CURRENT ISSUES OF EFFECTIVENESS AND SAFETY OF UTERINE ARTERY EMBOLIZATION IN PATIENTS WITH UTERINE LEIOMYOMA

© P.G. Korobova¹, A.N. Sulima¹, A.A. Mkrtchyan², Z.S. Rumyantseva¹, S.A. Korobov²

¹ Medical Academy named after S.I. Georgievsky, V.I. Vernadsky Crimean Federal University, Simferopol, Russia; 
² Republic Clinical Hospital named after N.A. Semashko, Simferopol, Russia


Received: January 17, 2020 Revised: February 20, 2020 Accepted: April 13, 2020

Uterine artery embolization (UAE) is a highly effective minimally invasive method for treating patients with symptomatic uterine leiomyoma, which becomes more popular between those refusing hysterectomy and conservative myomectomy for a number of reasons, including unrealized fertility. Some issues of UAE effectiveness and safety are still being investigated: optimization of method in order to guarantee radiation safety, extension of indications for UAE, recurrence risk prediction, choice of tactics according to individual anatomy of local blood supply, fertility impact assessment. The results of investigations demonstrate safety and high efficacy of UAE in the treatment of symptomatic uterine leiomyoma on condition that modern techniques of procedure optimization and an individualized approach to the selection and treatment of patients are used.

Keywords: leiomyoma; uterine artery embolization; fertility.

AKTUAL'NYE VOPROSY EFEKTVINITI I BEOAPASOSTI EMBOLIZACII MAOTNYX ARTERIX U PAXINTOK S LEJOIMOMOJ MATKI

© П.Г. Коробова¹, А.Н. Сулима¹, А.А. Мкртчян², З.С. Румянцева¹, С.А. Коробов²

¹ «Медицинская академия им. С.И. Городевского» (структурное подразделение) Федерального государственного автономного образовательного учреждения высшего образования «Крымский федеральный университет имени В.И. Вернадского» Министерства образования и науки Российской Федерации, Симферополь; 
² Государственное бюджетное учреждение здравоохранения Республики Крым «Республиканская клиническая больница имени Н.А. Семашко» Министерства здравоохранения Российской Федерации, Симферополь


Эмболизацию маточных артерий — высокоэффективный малоинвазивный метод лечения пациенток с симптомной лейомиомой матки — все более часто применяют у пациенток, отказывающихся от гистерэктомии и консервативной миомэктомии по ряду причин, в том числе при нереализованной репродуктивной функции. Продолжаются исследования ряда вопросов, связанных с эффективностью и безопасностью эмболизации маточных артерий: оптимизация методики для гарантирования лучевой безопасности, расширение показаний к эмболизации маточных артерий, прогнозирование риска рецидивирования миоматозных узлов и обусловленных ими симптомов, выбор тактики в зависимости от индивидуальных анатомических особенностей кровоснабжения, оценка влияния на фертильность. Результаты исследований свидетельствуют в пользу безопасности и высокой эффективности эмболизации маточных артерий при лечении симптомной лейомиомы матки при условии использования современных методик оптимизации процедуры и индивидуализированного подхода к отбору и лечению пациенток.

Ключевые слова: лейомиома матки; эмболизация маточных артерий; фертильность.
Uterine leiomyoma (LM) is currently one of the most common gynecological pathologies (13%–27%). By the age of 50 years, LM is diagnosed in 70% of women. In one-third of female patients, LM manifests itself depending on the location of pelvic organ compression symptoms, chronic pelvic pain syndrome, recurrent miscarriage, infertility, menstrual disorder, and abnormal uterine hemorrhage resulting in anemia. The European Society of Human Reproduction and Embryology defines myomatous nodules up to 5 cm as small and more than 5 cm as large [1].

There is no gold standard treatment for symptomatic LM, and a strictly individualized approach is required to resolve this issue. According to current tendencies in drug treatment of LM, ulipristal acetate is recognized as the most effective drug. Being a tissue-specific antigestagenic drug, it has the so-called progesterone receptor modulator-associated endometrial change effect [2]. This effect is reversible, and this drug is recommended, including as a preoperative preparation. The feasibility of the latter before conservative myomectomy (CM) is discussed since several authors argue that the LM nodule of reduced size is more difficult to enucleate.

Indications for surgical treatment, which are noted in 15% of LM patients, include infertility in the absence of other causes, LM growth in the postmenopausal period, LM sizes exceeding 12 weeks, nodule growth for more than 4 weeks for a year, chronic pelvic pain syndrome, dysfunction symptoms of the pelvic organs, cervical, isthmus, or interligamentous tumor localization, and amenoplastic uterine hemorrhage [1].

At present, hysterectomy for symptomatic LM accounts for 45.3% of abdominal interventions in gynecology. Hysterectomy, being a radical method, is associated with the loss of reproductive function; therefore, patients should be selected depending on extragenital pathology, which determines the anesthetic risk and reduces the quality of life due to complex metabolic and psychovegetative disorders that make up posthysterectomy syndrome [3]. The range of organ-preserving techniques includes uterine artery embolization (UAE), CM, Doppler-controlled transvaginal arterial occlusion, focused ultrasound ablation under magnetic resonance imaging (MRI), percutaneous laser ablation, and cryoablation [4]. UAE and CM are most often used.

UAE is an organ-preserving method for LM treatment and is a minimally invasive alternative to surgical techniques. It can also be used as the first stage before hysterectomy in patients with an increased risk of intraoperative hemorrhage [1]. This method was first used by the French gynecologist Ravina in 1991 to stop uterine hemorrhage in a patient with uterine myoma [5]. The principle of this procedure consists of occluding the branches of the perifibroid vascular plexus by administering an emboli suspension into the lumen of the vessel under angiographic control [6]. Because of the local cessation of blood flow in the myomatous nodule, several degenerative processes develop, such as intracellular acidosis, proteolytic enzyme and structural protein denaturation, and coagulation necrosis [7]. Today, UAE is widely used to reduce the diameter and manifestations of symptomatic LM in patients who refuse radical intervention for any reason, including those oriented toward the implementation of the reproductive function.

UAE has several advantages over other approaches, including reproductive function preservation, local anesthesia use, reduced infectious complication risk, shorter surgery duration, shorter rehabilitation and hospitalization terms, and ability to perform with both a single nodule and multiple LM, including the combination of LM with adenomyosis [8].

Absolute contraindications to UAE include pregnancy, an infectious process in the acute stage, and malignant neoplasms of the reproductive organs. Relative contraindications, which require close attention and preoperative correction, include an allergy to the radiopaque substance, impaired renal function, and coagulopathy [9].

The industry standard of the Cardiovascular and Interventional Radiological Society of Europe and the Society of Interventional Radiology provides the criteria for technical (cessation or significant reduction in blood flow in the myomatous nodule) and clinical (cessation or significant decrease in the severity of LM symptoms) efficacy of UAE in LM treatment [10].

Cases deserve consideration when patients decide to resort to UAE after an ineffective conservative treatment with gonadotropin hormone agonists. However, because the sizes of nodules often return to the initial ones after the cancellation of these drugs, UAE should be performed 3 months
after the treatment [11]. At the same time, the combined technique in the presence of large LM nodules with more than 10 cm diameter includes the prescription of gonadotropin hormone agonists to reduce the diameter of the nodule to 8 cm with subsequent UAE [12].

Being an effective minimally invasive method, UAE is nevertheless associated with certain radiation exposure during preoperative and intraoperative arteriography. Most patients are of reproductive age and prefer UAE because of reproductive plans. X-rays are directed to the region of the internal genital organs, which creates the greatest load on them [8]. Nikolic et al. evaluated the ovary-absorbed dose (OAD) and skin-absorbed dose (SAD) by placing dosimeters in the posterior vaginal fornix and on the skin surface at the ray entry point. The average OAD (0.223 Gy) and SAD (1.623 Gy) values for UAE exceeded those for hysterosalpingography and computed tomography of the trunk (0.004–0.006 and 0.001–0.019 Gy, respectively). However, this load does not exceed the threshold radiation values; therefore, there is no risk of radiation damage [13]. When conducting UAE, it is necessary to adhere to the “as low as reasonably possible” principle, namely, the maximum possible reduction in radiation exposure, which allows, simultaneously, to perform high-quality angiographic review and control of the procedure without harm to diagnostics and treatment. The optimization principle implies the following:

1. the use of pulsed fluoroscopy (OAD reduction by 1.7 times compared with full-frame fluoroscopy);
2. the use of frontal views (OAD reduction by 1.9 times compared with oblique views);
3. image minimization (OAD reduction by 1.1 times compared with the enlargement of images);
4. competence and proficiency of the doctor (which reduce the time of the study);
5. serviceability and quality of equipment.

It should be remembered that a high body mass index and the significant size of myomatous nodules increase the total absorbed dose [14].

The UAE method does not completely avoid this complication but significantly reduces the frequency of recurrence of myomatous nodules. During the first 10 years of the postembolization period, the growth of LM resumes in 10.3% of cases, or 20%–28% of cases, according to other sources [15]. Katsumori et al. compared the effectiveness of repeated and primary UAE. The second procedure led to a less significant decrease in the volume of the uterus and the diameter of the myomatous nodules, presumably because of the volume of the uterus and the diameter of the myomatous nodules, presumably because of the development of an extensive network of uterine and ovarian anastomoses [16]. Ananthakrishnan et al. compared the follow-up data of patients after CM and UAE by performing an MRI 5 years after the intervention. The formation of new LM nodules was recorded in 60% of patients after myomectomy and only in 7% of women who underwent UAE [17]. From 2013 to the present, the University of Birmingham has been conducting a randomized FEMME study, which aimed to compare the effects of UAE and myomectomy on the quality of life of LM patients who want to avoid hysterectomy [18].

The individual characteristics of the blood supply to the pelvic organs in LM patients, namely, the presence of anastomoses, represent a factor that largely determines the intraoperative complication risks and UAE effectiveness. Gomez-Jorge et al. [19] described four anatomical variants of branching of the uterine artery, based on which an angiographic classification of this vessel was created. Moreover, there are cases when the myomatous nodule received additional blood supply from the inferior mesenteric artery, arteries of the round ligament of the uterus, and internal pudendal artery [15]. In 10% of women, the ovarian branch of the uterine artery is the main source of blood supply to the ovaries, which, as previously believed, bears a risk of ovarian hypoperfusion and postembolization amenorrhea development. Blood supply to the uterine fundus in 10% of cases is exclusively due to the ovarian artery, which, in the case of LM localization in this section, makes classical UAE ineffective [20]. In this regard, MRI scan before UAE seems important to clarify the anatomy of the blood supply to the uterus and ovaries in patients with unimplemented reproductive function, with the localization of the LM nodule in the uterine fundus, or in case of a history of surgical interventions on the pelvic organs.

The UAE procedure is painless for 70% of women, but after it, more than 90% of patients report pain syndrome of varying severity [21]. In addition, in 50% of patients, in the first 72 h after
UAE, postembolization syndrome is noted, which components are caused by pathogenetic changes induced by embolization [22]. Hypoperfusion and acute ischemia of the myomatous nodule, which develops as a result of occlusion of the small arteries of the perifibroid plexus with emboli, cause pain syndrome that is aggravated by compression of the edematous myomatous nodule of the surrounding myometrium. Because of the drainage of the ischemic nodule into the uterine cavity, bloody discharge from the genital tract is often registered. Symptoms of hyperthermia (subfebrile temperature increase within 2–3 days) is a manifestation of the generalized reaction of the body to acute ischemia of the myomatous nodule. Moderate leukocytosis presumably develops as a standard response of the hemostatic system to uterine vascular thrombosis [5]. To assess the manifestations of postembolization syndrome, a visual-digital scale is used. Depending on its severity, antispasmodic and nonsteroidal anti-inflammatory drugs, as well as nonnarcotic analgesics, are prescribed for degree I, infusion crystalloid and intramuscular antibacterial therapies for degree II, narcotic analgesics, infusion and detoxification therapy, and intravenous antibacterial therapy for degree III, and also, the rheological properties of blood and hemostasis are corrected. A prospective randomized study demonstrated the efficacy of intravenous administration of 10 mg dexamethasone 1 h before UAE, which resulted in a significant decrease in the levels of C-reactive protein, interleukin-6, and cortisol on day 1 after the manipulation [12]. In another prospective randomized study, it was revealed that the administration of 10 mL of 10% lidocaine (100 mg) into the lumen of the uterine artery after its embolization decreased postoperative pain and, consequently, lowered the necessary anesthetic dose [23].

To date, there is no single opinion regarding the effect of UAE on the ability to conceive and bear a child [24]. It was believed that female patients’ reproductive plans are a contraindication to embolization. Recently, several studies have been conducted that demonstrated the comparability of the onset of pregnancy and bearing at full-term in LM patients after UAE and CM and in LM patients who have not been treated.

Proponents of the idea of the negative impact of UAE on fertility explain this effect of irreversible ischemic damage to the endometrial site, as well as a decrease in ovarian reserve due to deprivation of the ovary of a certain part of its blood supply [25]. Pregnancy complications are associated with a necrotized site in the endometrium, which can contribute to habitual miscarriage, premature birth, placental disorders, and postpartum hemorrhage [26, 27]. Thus, in a randomized controlled trial by Mara et al., the pregnancy rate was 50% after UAE and 78% after laparoscopic CM, and the rates of miscarriage were 53 and 19%, respectively. The FIBROID study demonstrated that premature menopause occurs in 7% of patients, but most of them are older than 45 years [28]. When comparing the outcomes of UAE and CM in the study of Arthur et al. [29], a more significant decrease in the level of antiMullerian hormone (AMH) and the number of antral follicles after UAE compared with CM was noted, whereas the levels of estradiol and follicle-stimulating hormone (FSH) did not differ significantly. Mara et al. [30] examined a greater number of patients with increased levels of FSH after UAE than after CM.

Clinicians, who refute the pathological effect of UAE on the childbearing potential, argue that the disorders in patients after UAE are caused not by the procedure itself but by the LM presence [31]. LM negatively affects the ability to conceive and causes pregnancy complications due to changes in the normal anatomy of the uterus, local changes in contractility and hormonal disorders, and disorders of blood supply [32]. Thus, it is impossible to distinguish reliably between the contribution of these two factors (LM and UAE) in reproductive dysfunction. Thus, according to Mohan et al., the frequency of pregnancy and termination of pregnancy after UAE in women with an average age of 35.9 years was 58.6% and 28%, respectively. The frequency of preterm birth and placental disorders was 7.3% and 6.3%, respectively [33]. When comparing the fertility of LM patients after CM and UAE in a systematic review of the Cochrane community in 2012, it was revealed that the number of pregnancies and childbirth was comparable (odds ratio [OR] 0.29, 95% confidence interval [CI] 0.10 and OR 0.33, 95% CI 0.11, respectively) [34]. Antropova et al. compared the aspects of pregnancy in LM female patients without treatment and LM patients after the UAE procedure for this pathology. In female patients in Group 2,
the enlargement of the myomatous nodules during pregnancy was less pronounced, and there were fewer cases of threatening termination of pregnancy, and during cesarean section, the blood loss level was lower [35]. The arguments in favor of the advantage of UAE over CM in relation to fertility also include a higher relapse rate after CM (about 44%) compared with UAE (from 10% to 20–28%, according to different authors) [36]. In this regard, pregnancy is recommended in the first 6 months after CM until the possible emergence of new nodules, which is not suitable for young patients who are not planning a pregnancy. Thus, the authors consider UAE as a method that does not limit the reproductive plans of patients to a 6-month period [31]. In a study that included patients after UAE, under the age of 40 years, there was no change in AMH level 6 months after the procedure compared with the preoperative level [37]. Lanciego et al., when analyzing the indicators of patients after UAE, concluded that the risk of amenorrhea is significantly affected not by the procedure itself but by the age of the patients and the initial state of ovarian function, as the vast majority of amenorrhea cases after UAE occur in patients of older reproductive age with ovarian dysfunction before the intervention. Hu et al. [15] proved that even targeted embolization of the ovarian artery (which is sometimes applied in the case of a significant blood supply to the LM nodule through this vessel) does not terminate the functioning of the ovaries.

Thus, reasonable traditional alertness regarding fertility decline after UAE is exaggerated. The common idea of the absolute incompatibility of UAE and the patient’s future reproductive plans should be abandoned, bearing in mind that the reproductive prognosis depends on factors such as the woman’s age, history, and initial fertility state.

Conclusions

UAE is a minimally invasive organ-preserving method of treating symptomatic LM, which is recognized as sufficiently effective and safe for widespread use in patients who want to preserve fertility and who have contraindications for surgical intervention, including risk of complications in general anesthesia. The method is relatively new, and it has several unique advantages over surgical methods and some absolute contraindications. Several questions regarding UAE remain open, including the dosing of radiation exposure, frequency of recurrence of myomatous nodules and associated symptoms, influence on reproductive function, possibility and features of application in the presence of large LM nodules, and variability of the anatomical structure of the uterine artery and blood supply to the uterus and ovaries. Scientific research continues in the fields indicated above. Studies have been conducted that demonstrate the preservation of fertility in female patients without prior infertility. There are techniques to reduce radiation exposure when performing angiographic study and control. Approaches have been developed in the case of atypical blood supply to the uterus and ovaries to avoid insufficient or excessive embolization to reduce the risk of nodule recurrence and ischemia of reproductive significant structures. Given these circumstances, UAE is an effective and safe method for the treatment of symptomatic LM, subject to an individualized approach to the selection and treatment of patients, the use of recent advances, due to which the procedure can be optimized as much as possible to reduce risks and increase efficiency.

References

5. Соколова Т.М., Карпенко А.А., Волков Р.В., и др. Эмболизация маточных артерий у пациенток с сердечно-


Information about the authors

Polina G. Korobova — Resident. The Department of Obstetrics, Gynecology, and Perinatology No. 1, the First Medical Faculty, Medical Academy named after S.I. Georgievsky, V.I. Vernadsky Crimean Federal University, Simferopol, Russia. https://orcid.org/0000-0002-3917-2363. E-mail: polina20may@ya.ru.

Anna N. Sulima — MD, PhD, DSci (Medicine), Professor. The Department of Obstetrics, Gynecology, and Perinatology No. 1, the First Medical Faculty, Medical Academy named after S.I. Georgievsky, V.I. Vernadsky Crimean Federal University, Simferopol, Russia. https://orcid.org/0000-0002-2671-6985. E-mail: gsulima@yandex.ru.

Polina Gennadievna Korobova — клинический ординатор кафедры акушерства, гинекологии и перинатологии № 1 первого медицинского факультета. Медицинская академия им. С.И. Георгиевского (структурное подразделение) ФГБОУ ВО «КФУ им. В.И. Вернадского», Симферополь. https://orcid.org/0000-0002-3917-2363. E-mail: polina20may@ya.ru.

Anna Nikolaevna Sulima — д-р мед. наук, профессор кафедры акушерства, гинекологии и перинатологии № 1 первого медицинского факультета. Медицинская академия им. С.И. Георгиевского (структурное подразделение) ФГБОУ ВО «КФУ им. В.И. Вернадского», Симферополь. https://orcid.org/0000-0002-2671-6985. E-mail: gsulima@yandex.ru.
Azat A. Mkrtchyan — MD, Head of the Department of Radiosurgery, Republic Clinical Hospital named after N.A. Semashko, Simferopol, Russia. https://orcid.org/0000-0002-6568-5632. E-mail: mkrtchyan@list.ru.

Zoya S. Rumyantseva — MD, PhD, Assistant Professor, Acting Head of the Department of Obstetrics, Gynecology, and Perinatology No. 1, the First Medical Faculty, Medical Academy named after S.I. Georgievsky, V.I. Vernadsky Crimean Federal University, Simferopol, Russia. E-mail: zoyarum@inbox.ru. https://orcid.org/0000-0002-1711-021X.

Sergey A. Korobov — MD. The Department of Gynecology, Republic Clinical Hospital named after N.A. Semashko, Simferopol, Russia. https://orcid.org/0000-0003-1109-1887. E-mail: imhotep-cci-rbc@yandex.ua.

Azat Ashotikovich Mkrtchyan — заведующий отделением рентгенорадиологических методов диагностики и лечения. ГБУЗ РК «Республиканская клиническая больница имени Н.А. Семашко» Минздрава России, Симферополь. https://orcid.org/0000-0002-6568-5632. E-mail: mkrtchyan@list.ru.

Зоя Сергеевна Румянцева — канд. мед. наук, доцент, и.о. заведующего кафедрой акушерства, гинекологии и перинатологии № 1 первого медицинского факультета. Медицинская академия им. С.И. Георгиевского (структурное подразделение) ФГБОУ ВО «КФУ им. В.И. Вернадского», Симферополь. E-mail: zoyarum@inbox.ru. https://orcid.org/0000-0002-1711-021X.

Сергей Анатольевич Коробов — врач отделения гинекологии. ГБУЗ РК «Республиканская клиническая больница имени Н.А. Семашко» Минздрава России, Симферополь. https://orcid.org/0000-0003-1109-1887. E-mail: imhotep-cci-rbc@yandex.ua.