis of uterine myoma are based on scientific facts in the field of cytogenetics, molecular genetics, endocrinology, immunology, and the sphere of intercellular interaction. Thus, there is no single cause for the occurrence and development of uterine myoma. Many different factors are involved in this process, which explains its frequent spread and the heterogeneity of the tumor itself, both in terms of morphohistochemical features, location, number of nodes and the nature of their growth, and in terms of clinical manifestations. Given the high medical and social significance, the problem of uterine myoma requires further detailed study of the etiology, pathogenesis, and methods of its timely diagnosis and treatment.

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