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**ANALYSIS OF THE EXPERIENCE OF USING ALTERNATIVE METHODS OF TREATMENT OF  
 UTERINE FIBROIDS**

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**საშვილოსნოს ფიბროიდების მკურნალობის ალტერნატიული მეთოდების გამოყენების  
 გამოცდილების ანალიზი**

მეანობა-გინეკოლოგიის სამეცნიერო-კვლევითი ინსტიტუტი, ბაქო, აზერბაიჯანი

**რეზიუმე**

სტატიაში მოცემულია საშვილოსნოს მიომის ტრადიციული და თანამედროვე მკურნალობის მეთოდების აღწერილობა. როგორც ინოვაცია, ავტორების მიერ მონოღებულია ზოოლიტი და მაგნიტიზებული წყალი, როგორც ალტერნატიული მკურნალობის მეთოდი ფიბროიდების მკურნალობისას და ორივე ნივთიერების ზოგადი სამედიცინო-ბიოლოგიური თვისებების შესწავლის სხვადასხვა კვლევების შედეგების გათვალისწინებით, საშვილოსნოს მიომში ორივე ნივთიერების ეფექტურობის იდეა. მკვლევარები ხაზს უსვამენ ამ მიმართულებით კლინიკური კვლევების ჩატარების აუცილებლობას და აპირებენ ამ მიმართულებით მუშაობის გაგრძელებას.

Uterine leiomyomata are the direct cause of a significant health-care burden for women, their families, and society as a whole. Because of the long experience with the mode of treatment, surgical myomectomy remains the gold standard for treating reproductive-age women; however, in the recent years, the wide evolution of less invasive approaches led to a change in the options used by the clinician to treat symptomatic fibroids. Minimally invasive procedures such as uterine artery embolization (UAE) are increasingly used to treat symptomatic fibroids. Other alternative treatments are becoming more diffuse, such as magnetic resonance-guided high-frequency focused ultrasound surgery (MRgFUS), cryomyolysis, vaginal occlusion, and laparoscopic closure of the uterine arteries. Both advantages and limitations of these techniques under development must be taken into account, but this wider range of choices is being increasingly considered for a tailored treatment [1].

Treatment options for fibroids vary - severity of the symptoms, size and location of the fibroid lesions, the patients desire to maintain fertility - with the ultimate goal of therapy being relief of the symptoms. As we learn more about the impact of fibroids on fertility, it becomes important for patients and their physicians to have a toolbox of therapeutic options with viable drug therapies being one of those tools. To this end, promising drug therapies, their chemistry, mechanism of action, pharmacology, clinical efficacy and side effects, focusing first on innovative drug delivery approaches, will be highlighted [2].

The development of nanocarriers designed to deliver and protect drug therapeutics (e.g., anti-fibrotic, aromatase inhibitors, progestins, etc.) is an emerging field. Advances in guided-ultrasound technology (e.g., human in vitro fertilization where oocytes as small as 3-5 mm are manipulated) [3] make it feasible to envision utilizing nanocarriers to create a drug depot inside the fibroid by local injection. Thus, skilled physicians could inject the therapy into the uterine fibroid under guided-ultrasound in an outpatient setting. This approach would impede diffusion and distribution of the drug away from the injected fibroid, prolong release, delay inactivation, and therefore reduce the need for repeat injections. Examples of the most promising thermoresponsive delivery systems are given below.

The effectiveness of conservative hormonal therapy for uterine fibroids and adenomyosis is constantly discussed. According to most authors, none of the hormonal drugs used can be considered a means of radical treatment of either one or the other pathology [4,5]. Insufficient efficacy and a high percentage of side effects of hormonal therapy for uterine fibroids and adenomyosis contributed to the development of new directions in the conservative treatment of these diseases, which include uterine artery embolization (UAE) in uterine myoma and selective immunotherapy (SI) in the program of conservative treatment of endometriosis [6].

The need for alternatives to surgical intervention is very real, especially for women seeking to preserve their fertility. These options now exist, with SPRMs proven to treat fibroid symptoms effectively.

Gynecologists now have new tools in their armamentarium, opening up novel strategies for the management of uterine fibroids [7].

To date, genetic and epigenetic factors, sex steroids, growth factors, cytokines, chemokines and ECM components have been identified as being implicated in the pathogenesis of leiomyomas [8]. Many growth factors and also activin and myostatin play a role in the mechanisms involved in the development of leiomyomas [9]. Of course, estrogen and progesterone and their respective receptors also have a very significant impact on leiomyoma growth [10]. Recently, Wong et al. (2016) demonstrated that testosterone was additionally implicated in the growth of uterine fibroids. In vitro studies have also shown that fibroid development depends on miRNA regulation of gene targets which impact cellular processes [11]. The initial event that triggers the first stages of tumorigenesis nevertheless involves somatic mutations [12]. In the past, estrogen was considered to be the major growth factor in myoma development. However, already in the 1990s, a number of studies reported increased the expression of both progesterone receptor A (PR-A) and progesterone receptor B (PR-B) in leiomyoma tissue [13].

Very recently, Tsigkou et al. showed that PR-B mRNA and PR-A and PR-B proteins were more concentrated in leiomyomas than in matched myometrium [14].

Levels of PR-B mRNA in leiomyoma tissue were directly associated with the number of myomas, but inversely correlated with the intensity of symptoms. Moreover, higher proliferative activity, demonstrated by proliferating cell nuclear antigen (PCNA) and the mitotic index, was observed in leiomyomas during the luteal (secretory) phase [15]. There is evidence from preclinical and clinical trials, as well as from histological and pharmacological studies, that progesterone and its receptors play a key role in uterine fibroid growth [16].

In a review, Kim and Sefton (2012) described, in detail, the activation of signaling pathways in leiomyomas by both estrogen and progesterone. Progesterone is able to cause rapid, membrane-initiated effects, independent of gene transcription, that alter the production of second messengers involved in cell signaling transduction pathways. The PI3K/AKT pathway is mediated by progesterone which, through its receptors, can quickly activate this pathway, which is increasingly considered to be a potential promoter of leiomyoma growth. PTEN, on the other hand, should be considered as a negative regulator of AKT. Progesterone and growth factor signaling pathways are interconnected and govern numerous physiological processes such as proliferation, apoptosis and differentiation. Progesterone can modulate the expression of growth factor signaling proteins and is implicated in the regulation of genes associated with proliferation and apoptosis, but these genes have not yet been fully identified or studied in detail [16]. There is therefore evidence that progesterone plays a crucial role, but the mechanism by which it promotes proliferation, the repertoire of genes involved, and how it crosstalk with growth factor signaling pathways all need to be investigated in greater depth. The recent discovery of stem cells and their paracrine interactions with more differentiated cell populations within leiomyoma tissue may lead to the development of therapeutics that temper leiomyoma growth as well as those that eradicate them [16].

Having established the crucial role of progesterone in the growth and development of myomas, we can modulate the progesterone pathway by use of selective progesterone receptor modulators (SPRMs) [17]. SPRMs are synthetic compounds that exert either an agonistic or antagonistic effect on PRs. Their binding allows these receptors to interact with coactivators and/or corepressors, and this is further impacted by the presence of coregulators in a particular cell type, which will dictate whether an SPRM acts more as an agonist or antagonist [18]. Hence, the mechanism of action of SPRMs on PRs depends on their structure and how they alter the PR conformation, resulting in exposure or inactivation of particular binding domains. Their activity is also mitigated by tissue types and physiological contexts [16].

Symptomatic uterine fibroids require surgical and/or medical therapy according to the severity of symptoms, age, infertility, wish to preserve the uterus and FIGO classification. Current strategies involve mainly surgical intervention, such as hysterectomy, myomectomy by hysteroscopy and myomectomy by laparoscopy or laparotomy. Hysterectomy provides the most effective treatment for fibroids, but is not appropriate in many cases. The choice between less invasive techniques (uterine-sparing options such as myomectomy) is guided by the size, number and location of fibroids as well as the personal experience of the gynecologist and available equipment. Other surgical techniques, such as laparoscopic cryomyolysis,

is now growing evidence of the crucial role of progesterone in pathways in the pathophysiology of uterine fibroids by the use of SPRMs. UPA (one member of the SPRM compound family) has been studied in large clinical trials and its long-term intermittent administration has been evaluated, yielding promising results for new treatment perspectives. It was found that more than one three-month course of UPA maximizes its potential benefits in terms of bleeding control and fibroid volume reduction. Hence, depending on age and symptoms (infertility, bleeding, etc.), SPRMs should be considered an alternative to surgical therapy, or at least an adjunct to surgery, in some circumstances, as illustrated in the algorithms. In conclusion, asymptomatic fibroids do not require treatment once the diagnosis is confirmed by ultrasonography or MRI. Women should be made aware of all available treatment options (medical, radiological and surgical) and why they may or may not be appropriate. Gynecologists now have new tools in their armamentarium opening up novel strategies for the management of uterine fibroids.

We have also started research in order to continue the search for alternative treatment methods. Taking into account the widespread use of zeolite and magnetized water in medicine and their effectiveness in the complex treatment of many pathologies, we conducted research in the direction of developing a treatment scheme and conducting clinical trials of their use in uterine fibroids.

Although ion-incorporated zeolite may enhance the antimicrobial properties of dental materials, the mechanical properties of some materials, such as MTA and acrylic resin, may be compromised. Therefore, since the decrease in mechanical properties depends on zeolite concentration in the restorative material, it is generally recommended to add 0.2-2% zeolite by weight [19].

The current study suggested that zeolite formulations could be combined with various materials used in manufacturing medical devices, surfaces, textiles, or household items where antimicrobial properties are required [20].

Zeolite significantly adsorbs vitamins B1, B2 and B6 in acid and neutral solutions at 37 degrees C, already in the first 10 min of the contact. Adsorption was irreversible, but partly reversible after changing pH from acid to neutral. This is a significant ions competition for adsorption on zeolite in neutral solution, so no statistically significant vitamins B1, B2 and B6 adsorption occurs, while in acid solution competition is less, thus zeolite significantly adsorbs these vitamins, although in less degree than in conditions with no concurrent ions [21]. Zeolites encompass a broad range of biomedical applications, e.g., utilization as antidiarrheal agents, antitumor adjuvants, antibacterial agents, MRI contrast agents, their employment in studies on bone formation, Alzheimer's disease development, and their hemodialytic, drug delivery, and dental applications [22].

The effect of a static magnetic field on hydrogen bonding of liquid water has been examined by frictional experiments in this paper. It was found that the friction coefficient was smaller in different intensity magnetized water than in water, and became larger with the increasing water temperature. According to the thermal motion of water molecule known to become stronger and thus hydrogen-bonding gets weaker when water temperature increases, a thermal dynamic effect analogous to the increase of temperature was assumed, and the frictional differences were probably because of the weak effect of the magnetic field on hydrogen bonding among water molecules [23].

These discrepancies, which caused controversy for many years, could most likely be attributed to differences in experimental conditions (the flow rate of the water through the magnetic field, the impurities in the water, and the distribution of the magnetic field) and other subtle effects (if any) that which are easily hidden by measurement errors. Despite these controversies arguments, the increased evaporation rate of water in a magnetic field is a somewhat less disputed phenomenon [24].

This research investigates the shrinkage cracking of concrete, which were mixed with magnetic water. Magnetic water was obtained by the independent designed magnetizing equipment. Ring-test method and flat-test method were used to test early-age shrinkage cracking of concrete. Results show that the strain rate factor ( $\alpha$ ) and the total cracking area of unit area ( $c$ ) of concrete were decreased when used magnetic water, which means the early-age shrinkage cracking resistance of concrete mixed with magnetic water is improved than those mixed with tap water. The best increase in early-age shrinkage cracking resistance of concrete is achieved when the magnetic strength is 260 mT and the length of magnetic field is 280 mm. Additionally, the compressive and split strength of concrete mixed with

magnetic water increased greatly. It is also found that the length of magnetic field has direct effect on the growth of concrete strength [25]. These discrepancies, which caused controversy for many years, could most likely be attributed to differences in experimental conditions (the flow rate of the water through the magnetic field, the impurities in the water, and the distribution of the magnetic field) and other subtle effects (if any) that which are easily hidden by measurement errors. Despite these controversies arguments, the increased evaporation rate of water in a magnetic field is a somewhat less disputed phenomenon [26].

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It was found that the activity of glutamate decarboxylase can increase by 30 % in magnetized water. The mechanism of increased enzyme activity was discussed in the present paper. Such a new finding will probably lead to some new explanations for the physiological and biological mechanism of the effect of magnetized water on living organisms, thus providing a new approach to the study of the effect of magnetized water [28]. Although previous studies with magnetized water have shown promising results on certain beneficial effects on human and animal health, these studies are very limited and poorly designed experimentally. The well-designed double-blind studies are seldom found on the subject. Also, the studies reported are mostly non-controlled observational studies that were performed between 20 and 30 years ago, and few scientists were involved in the area. Thus, rigorous and serious scientific analysis is needed, utilizing well-designed clinical studies in experimental animals and humans in the future to confirm the health-beneficial effects of magnetized water [29].

In conclusion, the 8-week intake of magnetized water and zeolite in our study showed very high effectiveness. From these results, it is suggested that the long-term intake of magnetized water and zeolite may be beneficial in both prevention and treatment uterine myomas. More extensive studies are needed to find out the mechanism of action of the magnetized water and zeolite.

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#### SUMMARY

The article presents a description of alternative treatment methods along with traditional and modern treatment methods of uterine myoma. As an innovation, the authors proposed zeolite and magnetized water as an alternative treatment method in the treatment of fibroids. Taking into account the results of various studies studying the general medical-biological properties of both substances, the idea of the effectiveness of both substances in uterine myoma is put forward. Researchers emphasize the necessity of conducting clinical studies in this direction and have announced that they will continue their work.

**Keywords:** uterine fibroids, treatment, zeolite, magnetized water.