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REVIEW

Modern methods of treatment of precancerous vulvar diseases, with a focus on photodynamic therapy: literature review

N. A. Shanazarov[1]✉, S. V. Zinchenko[2], S. D. Kisikova[1], M. A. Alchimbaeva[1], K. S. Seitbekova[1], I. Z. Galiev[2], M. I. Ibragim[3]

[1] Medical Center Hospital of the President's affairs Administration of the Republic of Kazakhstan, Astana, Republic of Kazakhstan
[2] Kazan (Volga Region) Federal University, Kazan, Russian Federation
[3] Medical Center "Aya", Astana, Republic of Kazakhstan
✉ tayson87@mail.ru

ABSTRACT

Precancerous diseases of the vulva, such as dysplasia and leukoplakia and lichen sclerosus, are a significant problem in gynecology, since their progression can lead to the development of invasive cancer, which endangers the health and life of women. Modern treatment methods, including surgery and topical medications, do not always provide adequate effectiveness, which underscores the importance of finding alternative approaches. Photodynamic therapy (PDT), which is an innovative method, shows promising results in the treatment of precancerous and early tumor diseases, including those affecting the mucous membranes of the vulva. This method, acting on pathological cells with the help of photosensitive drugs and light, minimizes damage to healthy tissues, which makes it promising in clinical practice. The novelty of this study lies in the systematic analysis of the use of PDT specifically for the treatment of precancerous diseases of the vulva, which is still poorly understood.

Purpose of the study. To study the effectiveness of various methods of treating precancerous diseases of the vulva, with a focus on photodynamic therapy (via literature review).

Materials and methods. A literature search for studies published over the past 5 years was conducted in the Pubmed, Google Scholar, ClinicalTrial.gov, The Cochrane Library, NICE, eLIBRARY and CyberLeninka databases in English and Russian. Global statistical data on tumors of the female genital organs were also studied, especially in the Russian Federation and the Republic of Kazakhstan. As a result of a search query, 5,369 articles were submitted to the above databases. In total, this review examines 50 scientific articles exploring various methods of treating precancerous diseases of the vulva.

Results. The results of the study showed that various treatments for precancerous vulvar diseases, including surgical and drug approaches, have limited effectiveness and may be accompanied by side effects such as scarring or recurrence. At the same time, photodynamic therapy has demonstrated high clinical efficacy, providing significant improvement in tissue condition with minimal damage to healthy cells. The method has shown good results in reducing pathological changes such as hyperkeratosis and dysplasia, with a low recurrence rate and rapid tissue repair. In addition, PDT has demonstrated good tolerability and safety, which confirms its promise as an effective and minimally invasive method of treating precancerous diseases of the vulva.

Conclusion. PDT can provide high efficiency in disease regression and human papillomavirus (HPV) clearance, as well as help reduce the recurrence of precancerous vulvar diseases.

Keywords: vulvar leukoplakia, vulvar kraurosis, vulvar lichen sclerosus, vulvar intraepithelial neoplasia, High-grade SIL of the vulva, vulval HSIL, etiology, pathogenesis, oncogenicity

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For correspondence: Nasrulla A. Shanazarov – Dr. Sci. (Med.), Professor, Deputy Director for Strategic Development, Science and Education, RSE "Medical Center Hospital of the President's affairs Administration of the Republic of Kazakhstan" on REU, Astana, Republic of Kazakhstan
Address: 80 Mangilik Avenue, Astana 010000, Republic of Kazakhstan
E-mail: tayson87@mail.ru
ORCID: https://orcid.org/0000-0002-2976-259X
SPIN: 6224-3395, AuthorID: 633414
ResearcherID: A-9433-2019
Scopus Author ID: 57207467603

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ОБЗОР

Современные представления о возможности фотодинамической терапии в лечении предопухолевых заболеваний вульвы: обзор литературы

Н. А. Шаназаров[1]✉, С. В. Зинченко[2], С. Д. Кисикова[1], М. А. Алчимбаева[1], К. С. Сейтбекова[1], И. З. Галиев[2], М. И. Ибрагим[3]

[1] РГП «Больница Медицинского центра Управления делами Президента Республики Казахстан» на ПХВ, г. Астана, Республика Казахстан
[2] ФГАОУ ВО «Казанский (Приволжский) федеральный университет», г. Казань, Российская Федерация
[3] Медицинский центр «Айя», г. Астана, Республика Казахстан
✉ tayson87@mail.ru

РЕЗЮМЕ

Предопухолевые заболевания вульвы, такие как дисплазия и лейкоплакия и крауоз, представляют собой значимую проблему в гинекологии, поскольку их прогрессирование может привести к развитию инвазивного рака, что ставит под угрозу здоровье и жизнь женщин. Современные методы лечения, включая хирургическое вмешательство и местные препараты, не всегда обеспечивают должную эффективность, что подчеркивает важность поиска альтернативных подходов. Фотодинамическая терапия (ФДТ), являющаяся инновационным методом, показывает многообещающие результаты в лечении предопухолевых и ранних опухолевых заболеваний, включая те, что затрагивают слизистые оболочки вульвы. Этот метод, воздействуя на патологические клетки с помощью светочувствительных препаратов и света, минимизирует повреждения здоровых тканей, что делает его перспективным в клинической практике. Новизна данного исследования заключается в систематическом анализе применения ФДТ именно для лечения предопухолевых заболеваний вульвы, что до сих пор малоизучено.

Цель исследования. Изучить эффективность различных способов лечения предопухолевых заболеваний вульвы с углублением на фотодинамическую терапию (по данным литературы).

Материалы и методы. Проведен поиск литературы в базах данных Pubmed, Google Scholar, ClinicalTrial.gov, The Cochrane Library, NICE, eLIBRARY и КиберЛенинка на английском и русском языках, опубликованной в течение последних 5 лет. Также изучены общемировые статистические данные опухолей женских половых органов, в особенности в Российской Федерации и Республике Казахстан. По результату поискового запроса вышеуказанных базах данных было представлено 5 369 статей. В общей сложности в настоящем обзоре рассмотрено 50 научных статей, изучающих различные способы лечения предопухолевых заболеваний вульвы.

Результаты. Результаты исследования показали, что традиционные методы лечения предопухолевых заболеваний вульвы имеют ограниченную эффективность и могут вызывать побочные эффекты. В то же время фотодинамическая терапия продемонстрировала высокую клиническую эффективность, улучшая состояние тканей с минимальными повреждениями здоровых клеток. Метод показал хорошие результаты в уменьшении гиперкератоза и дисплазии, с низким уровнем рецидивов и быстрой регенерацией, а также хорошей переносимостью и безопасностью.

Заключение. ФДТ может обеспечить высокую эффективность в регрессии заболевания и клиренсе вируса папилломы человека (ВПЧ), а также способствовать снижению рецидивов предопухолевых заболеваний вульвы.

Ключевые слова: лейкоплакия вульвы, крауроз вульвы, склерозирующий лишай вульвы, интраэпителиальная неоплазия вульвы, SIL вульвы высокой степени тяжести, HSIL вульвы, этиология, патогенез, онкогенность

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Для корреспонденции: Шаназаров Насрулла Абдуллаевич – д.м.н., профессор заместитель директора по стратегическому развитию, науке и образованию, РГП «Больница Медицинского центра Управления делами Президента Республики Казахстан» на ПХВ, г. Астана, Республика Казахстан
Адрес: 010000, Республика Казахстан, г. Астана, проспект Мангилик Ел, д. 80
E-mail: tayson87@mail.ru
ORCID: https://orcid.org/0000-0002-2976-259X
SPIN: 6224-3395, AuthorID: 633414
ResearcherID: A-9433-2019
Scopus Author ID: 57207467603

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INTRODUCTION

Cancer of the vestibule of the vulva (or vulvar cancer) is a malignant neoplasm that develops on a woman's external genitalia, including the vulva, clitoris and labia. This is a relatively rare disease that accounts for less than 5 % of all cases of cancer of the reproductive system in women, however, it has a significant impact on the health and quality of life of patients [1].

According to the WHO, in 2022, there were about 20 million new cases of cancer and 9.7 million deaths. The estimated number of people who were alive within 5 years of being diagnosed with cancer was 53.5 million. Approximately 1 in 5 people develop cancer during their lifetime, approximately 1 in 9 men and 1 in 12 women die from this disease [2].

Worldwide, cancer of the female genital organs (further referred to as FGM) – vulva, vagina, cervix, uterus, ovaries accounts for approximately 15 % of all fatal cancers in women. According to Chinese researchers, 1,472,801 new cases and 680,041 deaths related to female genital cancer were reported worldwide in 2022 [3].

According to WHO GLOBOCAN data (2022) [4], vulvar cancer ranks 4th in terms of prevalence worldwide, also similar in the Russian Federation and the Republic of Kazakhstan (RF and RK). Globally, 47,336 new cases (0.83 per 100,000 population) and 18,579 deaths (0.30 per 100,000) are recorded annually. In the Russian Federation, the incidence of GPO cancer is 1.1, and the mortality rate is 0.51 per 100,000 population. In the Republic of Kazakhstan, morbidity and mortality are similar to global data: 0.92 per 100,000 and 0.34 per 100,000, respectively. These data indicate that vulvar cancer is characterized by a low prevalence and mortality rate.

In addition, according to the researchers' forecasts, if the incidence remains stable, and population growth and population aging continue in accordance with recent trends, it is predicted that by 2040, the incidence of cancer worldwide will increase by 55 % compared to 2024 (approximately 28 million new cases) [5], and by By 2050, more than 35 million new cases of cancer will be registered, which is an increase of 77 % [2].

Purpose of the study: To study the effectiveness of various methods of treating precancerous diseases of the vulva, with a focus on photodynamic therapy.

MATERIALS AND METHODS

A literature search was conducted in the databases Pubmed, Google Scholar, ClinicalTrial.gov, The Cochrane Library, NICE, eLIBRARY, CyberLeninka using the following keywords: vulvar leukoplakia, vulvar kraurosis, vulvar lichen sclerosus, intraepithelial neoplasia of the vulva, high-severity vulvar SIL, vulvar HSIL etiology, etiology, pathogenesis, pathogenetic development, oncogenicity. Exclusion criteria included articles that did not match keywords, poor quality, or insufficient information in the articles. As a result, 50 articles were analyzed that explore various aspects of the treatment and pathogenesis of precancerous vulvar diseases.

The following types of articles in English and Russian were included: systematic review, meta-analysis, review, guideline, randomized controlled trial, clinical trial. The search depth was 5 years (from 2019 to July 2024).

We also studied the global statistical data of FGO tumors, especially in the Russian Federation and the Republic of Kazakhstan.

Over the years, different terms have been used to refer to vulvar diseases, which has led to different interpretations between clinicians and pathologists. In this regard, in 1993, the International Society for the Study of Vulvar and Vaginal Diseases (ISSVD), together with the International Society for Gynecological Pathology (ISGP), developed and implemented a new classification of vulvar diseases based on pathomorphological changes in the tissues of FGO. This classification, accepted and widely used all over the world, includes three main groups [6–8]:

– Precancerous diseases (sclerotrophic lichen, squamous cell hyperplasia, other dermatoses);
– Intraepithelial neoplasia of the vulva (VIN), which is divided into VIN 1 (mild dysplasia), VIN 2 (moderate dysplasia), VIN 3 (severe dysplasia and cancer in situ) and non-squamous cell intraepithelial neoplasia (Paget's disease, melanoma in situ);
– Invasive cancer.

STUDY RESULTS

The main goal of therapy is to eliminate itching in the genitals, which is a serious problem for the patient. Treatment of vulvar itching can be divided into four stages: identification of the underlying disease; restoration of the barrier function of the skin; reduction of any inflammatory complications; and elimination of the itching cycle by psychological methods. Asymptomatic cases of vulvar lichen sclerosis (VLS) also need treatment. Topical corticosteroids are the gold standard of treatment for this group of patients. Potent corticosteroid ointments or creams are used. According to the results of clinical studies, they alleviate the symptoms in almost all patients: in about 70 % of cases, the symptoms disappear completely, and in 20 % there is a complete restoration of the skin [9].

Treatment of vulvar leukoplakia is a significant challenge due to a variety of factors, including vulvovaginal dysbiosis on the background of immune disorders and the lack of a unified pathogenetic approach to therapy [10]. Microflora disorders and immune dysfunctions support the pathological processes of keratinization, creating a risk of recurrence and complicating the restoration of the epithelium. As a result, recurrence of hyperplastic dystrophy is observed in 45–67 % of cases [11].

According to the European Guidelines for the Treatment of Vulvar Diseases from 2021, the treatment of lichen sclerosing (LS) includes the use of ultra-strong or potent topical steroids (for example, clobetazole propionate, mometasone furoate) as the first line of therapy for genital LS, with mandatory adherence to the regimen of use. Proactive ointments (mometasone furoate 0.1 %, clobetazole propionate 0.05 %) are effective for maintaining remission. In case of secondary infection, antibacterial and antifungal agents are used. Alternative second-line methods include topical calcineurin inhibitors, systemic retinoids, phototherapy, therapy, surgery (only with concomitant changes), as well as stem cells and PRP plasma (low level of evidence). Surgical intervention may be required to treat adhesions and scarring, but is contraindicated in cases of active inflammation.

Treatment of intraepithelial neoplasia of the vulva (VIN) in HSIL includes the following methods: surgical treatment remains the main choice, however, it is associated with a high recurrence rate and a negative impact on quality of life and sexual function. Imiquimod cream (an immune response modifier with antiviral and antitumor properties) (GRADE 1B), laser CO_2 therapy, loop electrosurgical excision (LEEP) and surgical excision by cold plasma coblation are also used. In some cases, it is possible to follow up without treatment, expecting spontaneous regression. Surgical excision by cold plasma coblation is preferable for differentiated vulvar intraepithelial neoplasia (dVIN) [12].

According to the Bulletin of the American College of Obstetricians and Gynecologists, for the initial treatment of lichen sclerosis, it is recommended to use a local corticosteroid ointment of medium or high efficacy, such as 0.05 % ointment with clobetazole propionate or 0.1 % ointment with mometasone furoate. According to the recommendations of experts, in particular the British Association of Dermatologists, clobetazol propionate should be applied once a day at night for 4 weeks, then alternated at night for the next month, and then twice a week for 4 weeks. Follow-up is necessary after 3 months to assess the response to therapy and the correctness of the drug use. With good disease control, a follow-up examination should be carried out after 3–6 months, with poor control, more frequent visits are necessary. Patients should seek medical attention if persistent ulceration or neoplasm occurs; in such cases, a biopsy is important to rule out intraepithelial neoplasia or invasive squamous cell carcinoma. A randomized study of 27 patients with lichen sclerosis showed that twice weekly administration of 0.1 % mometasone furoate ointment for 56 weeks effectively prevents relapses without side effects [13]. A prospective cohort study involving 507 patients who had been followed for at least 2 years demonstrated that compliance with long-term corticosteroid therapy (defined as permanent or in most cases) significantly exceeds partial compliance in symptom control (93.3 % vs. 58.0 %; $p < 0.001$), prevention of adhesions and scarring (3.4 % vs. 40.0 %; $p < 0.001$) and reduction of vulvar cancer prevalence (0 % vs. 4.7 %; $p < 0.001$) [14].

A study by Gallio N, et al. (2024) revealed a high risk of developing both primary and recurrent squamous cell carcinoma of the vulva in patients with dVIN. It was recommended to optimize early detection of diseases, long-term follow-up, and adequate topical treatment with ultrapotent corticosteroids. The use of laser ethylmethylhydroxypyridine succinate can significantly improve the results of treatment of kraurosis, although contraindications and potential problems with resistance must be taken into account [15].

Also, a study conducted by Popa A, et al. (2024) shows that potent topical corticosteroids are currently widely recognized as the most effective treatment method for achieving remission in LS, but given the potential complications of long-term treatment, understanding the evolution of LS during puberty becomes especially important to determine the need for aggressive or more conservative therapeutic interventions. New treatments, including PRP (platelet-rich plasma), stem cell therapy, and energy-based laser therapy such as fractional carbon dioxide (CO_2) laser and yttrium aluminum garnet doped neodymium (Nd-YAG) laser, are being investigated to identify more effective treatments for LS than potent topical corticosteroids. Currently, the use of clobetazol 0.05 % ointment on a daily basis for 4–12 weeks is the gold standard for the treatment of LS [16].

In recent years, there has been increasing evidence regarding the effectiveness of using PRP in various fields of medicine [17]. The basis of the action of various varieties of PRP is the release of biologically active factors from alpha-granules of platelets. Leukocytes and fibrin contained in some of its varieties, as well as other components (for example, hyaluronic acid), also contribute to the action of PRP. Activated PRP has a higher biological activity than inactive PRP. PRP preparations are widely used in the field of traumatology, cosmetology and trichology, surgery and proctology, gynecology and urology [18, 19]. The method is based on the collection of 10–20 ml of the patient's own whole blood, which is placed in a specialized tube, where it is centrifuged to obtain platelet-rich plasma. Several milliliters of this enriched plasma obtained by centrifugation are injected into the required tissue. There are several types of tubes for PRP preparations: a tube designed to produce autologous platelet-rich plasma with prolonged platelet degranulation, which ensures maximum tissue regeneration effect; a tube designed to produce an autologous thrombin-fibrin gel, which serves as a volumetric matrix and activator of platelet growth factors degranulation formed in the previously mentioned tube; The cell matrix method, which uses test tubes to produce a patented combination of hyaluronic acid and platelet-enriched plasma [20]. Plasma administration in periodic courses demonstrates a steady positive effect even in those women in whom standard glucocorticoid therapy has proved ineffective [21].

The literature describes clinical cases of improvement in the histological picture and female sexual function index after plasma therapy [22–24]. In a study by Behnia-Willison F, et al. (n = 28) patients with LS that did not respond to steroid therapy received PRP injections 3 times with an interval of 4–6 weeks and again a year later in all affected areas of the vulva. The patients showed clinical improvements, including a reduction in the size of the lesions, and 28.6 % of them had complete disappearance of the lesions after a course of PRP therapy. The author of the study concluded that PRP injections can be considered as an effective method of treating LS [25]. Although the use of PRP drugs is usually effective and safe, there are a number of contraindications for which caution should be exercised when prescribing this procedure. Contraindications to PRP include thrombocytopenia, septicemia, platelet dysfunction syndrome and exogenous diseases, hypofibrinogenemia, systemic connective tissue diseases, anemia, and the use of corticosteroids or nonsteroidal anti-inflammatory drugs (NSAIDs) prior to the procedure [18].

According to research, against the background of laser therapy, patients experienced a significant regression in complaints related to dystrophic diseases of the vulva, and there was also an increase in satisfaction with the quality of sexual life. Patients in the control group who used local glucocorticosteroids noted a resumption of itching symptoms in the vulvar region, which required continued maintenance therapy for up to 6 months and indicated a short-term effect of glucocorticosteroids [26, 27].

One potential solution that can meet these criteria is photodynamic therapy (PDT). PDT is a recommended treatment for precancerous diseases of the vulva [28–30]. The PDT mechanism is based on the use of photosensitizers in combination with visible light of a certain wavelength to produce oxygen and free radicals, which leads to apoptosis and necrosis of cells in the affected area to alleviate skin damage without affecting the surrounding normal tissues and cells [31–33].

Studies show that PDT can alleviate clinical symptoms and signs such as itching and loss of skin elasticity by improving microcirculation in skin lesions, regulating local cellular immune function, stimulating fibroblast activity and synthesis of types I and III collagen [34, 35].

Some researchers also note that the use of curcumin with PDT may become a promising therapy in the treatment of vulvar lesions, leading to the death of only cells exposed to radiation [36, 37]. Since curcumin is a natural bioactive compound with antitumor properties. The use of nanoparticles containing curcumin can provide better efficacy of this compound in therapy, because they achieve good biocompatibility and do not exhibit cytotoxicity [38, 39].

In addition, preclinical studies are available for the potential use of other types of molecules in PDT that can destroy precancerous and cancer cells, such as hypericin [40, 41], indocyanine green (ICG) [42], methylene blue dye [43], zinc phthalocyanine, and other chlorophyll derivatives other than E6 chloride [44], methyl violet [45], bacteriochlorins [46], fullerenes [47, 48], xanthene molecules (eosin and erythrosine) [49].

Against the background of PDT use, 95 % of patients experienced complete clinical remission, confirmed by cytological and morphological studies. This indicates the high efficiency of PDT as an organ-preserving treatment method, which has a minimal level of side effects [50, 51].

Maździarz A (2019) used 5 % aminolevulinic acid (5-ALA) with 2 % dimethyl sulfoxide, performing 10 procedures with a weekly interval, which led to partial remission and negative results on human papillomavirus (HPV) DNA in 50 % of patients. Li Z, et al. (2020) used 20 % 5-ALA with fewer procedures (4–9), which resulted in a significant reduction in symptoms in 92.31 % of patients, although relapses were observed in 20 %. Liu J, et al. (2021) also used 20 % 5-ALA, but with more treatments (6) such as improved clinical and dermatoscopic characteristics, although pain and erosion were common. Zhang F, et al. (2021) and Zielińska A, et al. (2021) used different concentrations of 5-ALA and treatment regimens. Zhang F, et al. a significant decrease in lesions was observed in 56.6 % of patients and an improvement in histological results. Zielińska A, et al. Clinical remission was recorded in 75.3 % of patients, but histopathological remission was low (2.7 %). All studies noted complications such as pain and burning, which varied in severity and duration. Study participants typically experienced short-term discomfort such as pain and burning for several days after the procedures, as well as paresthesia, erythema, and edema.

Zhou M, et al. (2023) note that photodynamic therapy with 5-aminolevulinic acid (ALA-PDT) has demonstrated the same clinical efficacy as surgical intervention in the treatment of vulvar SIL, but with milder side effects and preservation of the integrity of the vulvar structure. In a prospective study by Han Q, et al. (2022), cases of recurrence are observed, indicating the need for long-term follow-up and possible re-treatment to achieve better HPV clearance. Studies have also reported various complications, including itching and mild pain. These data indicate the high potential of 5-ALA therapy in the treatment of VIN but emphasize the importance of further monitoring and management of possible complications and relapses.

In a recent study, Avin M and Gomberg MA (2024) compared the effectiveness of treatment of patients suffering from involutive changes in the vulva using PDT and PDT combined with PRP plasma therapy. As a result, there was no statistically significant difference in the effectiveness of the effect on quality of life ($p = 0.07$), however, combining PDT with PRP showed a significant improvement in symptoms such as burning and dryness, while no side effects were observed ($p < 0.001$), which further positively affected physical activity, psycho-emotional state and sexual activity. the life of patients [50, 51].

Antimicrobial photodynamic therapy (aPDT) is also one of the fundamental tools in modern therapy of precancerous conditions and cancers

associated with HPV, in particular, due to the increasing versatility of photosensitizers and the numerous possibilities of combining aPDT with other antimicrobial treatments to combat localized infections [52]. Thus, aPDT and its numerous therapeutic combinations can become an advanced routine treatment method for combating microorganisms [53].

Ozone-bacteriophage therapy is noted as another method of treating involutive and dystrophic LPO processes, which, according to the authors, contributed to the restoration of the expression of estrogen and progesterone receptors in the glands and stroma of the endometrium [56].

In addition, scientists from Russia note that in the treatment of precancerous vulvar conditions, the factor of the psychoemotional state of women is very important, in the treatment of which supportive and cognitive behavioral therapy, as well as methods of distraction from negative inner feelings, are effective. Autogenic training combined with meditation can help improve the emotional background. Couples therapy, which includes discussing sexual issues and fears with a partner, can be helpful. In addition, it is important to conduct educational conversations that help increase treatment adherence, as the doctor's recommendations can slow down the progression of the disease and improve the condition of patients [54].

CONCLUSION

The treatment of precancerous vulvar diseases covers a wide range of methods and tools, but the use of topical corticosteroids remains the gold standard of therapy. In recent years, PDT has established itself as a promising treatment method, demonstrating significant potential in combating precancerous vulvar conditions.

Existing studies show that PDT can be highly effective in disease regression and HPV clearance, as well as help reduce relapses. Despite the positive results, there is a need for further study and publication of modern randomized clinical trials and systematic reviews that could provide a more extensive and reliable assessment of the effectiveness of PDT in the treatment of precancerous vulvar conditions.

To improve understanding and optimize the treatment of precancerous vulvar conditions, it is recommended to conduct research aimed at studying combined treatment methods, which, according to some reports, can lead to improved treatment outcomes, reduced relapses and reduced risk of complications. Studies of combined approaches will allow us to determine the most effective strategies and optimal treatment regimens, considering the individual characteristics of patients.

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Information about authors:

Nasrulla A. Shanazarov ✉ – Dr. Sci. (Med.), Professor, Deputy Director for Strategic Development, Science and Education, RSE "Medical Center Hospital of the President's affairs Administration of the Republic of Kazakhstan" on REU, Astana, Republic of Kazakhstan
ORCID: https://orcid.org/0000-0002-2976-259X, SPIN: 6224-3395, AuthorID: 633414, ResearcherID: A-9433-2019, Scopus Author ID: 57207467603

Sergey V. Zinchenko – Dr. Sci. (Med.), Associate Professor, Head of the Department of Surgery, Kazan (Volga Region) Federal University, Kazan, Russian Federation
ORCID: https://orcid.org/0000-0002-9306-3507, SPIN: 5381-4389, AuthorID: 905414, ResearcherID: S-9423-2018, Scopus Author ID: 35363234100

Saule D. Kisikova – Dr. Sci. (Med.), Advisor to the Director, RSE "Medical Center Hospital of the President's affairs Administration of the Republic of Kazakhstan" on REU, Astana, Republic of Kazakhstan
ORCID: https://orcid.org/0000-0003-4584-9342

Makpal A. Alchimbayeva – Leading Specialist at the Department of Health Technology Assessment and Strategic Development, RSE "Medical Center Hospital of the President's affairs Administration of the Republic of Kazakhstan" on REU, Astana, Republic of Kazakhstan
ORCID: https://orcid.org/0000-0002-3086-5465

Kaldygul S. Seitbekova – MD, Gynecologist at the PDT Center, RSE "Medical Center Hospital of the President's affairs Administration of the Republic of Kazakhstan" on REU, Astana, Republic of Kazakhstan
ORCID: https://orcid.org/0009-0006-4570-0571, ResearcherID: LWH-5765-2024

Ilfat Z. Galiev – Senior Lecturer at the Department of Surgery, Kazan (Volga Region) Federal University, Kazan, Russian Federation
ORCID: https://orcid.org/0000-0001-8926-8799

Makhabbat M. Ibragim – MD, Psychiatrist, Medical Center "Aya", Astana, Republic of Kazakhstan

Contribution of the authors:

Shanazarov N. A., Zinchenko S. V., Alchimbaeva M. A. – study concept and design development;
Shanazarov N. A., Kisikova S. D., Seitbekova K. S. – data collection;
Alchimbaeva M. A. – statistical analysis;
Shanazarov N. A., Alchimbaeva M. A., Kisikova S. D. – analysis of the obtained data;
Seitbekova K. S., Galiev I. Z. – writing the article;
Shanazarov N. A., Alchimbaeva M. A. – editing of the article;
Shanazarov N. A., Ibragim M. I., Alchimbaeva M. A. – general responsibility.