

New Trends in Management of Uterine Submucus Fibroids by Hysteroscopy

Ali Elshabrawy Ali , Shehab Eldein Alsayed Mahmoud, Attya Mohamed Attya, Ahmed Ismail Mohamed

Department of Obstetrics and Gynecology, Faculty of Medicine, Zagazig University, Egypt

Corresponding author: Shehab Eldein Alsayed Mahmoud

ABSTRACT

Background: Uterine leiomyomata, also known as uterine fibroids, are the most common benign gynecologic tumors originating from smooth muscle cells within the myometrium. They may cause abnormal uterine bleeding, pelvic pain, infertility, and reproductive complications. Hysteroscopic myomectomy represents an important minimally invasive approach for the management of submucosal fibroids. Oxytocin and tranexamic acid are among the pharmacological agents used to reduce bleeding during myomectomy. Furthermore, hormonal factors and genetic alterations play important roles in fibroid development, while gene therapy has emerged as a potential therapeutic approach.

Objective: To review uterine fibroids, their diagnosis and management, with particular emphasis on hysteroscopic myomectomy, the hemostatic roles of oxytocin and tranexamic acid, genetic predisposition, and emerging gene therapy approaches for uterine leiomyomas.

Conclusion: Hysteroscopic myomectomy is an important uterus-preserving treatment option for submucosal fibroids. Oxytocin and tranexamic acid represent pharmacological approaches aimed at minimizing surgical blood loss. Understanding the hormonal and genetic mechanisms involved in uterine fibroid development may contribute to improved management strategies. Gene therapy represents a potential future therapeutic approach, although further investigation is required to establish its clinical application.

Keywords: Uterine fibroids; Hysteroscopic myomectomy; Oxytocin; Tranexamic acid; Genetic predisposition; Gene therapy.

Introduction

Uterine leiomyomata, also known as uterine fibroids, are the most common benign gynecologic tumors, occurring in 50% to 70% of females. Leiomyomata originate from uterine smooth muscle cells in the myometrium, and their growth is primarily stimulated by circulating estrogen. Uterine fibroids are classically diagnosed on physical exam and ultrasound imaging, which is highly sensitive for this pathology (1).

While many leiomyomata are asymptomatic and discovered incidentally, 25% to 30% of women experience a spectrum of symptoms that increase morbidity and adversely affect their quality of life. The most common symptoms include abnormal uterine bleeding (AUB), heavy menstrual bleeding (HMB), pelvic pain and pressure, low back pain, anemia, and bladder and bowel dysfunction. They continue to be the leading indication for hysterectomy. Additionally, the presence of 1 or multiple leiomyomata may affect fertility, as the distortion of the uterus can prevent successful implantation and the continued survival of an intrauterine pregnancy. Uterine fibroids also increase the risk of certain obstetric complications, including recurrent pregnancy loss (RPL), preterm labor (PTL), abnormal placentation, the need for cesarean birth, and postpartum hemorrhage (2,3).

Etiology and Molecular Background

Uterine fibroids are benign monoclonal tumors originating from smooth muscle cells within the uterus. The exact initiating factor of fibroid formation remains unclear. However, prevailing theories highlight the role of reproductive hormones, inherent abnormalities of the myometrium, and predisposing genetic variations that affect cell signaling pathways(4).

Several molecular studies have identified specific gene mutations associated with leiomyomata, the most common of which is the MED12 gene located on chromosome X at position q13. The MED12 gene codes for one of the key proteins in the mediator complex (subunit 12) that regulates RNA polymerase II; a mutation in this gene occurs in approximately 70% of uterine leiomyomas. Other common mutations associated with leiomyomas include high mobility group AT-hook 1 and 2 (HMGA1 and HMGA2) and collagen type IV alpha 4 and 6 (COL4A4 and COL4A6). Mutations in fumarate hydratase increase the risk for hereditary leiomyomatosis and renal cell carcinoma (HLRCC) syndrome, which often present with uterine leiomyomata; however, uterine leiomyomata associated with HLRCC are much less common than sporadic fibroids associated with MED12 mutations (5,6).

Additionally, uterine leiomyomata are hormonally sensitive tumors, and evidence has demonstrated that leiomyomas overexpress certain estrogen and progesterone receptors when compared to normal surrounding myometrium. Studies indicate that the ovarian steroids estradiol and progesterone promote the growth of leiomyomas, and myometrial cells with high levels of estrogen and progesterone receptors can stimulate the growth of adjacent uterine leiomyomata stem cells in a paracrine fashion. Additionally, the size of uterine leiomyomata typically declines during the postpartum period, with the use of hormone-suppressing gonadotropin-releasing hormone (GnRH) analogs, and after menopause, when levels of those hormones fall (7).

Diagnosis of Uterine Fibroids

Transvaginal ultrasound provides better image quality than abdominal ultrasound, but both methods might be necessary if the uterus is markedly enlarged with uterine fibroids. Since overlying bowel may limit the visualization of the uterus, abdominal ultrasound is performed with the bladder full enough to provide a “window” for the uterus. Vaginal ultrasound studies are performed with an empty bladder for patient comfort (8).

Saline infusion sonohysterography (SIS) is also helpful when a submucous or sessile myoma is suspected based on clinical history or ultrasound examination (9). Saline infusion sonography is performed by filling the uterus with saline while assessing the uterine cavity by transvaginal ultrasound. If evaluation of tubal patency is needed, a foam or bubble/saline infusion system may be beneficial (10).

Magnetic resonance imaging (MRI) is a highly sensitive method to define the size, number, and location of fibroids. While the expense of the test limits the widespread utilization, in some circumstances when myomectomy is planned, MRI can help determine whether abdominal or laparoscopic myomectomy is the more appropriate route. MRI can also be useful to visualize an extremely large uterus, whereas the field of visualization is limited with ultrasound. MRI is beneficial to visualize the uterus when calcifications make adequate assessment difficult with transvaginal or abdominal ultrasound. Finally, MRI can help differentiate fibroids and adenomyosis (11).

Overview of Management Options

Observation is reasonable for infertile women who are asymptomatic, especially with intramural fibroids smaller than 3 cm, especially those that do not contact the endometrium. Furthermore, observation is appropriate for symptomatic infertile women with subserosal or pedunculated fibroids, as long as the severity of symptoms does not warrant surgery (12).

Newer treatments are becoming available for the medical treatment of uterine fibroids, primarily gonadotropin-releasing hormone agonists and antagonists (GnRHa) and selective progesterone receptor antagonists. There is limited evidence of benefit for older hormonal treatments used for fibroids such as

combined oral contraceptive pills or continuous progestin pills. At best, oral contraceptives and progestins may be considered as temporizing measures (13). Injectable GnRH agonists and now oral GnRH antagonists such as elagolix may be used to decrease menorrhagia, especially in preparation for surgery to allow for recovery of anemia or thin the endometrial lining to facilitate hysteroscopic resection of a submucous fibroid. GnRHa reduces the diameter and volume of fibroids, while the patient is hypoestrogenic, but rapid regrowth of fibroids occurs when the medication is discontinued. GnRHa use before myomectomy can make the procedure more difficult and increases the likelihood of persistent or recurrent fibroids. Cost and side effects of these medications limit their long term (14).

Myomectomy is usually the best option for young women who desire preservation of the uterus. The type of myomectomy, hysteroscopic, open, or laparoscopic, is chosen based on patient symptoms; location, size, and number of fibroids; and the skill and experience of the surgeon. Considerations to the route of surgery must include selection of the approach that provides greatest improvement in the prognosis, a high safety profile. The decision should be made with the knowledge of the length of patient recovery and cost of the procedure, but these should not be the deciding factors for choosing the surgical route (15).

Hysteroscopic Myomectomy

Direct visualization of the uterine cavity via hysteroscopy for diagnosis and management is essential for the care of all women with abnormal uterine bleeding, infertility, and suspected intra-uterine pathology. The technologic advances in optics, scope diameters, fluid management, tissue removal systems, and electrosurgery have enabled this minimally invasive approach for the conservative management of intra-uterine pathology and has expanded the ability to perform hysteroscopy in the outpatient setting, making many blind procedures less favorable. This manuscript will focus on advances in hysteroscopic myomectomy for the safe and effective management of submucosal myoma (16).

The main indications for hysteroscopic myomectomy include abnormal uterine bleeding (AUB), infertility, and recurrent pregnancy loss. Studies have shown that infertility is the most common reason for performing hysteroscopic myomectomy in Nigeria, followed by heavy menstrual bleeding. These fibroids, when submucosal, can distort the uterine cavity, leading to symptoms and complications that justify removal (17).

Regarding infertility, submucosal fibroids are known to negatively affect fertility rates. Removing these fibroids has been shown to improve reproductive outcomes, making hysteroscopic myomectomy a valuable intervention for women seeking to conceive (18).

As for recurrent pregnancy loss, although the link between submucosal fibroids and first-trimester miscarriage remains somewhat unclear, there is evidence indicating that removing these fibroids can help reduce the incidence of recurrent losses. Thus, hysteroscopic myomectomy may be beneficial for women experiencing repeated pregnancy failure (19).

Contraindications to hysteroscopic myomectomy fall under the general contraindications to hysteroscopy. The procedure should not be performed in cases of intrauterine pregnancy, pelvic infection, cervical carcinoma, or endometrial carcinoma. These conditions make the procedure unsafe or inappropriate due to the potential risks involved (20).

Imaging plays a central role in the pre-operative assessment. Transvaginal ultrasound is considered the first-line modality, as it provides information about the number, size, and location of the fibroids. In cases where visualization of the uterine cavity is limited, saline infusion sonohysterography (SIS) improves delineation of intracavitary lesions by enhancing the contrast between fibroids and surrounding endometrium. Diagnostic hysteroscopy may also be performed to directly assess the extent of fibroid protrusion into the cavity and its classification based on FIGO or ESGE systems, which guides the decision between single-session or staged removal. Magnetic resonance imaging (MRI) is reserved for selected cases—particularly in women with multiple fibroids, suspected deep intramural extension, or unclear findings on ultrasound (21).

Hysteroscopic myomectomy is performed in the operating theater, typically under general anesthesia, though regional or local anesthesia may be considered in selected cases. The patient is positioned in the lithotomy

position, and aseptic preparation of the cervix and vagina is carried out. Cervical dilation is performed gradually to allow the introduction of the hysteroscope and resectoscope. Once the hysteroscope enters the uterine cavity, a distention medium—either electrolyte-free fluid for monopolar energy or normal saline when bipolar energy is used—is infused to provide adequate visualization and allow instrument manipulation (22,23).

The fibroid is inspected for size, vascularity, and degree of intramural versus intracavitary involvement, as this determines the surgical strategy. Resection is carried out using a monopolar or bipolar loop electrode, removing the fibroid in a stepwise fashion through repeated slicing motions. The fragments are flushed out or removed mechanically. Continuous monitoring of inflow and outflow of distending fluid is essential to prevent fluid overload or hyponatremia, particularly when non-electrolytic media are used. In cases of deeply embedded intramural fibroids, excessive resection should be avoided to reduce the risk of uterine perforation. Instead, the surgeon may intentionally perform only a partial removal, allowing spontaneous expulsion of the remaining intramural part after hormonal therapy or planning a second-stage hysteroscopy (24,25).

Hemostasis is achieved primarily by maintaining appropriate intrauterine pressure and by using electrosurgical coagulation when necessary. After ensuring that the uterine cavity is free of residual tissue and that there is no active bleeding, the instruments are withdrawn. Postoperative monitoring includes assessment of fluid balance, bleeding, and uterine cramping. Patients are usually discharged on the same day, and postoperative care may include analgesics, prophylactic antibiotics, or hormonal therapy to prevent adhesion formation or recurrence in selected cases. Follow-up imaging or diagnostic hysteroscopy may be performed to confirm cavity restoration, especially in women undergoing the procedure for fertility enhancement (26,27).

Uterine perforation most often occurs during cervical dilatation. That can be caused by cervical stenosis, severely retroverted or anteverted uterus and in nulliparous or postmenopausal women. Perforation during electro-resection can lead to intestinal, bladder or vessel injury. This complication is uncommon but its rate increases in the case of fibroids with intramural component. A concomitant laparoscopy is recommended in these cases to decrease the risk of such complications (28).

Glycine overload causes electrolyte imbalance (hyponatremia, hypoproteinemia and low hematocrit). Patients complain of nausea, vomiting, headache and confusion. Pulmonary and brain edema can take place. Fluid overload is also possible with isotonic saline but its effects are less serious than those with a glycine medium. Guidelines indicate that intravasation of 750 ml requires the planned termination of surgery. A balance exceeding 1000-2000 ml requires an immediate termination of the surgery (29).

A 35-45% rate of post-operative adhesions was reported with monopolar energy, and 7.5% with bipolar energy. Many barrier methods have been attempted to avoid the formation of adhesions. Some of them have limited effectiveness (intrauterine device, hormonal therapy) while others appear to be promising (Foley catheter balloon and hyaluronic gel). The latter has to be evaluated in randomized controlled trials. A control diagnostic hysteroscopy is recommended between 6 and 8 weeks after the procedure to ensure the absence of postoperative adhesions (10% of cases) (30).

A success rate of 70-99% has been reported by different studies. Success rates seem to decline as the follow-up period increases because of either incomplete removal or an occurrence of other dysfunctional factors. Some predictors of failure have been identified in prospective studies (number of fibroids, fibroid size, uterine size and incomplete surgery). When there is no desire for pregnancy any more, a concomitant endometrial ablation resulted in amenorrhea in up to 95.5% of patients (25).

Submucosal fibroids have negative impact on pregnancy rates. Surgical resection by hysteroscopy improves pregnancy rates in submucosal fibroids while myomectomy for intramural myoma is still debated. In submucous type 0 fibroids, Casini et al. reported an increase in pregnancy rates from 27 to 43% (23).

Oxytocin in Fibroid Management

Exogenous oxytocin administration causes the same response in the female reproductive system as endogenous oxytocin release. Both forms of oxytocin stimulate uterine contractions in the myometrium by causing G-protein coupled receptors to stimulate a rise in intracellular calcium in uterine myofibrils. Oxytocin

receptor activation causes many signals that stimulate uterine contraction by increasing intracellular calcium levels, which is where positive feedback comes into play. When oxytocin is released, it stimulates uterine contractions, and these uterine contractions, in turn, cause more oxytocin to be released; this is what causes the increase in both the intensity and frequency of contractions and enables a mother to carry out vaginal delivery completely. The head of the fetus pushes against the cervix, and the nerve impulses from this action travel to the mother's brain, which activates the posterior pituitary to secrete oxytocin. This oxytocin is then carried through the blood to the uterus to increase uterine contractions further, and the cycle continues until parturition (31,32).

Common adverse reactions associated with oxytocin administration include erythema at the site of injection, intensified contractions, more frequent contractions, nausea, vomiting, stomach pain, and loss of appetite. Serious adverse effects that require monitoring after oxytocin administration include cardiac arrhythmias, seizures, anaphylaxis, confusion, hallucinations, severe blood pressure elevations, and blurred vision (33).

Recent research has highlighted a potential therapeutic role for oxytocin in the management of uterine fibroids. Oxytocin infusion has been shown to significantly reduce blood flow to fibroid tissue without affecting the patient's blood pressure or heart rate, and with excellent tolerability and no reported adverse effects. While baseline blood flow values in fibroids can vary depending on the fibroid's characteristics and vascularity, oxytocin consistently results in a marked decrease in perfusion. Interestingly, this reduction appears to be selective to fibroid tissue, as oxytocin does not significantly alter blood flow in the surrounding normal myometrium. This selectivity suggests that fibroids may express oxytocin receptors differently from normal uterine muscle, creating a localized response that can be therapeutically advantageous (34,35).

Although findings regarding oxytocin receptor distribution in fibroid tissue versus normal myometrium are somewhat contradictory, several studies indicate that the expression of oxytocin receptors can vary depending on hormonal influence and menstrual cycle phase. Fibroids have a unique hormonal environment characterized by local hyperestrogenism, and estrogen is known to increase oxytocin receptor expression. This may further enhance oxytocin's responsiveness in fibroid tissue. Oxytocin receptors are also found in blood vessel walls, and although oxytocin is generally associated with vasodilation, the opposite effect—vasoconstriction—seems to occur in fibroid vasculature, leading to reduced blood supply and decreased perfusion (36,37).

These findings have led to emerging clinical applications of oxytocin as an adjunct therapy in fibroid treatment. In non-surgical procedures such as High-Intensity Focused Ultrasound (HIFU), reduced blood flow results in less heat dissipation, making the fibroid more susceptible to thermal destruction and improving ablation rates. Studies have shown that oxytocin administration before or during HIFU increases the volume of non-perfused tissue and enhances treatment efficiency. In surgical settings, oxytocin has been used during myomectomy to decrease intraoperative blood loss by reducing fibroid vascularization, which can shorten operative time, lower the need for transfusion, and facilitate faster postoperative recovery. By improving both surgical and non-surgical treatment outcomes, oxytocin may expand treatment options for women who are candidates for conservative or fertility-preserving interventions (38,39).

Tranexamic Acid in Fibroid Management

Tranexamic acid is a synthetic lysine analog that competitively inhibits plasminogen activation, stabilizing fibrin clots and reducing bleeding (40).

The antifibrinolytic effects of TXA are due to reversible interactions at multiple binding sites within plasminogen. TXA is a synthetic, reversible, competitive inhibitor of the lysine receptor found on plasminogen. The binding of this receptor prevents plasmin (the activated form of plasminogen) from binding to and ultimately stabilizing the fibrin matrix. TXA used for hereditary angioedema works by its indirect effect of reducing complement activation. Reducing plasmin activity minimizes the consumption of C1 esterase inhibitors (41,42).

Renal impairment: TXA has not been well-studied in patients with renal impairment. Ninety-five percent of TXA is excreted unmetabolized in the urine, so renal dosing is recommended, and judicious administration is recommended for patients with severe renal impairment (43).

Adverse effects include seizures, headaches, backache, abdominal pain, nausea, vomiting, diarrhea, fatigue, pulmonary embolism, deep vein thrombosis, anaphylaxis, impaired color vision, and other visual disturbances. Seizures can occur due to accidental intrathecal administration (44).

Hormonal contraceptives: Because TXA is antifibrinolytic, concomitant use of combined hormonal contraception and TXA may increase the thrombotic risk associated with oral contraceptives. Concomitant use of TXA with combined hormonal contraceptives is avoided (45).

Tranexamic acid (TXA) is a non-hormonal antifibrinolytic agent used to manage heavy menstrual bleeding associated with uterine fibroids. It works by blocking plasminogen activation and preventing clot breakdown, which promotes hemostasis and significantly reduces menstrual blood loss—often by 40–50%. TXA is also used perioperatively in myomectomy to reduce intraoperative bleeding and the need for blood transfusion. Although some studies have reported drug-induced necrosis within fibroids, TXA does not reduce fibroid size and therefore is not considered a curative therapy for leiomyomas (46,47).

TXA is generally well-tolerated with mild, self-limiting side effects such as gastrointestinal discomfort, dizziness, or headache. Despite theoretical concerns about thromboembolic events due to its antifibrinolytic effect, most clinical studies in gynecology have not reported increased clotting complications when used appropriately. However, caution is advised in patients using hormonal contraceptives due to the potential additive risk of thrombosis. Current evidence supports TXA as a safe, effective option for reducing fibroid-related menorrhagia, but further large, double-blind randomized trials are needed to clarify optimal dosing, duration, and patient selection based on fibroid size and location (48).

Genetic Predisposition of Fibroids

The genetic mechanisms contributing to the development of leiomyomas are discussed in the pathogenesis section below. Epidemiological evidence suggests a heritable component, whereby more than two first-degree relatives with fibroids is associated with a 2.2-fold increased risk, indicating a degree of genetic predisposition to fibroid development. Longstanding evidence also demonstrates an increased risk when a sibling is diagnosed with leiomyomas. Additionally, rare autosomal dominant hereditary syndromes, like multiple cutaneous and uterine leiomyomatosis (Reed syndrome), further support a genetic origin for leiomyomas.(49).

Uterine leiomyomas exhibit diverse genotypes that underly their typical phenotype. Several genetic pathways contribute to the development of these tumors. Most fibroids arise from somatic mutations, primarily involving genes such as mediator complex subunit 12 (MED12), high-mobility group AT-hook (HMGA1 and HMGA2), and collagen type IV (COL4A5 and COL4A6). Inherited mutations in the fumarate hydratase (FH) gene constitute a distinct subgroup associated with hereditary leiomyomatosis and renal cell carcinoma (HLRCC) syndrome, which is a rare autosomal dominant syndrome linked to aggressive forms of cancer. Notably, genotype–phenotype relationships exist, with factors such as MED12 mutations frequently linked to smaller fibroids. Although some mutations seem to be mutually exclusive, the complex clonal nature of fibroids can result in multiple genotypes within the same uterus, suggesting redundant downstream signaling pathways for most groups, except for the FH group.(50).

Vitamin D deficiency, particularly among black women, is linked to increased fibroid risk. The potential mechanisms are complex. In some instances, leiomyomas may be associated with genetic polymorphisms involved in vitamin D metabolism, especially in women of African ancestry. It appears that there is a specific vitamin D receptor (VDR) through which the molecule exhibits its effects, including the inhibition of leiomyoma cell growth, as measured in vitro by levels of several growth markers. It also appears that increased levels of vitamin D may be associated with reduced expression of estrogen and progesterone receptors on leiomyoma cells, inhibiting the growth response of leiomyomas to progesterone. Further discussion of these roles can be found elsewhere. Animal studies have shown that uterine leiomyoma-like tumors exhibit reduced expression of growth biomarkers, accompanied by a corresponding reduction in tumor volume. A systematic review by Combs et al. demonstrated an inverse correlation between serum vitamin D levels and the presence of leiomyomas in 14 studies comprising 3535 patients. The same investigators found that in four of five clinical

studies, treatment with oral vitamin D was associated with reduced growth. A pilot study evaluating vitamin D for secondary prevention following myomectomy also showed evidence of efficacy.(51).

Gene Therapy of Uterine Leiomyoma

Gene therapy is the introduction of therapeutic nucleic acids, their synthetic analogs, or genome-editing systems into the cells and tissues for a targeted change in the level of expression or correction of a defect in a particular gene. The result of this approach can be the replacement or suppression of damaged genes, alterations in the DNA sequence, or the introduction of new functions into the cell. The main problem of gene therapy is the lack of effective and, at the same time, safe methods for delivering therapeutic genetic constructs to target cells. For effective gene therapy, the properties of a vector must include biodegradability, non-immunogenicity, the ability to include a large DNA sequence, and targeted delivery of therapeutic genetic constructs to certain organs and tissues. In order to increase the specificity of vectors and efficiency in overcoming extra- and intracellular transport barriers, different nucleic acid carriers of viral and nonviral nature are being actively developed. Adenoviruses, adeno-associated viruses, retroviruses, and others are used as viral vectors. Nonviral methods include delivery of nucleic acids using liposomes and polymers, as well as physical delivery methods.(52).

The role of ovarian steroid hormones in the pathogenesis of UL is supported by epidemiological, clinical, and experimental data. Estrogen receptors can be one of the targets for UL gene therapy. Disruption of estrogen binding to receptors and suppression of their activity leads to the decrease in the UL cell proliferation level. To suppress the UL cell proliferative activity, the dominant-negative estrogen receptor gene (DNER) is used, which encodes a form of estrogen receptor (ER) that is unable to activate transcription. DNER molecules also form dimers with native ERs and suppress their activity. The Ad-vectormediated delivery of the DNER gene into UL cells led to a decrease in the transduced cell proliferation level. In addition, DNER affects the expression of several estrogen-regulated genes that control apoptosis, proliferation, and extracellular matrix formation. In particular, Ad-DNER infected UL cells were characterized by the low level of the Bcl-2 protein along with the increased level of the BAX protein and the high level of caspase 3. A decrease in the production of the VEGF protein by UL cells after administration of Ad-DNER was also reported. However, no substantial contribution of VEGF to the pathogenesis of leiomyoma was identified.(53).

Intratumor injection of Ad-DNER to nude mice with UL led to a decrease in proliferation and the initiation of apoptosis in UL cells. Intratumor injections of Ad-DNER into Eker rats also led to cell death by initiation of both the intrinsic apoptotic pathway by increasing the production of the Bax and p53 proteins and the extrinsic pathway by increasing the expression of the FasL and Daxx genes.(54).

One of the popular approaches in gene therapy of tumors is the delivery of suicide genes into target cells. Most suicide gene therapy studies transfect cells with the herpes simplex virus thymidine kinase (HSV-TK) gene followed by treatment with ganciclovir (GCV). Ganciclovir, which is an acyclic nucleoside, is phosphorylated by herpes virus thymidine kinase, which makes this compound available for phosphorylation by cellular kinases; the resulting trinucleoside is incorporated into replicating DNA, disrupting replication and initiating the apoptotic cascade. It was demonstrated that the introduction of the HSV-TK gene into cells followed by ganciclovir treatment decreased the production of PCNA and cyclin D proteins responsible for proliferation and increased the production of proapoptotic protein Bax. An important advantage of this approach is the death of not only the cells with the inserted therapeutic gene construct but also some surrounding cells. This phenomenon, called the bystander effect, can be explained by possible transfer of phosphorylated ganciclovir to neighboring cells during their intercellular interactions.(55).

An adenovirus-mediated insertion of the HSV-TK gene into ELT-3 cells and primary UL cells followed by ganciclovir treatment showed a decrease in the level of proliferation of both cell cultures. The decrease in the proliferative activity of primary UL cells was dosedependent and depended on the number of introduced adenoviral vectors with the HSV-TK gene. ELT-3 cells infected with an adenoviral vector containing HSV-TK were then transplanted into nude mice with UL. The arrest of tumor growth after this procedure was demonstrated, and the absence of toxic effect associated with the insertion of a viral vector into uninfected

organs and tissues was confirmed. Experiments on intratumor adenovirus-mediated injections of HSV-TK into Eker rats showed a considerable reduction in tumor volume. (Salama, 2007).

Along with the development of delivery systems, the search for new targets is an urgent trend in the development of effective methods for UL therapy. As mentioned earlier, the main studies on gene therapy of UL are aimed at suppressing the estrogen receptor in UL cells and delivery of suicide genes. With the new data on the molecular genetic characteristics of UL, the number of potential targets for gene therapy has increased. The MED12 and HMGA2 genes, the mutations of which are present in 80–90% of UL, seem to be of greatest interest as potential therapeutic targets. For instance, specific downregulation of the mutant MED12 expression may be an effective strategy for UL therapy. Earlier, Al-Hendy et al. showed that silencing of the MED12 gene using RNA interference strategy led to a decrease in the level of the Wnt and β -catenin proteins and to a decrease in the immortalized UL cell proliferation level. Similarly, silencing of the HMGA2 gene, which is actively expressed as early as embryogenesis, can play an important role in the treatment of the disease. (56).

Another potential strategy for UL therapy may be the specific effect on genes that control the extracellular matrix (ECM) formation. It is known that the leiomyoma ECM differs from the ECM of healthy myometrial tissue in the increased content of type I collagen, fibronectins, and proteoglycans, as well as in dysregulation of metalloproteinase activity [118, 121]. Targeting the ECM components can lead to suppression of UL growth, disruption of the intercellular structure, and an increase in the availability of tumor cells for therapeutic drugs [118]. Combined treatment Fig. 3. The bystander effect after cell transfection with the HSV-TK thymidine kinase gene and subsequent ganciclovir treatment. Triphosphorylated ganciclovir enters neighboring cells, where it is incorporated into the DNA chain, terminating its replication and leading to apoptosis. Arrows show the pathways for the spread of phosphorylated ganciclovir to neighboring cells. The nuclei of the cells in which the HSV-TK gene is transcribed are shown in black. HSV-TK Ganciclovir1010 RUSSIAN JOURNAL OF GENETICS Vol. 57 No. 9 2021 SHYTKALOVA et al. based on suicide gene therapy and the ECM destruction can considerably increase the treatment efficacy for leiomyomas. It should be noted that myomatous nodes are surrounded by a dense membrane, a pseudocapsule, formed by normal myometrial cells. Understanding the mechanisms of pseudocapsule formation can help in the search for new targets for UL therapy.(57).

A promising approach to UL gene therapy is the activation of apoptosis within the tumor. It was demonstrated UL cells were characterized by downregulation of genes involved in the activation and regulation of programmed cell death. The transfer of apoptosis-inducing factors such as TNF, TRAIL, FasL, Bax, or activated caspases into UL cells enhanced the mechanisms of apoptosis in both extrinsic and intrinsic signaling pathways(53).

The role of vascularization and increased permeability of uterine vessels in the formation and development of UL was also reported. The processes of formation of new blood vessels are closely associated with tumor development; they determine the tumor growth pattern, as well as its clinical and morphological variants (simple and proliferating UL). In this regard, the methods associated with the effect on the processes of angiogenesis seem to be promising for the UL therapy. It was previously demonstrated that UL cells, compared to normal myometrium, were characterized by increased expression of the VEGF gene, which is a primary regulator of angiogenesis. Although UL are tumors with reduced vascularization, abnormally developed vasculature is present in the periphery and in the pseudocapsule. Silencing of angiogenesis-activating genes, such as VEGF and bFGF, can lead to a decrease in the UL growth intensity and volume. The target in this approach is vascular endothelial cells. It was demonstrated that injection of the recombinant PEDF factor into the myomatous nodes reduced the VEGF protein level. Thus, UL was found to be sensitive to the action of anti-angiogenic proteins, despite the small number of vessels inside the tumor itself. Antisense oligonucleotides or small interfering RNAs (miRNAs) that can specifically bind to the VEGFA gene transcripts and its receptor, as well as the transcripts of other genes of pro-angiogenic factors, can act as inhibitors of angiogenesis for UL gene therapy.(58,59).

It should be noted that, in most cases of UL gene therapy, transgene expression should be limited exclusively to tumor cells. The localized nature of UL helps to easily identify the target for the clinical application of gene therapy vectors and, therefore, avoids accidental transfection of the surrounding myometrial cells. Selective

transgene expression in UL can be achieved using UL-specific transcription factor promoters, as well as efficient vectors for targeted delivery of genetic constructs.(60).

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