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ОБЗОРНАЯ СТАТЬЯ

Uterine fibroids: modern methods of treatment, advantages and complications

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Abstract. The state of the reproductive system by women with uterine fibroids is considered as a part of this literature review. The main clinical manifestations of myomatous nodes were identified by writing the review: abnormal uterine and heavy menstrual bleeding, infertility, miscarriage, chronic pelvic pain, dysfunction of adjacent organs, which are indications for surgical treatment. It is noted that approximately 30 % of women with uterine fibroids suffer from abnormal uterine bleeding, leading to anemia and reduced quality of life. Chronic pelvic pain significantly reduces the quality of life of patients, worsening their functional and mental state and disrupting sexual function. This review focuses on reproductive problems in women with leiomyoma. Taking into consideration the high prevalence of this nosology and the need to preserve the fertility of patients, the review describes modern methods of treating patients with uterine myoma, including drug therapy surgical treatment and alternative methods. Currently, in order to stop the symptoms of uterine fibroids, as well as for preoperative preparation, conservative therapy is used, which allows to reduce pain, restore hemoglobin levels, reduce intraoperative blood loss and reduce surgery time. Reproductive disorders associated with uterine fibroids, such as infertility, recurrent miscarriage, and adverse obstetric outcomes, are a significant reason to improve organ-preserving therapies or develop new ones. Although hysterectomy is a radical treatment for uterine fibroids, it is unacceptable for patients who have not realized their reproductive function. Therefore, the most justified intervention is myomectomy with various surgical approaches, and as an alternative treatment, uterine artery embolization, radiofrequency ablation or high-intensity focused ultrasound treatment of uterine fibroids. These data allow us to conclude that the high prevalence and versatility of symptoms of uterine fibroids among patients of reproductive age determine the relevance of searching for optimal methods of treatment.

Key words: uterine fibroids, abnormal uterine bleeding, infertility, miscarriage, myomectomy, hysterectomy

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Introduction

Reproductive health by modern women is characterized by an increase in gynaecological diseases, including uterine fibroids [1, 2]. Often, fibroids require surgical treatment in order to improve the quality of life and preserve the fertility of patients [3], i.e. organ-preserving [4] and minimally invasive [5]. Myomatous nodes can cause abnormal uterine bleeding (AUB), heavy menstrual bleeding (HMB), infertility, miscarriage, chronic pelvic pain (CPP), dysfunction of adjacent organs, which are indications for surgical treatment [6–8]. Approximately 30 % of women with uterine fibroids suffer from abnormal uterine bleeding, leading to anaemia and reduced quality of life [8]. The cause of abnormal uterine bleeding associated with leiomyomas is associated with an increase in the surface area of the uterus, an increase in vascularity and vascular blood flow in the uterus, a decrease in myometrial contractility, ulceration of the endometrium over the submucosal leiomyoma, and compression of the venous plexus within the myometrium [9] (Fig.1).

Chronic pelvic pain significantly reduces the quality of life of patients, worsening their functional and mental state and disrupting sexual function. Uterine fibroids can also cause pelvic pain [10]. Pain in leiomyoma may be due to an increase in the number of nerve fibers in the endometrium and myometrium due to hyperestrogenism and an increase in nerve growth factor [11]. Reproductive disorders such as infertility, recurrent miscarriage and adverse obstetric outcomes can also be caused by uterine fibroids [12].

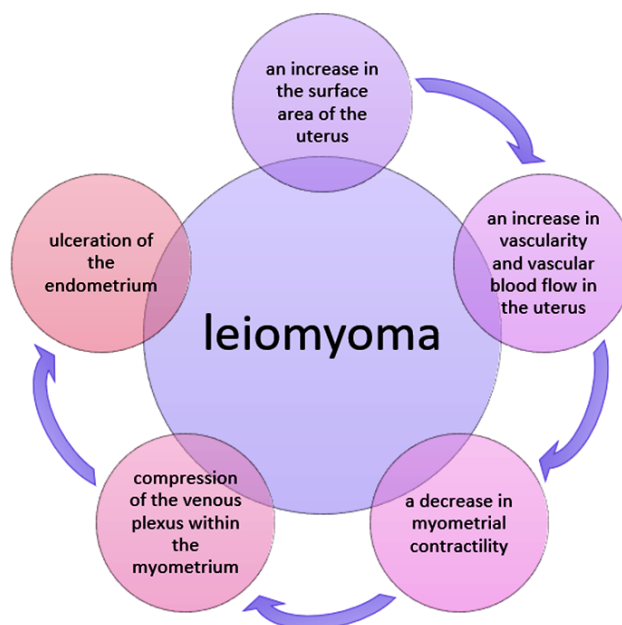


Fig. 1. Causes of abnormal uterine bleeding associated with uterine fibroids

Despite advances in the study of molecular processes in leiomyomas and associated changes in the myometrium and endometrium, there are no unambiguous data on the relationship of infertility with uterine myoma, and the mechanism of implantation disorders and the development of early pregnancy remains unclear [13]. It is known that the effect of leiomyoma on the conception and carrying of pregnancy depends on its localization: the most pronounced in the submucosal location, the least — in the subserous, and with the intramural location of the myomatous node, the data

are ambiguous and contradictory [3,12]. Thus, the high prevalence and versatility of symptoms of uterine fibroids among patients of reproductive age determine the search for optimal methods of treatment.

Conservative treatment

Drug therapy is currently used mainly to relieve or reduce the intensity of symptoms of uterine fibroids: abnormal uterine bleeding, heavy menstruation and pain [14, 15], as well as for preoperative preparation of patients in order to restore hemoglobin levels, reduce the size of myomatous nodes and intraoperative blood loss [16].

The main drugs for the treatment of uterine fibroids are the progesterone antagonist mifepristone and gonadotropin-releasing hormone (aGnRH) agonists, the effectiveness of which has been well studied and proven [17], and their use in Russia is regulated by current clinical guidelines [18]. Mifepristone counteracts the action of progesterone, which is necessary for the growth of fibroids [19]. It was found that its use at a dosage of 10 and 25 mg for 3 months reduced menstrual blood loss by 90 %, while the decrease in uterine volume was a dose-dependent effect [20]. With further use, mifepristone at a dosage of 50 mg/day led to a decrease in the size of the uterus by 34 %, compared with the group without treatment [21]. According to the study, the preoperative use of GnRH-a made it possible to reduce intraoperative blood loss, choose a less invasive surgical approach, reduce the operation time, and also contributed to the reduction of technical intraoperative difficulties in large intraligamentary and cervical uterine myomas [22].

The role of the selective progesterone receptor modulator Ulipristal acetate (UPA) in the treatment of uterine fibroids has been actively discussed in the literature. UPA is a selective progesterone receptor modulator that binds to progesterone receptors in the myometrium, endometrium, and fibrous tissue and inhibits ovulation without affecting antiglucocorticoid activity and estradiol levels. The drug has been used for the treatment of symptomatic uterine fibroids since 2012 as a preoperative treatment, and in 2015 UPA

was approved as a course treatment [23]. According to studies, this drug is effective in patients with AUB, amenorrhea occurred in approximately 70 % of patients while taking it [24], and an improvement in the quality of life was also noted [25]. However, since 2017, the use of Ulipristal has been limited due to reports of severe liver damage while taking it [26]. Further studies have shown that the risk of taking UPA is not higher than the risks associated with surgery [23], despite this, the drug retained approval only for the course treatment of uterine fibroids with restriction of use in patients with impaired liver function [23].

The trend towards organ-preserving treatment determines the need to search for new effective conservative, including medical, methods of treating uterine fibroids, which can improve the quality of life and preserve the possibility of reproductive function. Currently, oral forms of gonadotropin-releasing hormone (GnRH) antagonists, such as elagolix, relugolix and linsagolix, in combination with drugs of the estrogen and progesterone groups are being actively studied [27]. The authors of the studies note the high efficiency (up to 94 %) of these drugs in the treatment of heavy menstrual bleeding associated with uterine myoma [28]. The role of vitamin D in the pathogenesis and treatment of uterine fibroids is also actively discussed. The use of vitamin D in patients with vitamin D deficiency and uterine fibroids contributed to a decrease in the size of myomatous nodes 6 months after treatment [29], in another study, there was no decrease, but the absence of growth of myomatous nodes was noted [30].

Surgery

Myomectomy is the operation of choice if there are indications for its removal and the patient's unrealized reproductive function. Depending on the localization, size and number of myomatous nodes, the choice of surgical access is carried out: hysteroscopic, laparoscopic or laparotomic [3]. Widely used conservative myomectomy does not always lead to the improvement of women. According to a cohort study, 38 % of women after myomectomy had abnormal uterine bleeding, 13 % of patients reported pelvic pain,

and 17 % had a problem of unrealized reproductive function [9].

Recurrence of uterine fibroids after surgical treatment with various approaches occurred in 23 % of patients, and 5 % of women underwent repeated surgical intervention [31], in 35 % and 38 % of patients after myomectomy with various approaches, heavy menstrual bleeding and abnormal uterine bleeding, respectively, were observed [32]. According to an observational study, after hysteroscopic removal of FIGO types 0, 1, and 2 myomas, 46 % of patients required reoperation due to AUB recurrence, which is associated with incomplete resection of uterine fibroids [33].

Pelvic pain is an actual problem even after surgical removal of myomatous nodes. The proportion of patients with pelvic pain after myomectomy is 39 %, with 47 % of these patients undergoing laparoscopic myomectomy, 36 % laparotomy, and 27 % hysteroscopic [32]. When examining patients with a history of myomectomy, it was found that 31.8 % of women were bothered by dysmenorrhea [34]. In addition to the peculiarities of tissue innervation around the removed myomatous nodes, the cause of CPP after surgery is the adhesive process in the pelvic area. According to the literature, the incidence of adhesions after myomectomy by laparotomic and laparoscopic approaches was 22 and 15.9 %, respectively [35].

Removal of submucosal fibroids leads to the restoration of the normal anatomy of the uterus, contributing to successful conception. The effect of surgical treatment of other types of fibroids remains less clear. Removal of the intramural myomatous node can resolve disorders such as local inflammatory response of the endometrium and abnormal contractility of the myometrium, which can also lead to improved implantation of the ovum [3]. In addition, the effect of the number of fibroids on fertility is not well understood, although one systematic review reported that fewer fibroids were associated with improved reproductive outcomes after their removal [36]. Myomectomy improved pregnancy rates by 55.7 % in patients with unexplained infertility [37]. But studies also show a high incidence of complications in subsequent pregnancies after myomectomy. In those women who

became pregnant after the removal of 6 or more fibroids, 45.5 % had a premature birth, 45.5 % of the pregnancy ended in an early miscarriage, and 9.1 % had an ectopic pregnancy [38]. Undoubtedly, women with a uterine scar after myomectomy need personalized preconception preparation for a successful pregnancy, its safe course and delivery. It is necessary to take into account the viability of the scar on the uterus. The study revealed that 1 month after surgery, 50 % of patients were diagnosed with various changes in the area of the scar on the uterus: thinning of the uterine wall, local retractions, deformation of the wall in the form of a niche, microcalcifications and cysts, reduced or no blood flow in the scar area [39]. Such changes in the uterine wall in the area of the scar can lead to its failure and rupture of the uterus during pregnancy or childbirth, which is a life-threatening condition for the mother and fetus [40]. In a cohort study, two groups of patients after laparoscopic myomectomy were compared, in the first group women received anti-relapse therapy after surgery and underwent pregravid preparation, in the second group there were women who applied already with an onset pregnancy without pregravid preparation. It was found that in the second group, pregnancy was much more often complicated in the first trimester by threatening spontaneous miscarriage (RR) (OR=2.83 (95 % CI 1.77–4.52) and a lower chorionic vascularization index (11.78 ± 2.22 and 13.36 ± 2.44 , $p < 0.001$); in the second trimester — threatening CO (OR=4.57 (95 % CI 2.62–7.97); in the third trimester — threatening preterm birth (PR) (OR=2.76 (1.67–4.54)) [41].

Alternative organ-sparing therapies include uterine artery embolization (UAE), radiofrequency ablation (RFA) of the myoma, and High-intensity focused ultrasound (HIFU) for uterine fibroids [42]. According to a systematic review and meta-analysis, when comparing UAE and HIFU, uterine artery embolization showed an improvement in quality of life indicators, while in the group after ultrasonic ablation of uterine fibroids, the pregnancy rate was significantly higher [42]. In another study, it was found that after the use of focused ultrasound, changes occurred in the pre-implantation endometrium in the form of asynchronous maturation of pinopodium, which is associated with recurrent miscarriage in the early stages [43]. Although

uterine artery embolization is a highly effective way to reduce BUN and BVR, however, 15–50 % of patients require re-treatment [4]. A retrospective VITALITY study found that RFA improves the quality of life of patients, reduces the symptoms of uterine fibroids, and repeated surgical intervention was required in less than 12 % of patients 4–5 years after ablation [44].

For the purpose of radical treatment of patients with uterine myoma, the operation of choice is hysterectomy, which remains popular and at present, leiomyoma occupies the first bar among indications for removal of the uterus [14]. Removal of the uterus is performed mainly in women during the menopausal transition and in postmenopause [45]. The study found that in patients 1 year after hysterectomy, the quality of life improved significantly compared with patients after myomectomy, which is associated with the impossibility of recurrence of uterine fibroids and abnormal uterine bleeding [45]. But the disadvantage of hysterectomy performed by various surgical approaches is an increased risk of pelvic organ prolapse [46, 47].

Conclusion

The high prevalence of uterine fibroids among patients of reproductive age necessitates the use and further improvement of organ-preserving treatment methods, taking into account the presence and severity of leiomyoma symptoms, as well as the patient's reproductive plans.

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Миома матки: современные методики, преимущества и осложнения

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Аннотация. В рамках литературного обзора рассматривается состояние репродуктивной системы у женщин с миомой матки. При написании обзора авторы выявили основные клинические проявления миоматозных узлов: аномальные маточные и обильные менструальные кровотечения, бесплодие, невынашивание беременности, хроническая тазовая боль, нарушение функций смежных органов, которые являются показаниями для оперативного лечения. Отмечается, что примерно 30 % женщин с миомой матки страдают аномальными маточными кровотечениями, приводящими к их анемизации и снижению качества жизни. Хроническая тазовая боль заметно снижает качество жизни пациенток, ухудшая их функциональное и психическое состояние и нарушая сексуальную функцию. В данном обзоре особое внимание уделяется проблемам репродукции у женщин с лейомиомой. С учетом высокой распространенности данной нозологии и необходимости сохранения фертильности пациенток описаны современные методы лечения пациенток с миомой матки, включая медикаментозную терапию, хирургическое лечение и альтернативные методы. В настоящее время с целью купирования симптомов миомы матки, а также для предоперационной подготовки используется консервативная терапия, которая позволяет снизить болевой синдром, восстановить уровень гемоглобина, уменьшить кровопотерю во время операции и длительность операции. Нарушения репродуктивной функции, ассоциированные с миомой матки, такие как бесплодие, привычное невынашивание беременности и неблагоприятные акушерские исходы, являются весомым поводом для усовершенствования органосохраняющих методов лечения или разработки новых. Несмотря на то, что гистерэктомия является радикальным методом лечения миомы матки, она неприемлема для пациенток, которые еще не реализовали свою репродуктивную функцию. Поэтому наиболее оправданным вмешательством является миомэктомия различными хирургическими доступами, а в качестве альтернативного лечения — эмболизация маточных артерий,

радиочастотная абляция или высокоинтенсивное сфокусированное ультразвуковое лечение миомы матки. Приведенные данные позволяют сделать вывод, что высокая распространенность и многогранность симптомов миомы матки среди пациенток репродуктивного возраста определяют актуальность поиска оптимальных методов лечения.

Ключевые слова: миома матки, аномальные маточные кровотечения, бесплодие, невынашивание беременности, миомэктомия, гистерэктомия

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