Vera Yefimovna Balan, Larisa Anatolyevna Kovalova, Elena Vladislavovna Tikhomirova.

Genitourinary Syndrome of Menopause. Therapy Potentials.

1State-Funded Institution of Healthcare ‘Moscow Regional Scientific Research Institution for Obstetrics and Gynaecology’ of the Ministry of Health of the Russian Federation, Moscow, Russia
2State-Funded Educational Institution ‘I.M. Sechenov First Moscow State Medical University’ of the Ministry of Health of the Russian Federation, Moscow, Russia
3State-Funded Educational Institution ‘I.M. Sechenov First Moscow State Medical University’ of the Ministry of Health of the Russian Federation, Moscow, Russia

Abstract: The article represents a review of the literature that reflects modern aspects of the terminology, classification, pathogenesis, and treatment options of urogenital disorders in women at the menopause. It shows the sensibility of the lower parts of the urinary tract to sex steroids, which importance is beyond question in the genesis of vaginal and urinary symptoms. The article discusses the issues of the effectiveness of systemic and local hormone replacement therapy a variety of treatments.

Keywords: menopause, menopausal genitourinary syndrome, urogenital disorders, oestrogens, hormone replacement therapy.

The climacteric period (menopause) is a universal physiological process related to the fall of the secretion of the ovarian hormones (oestrogens, progesterone). The phases of menopause include the menopausal transition, menopause, perimenopause, and postmenopause. Menopause is the last independent menstruation, which date is set in retrospect after 12 months of the absence of the menstruation. The age of menopause varies from 45 to 55, with an average of 51 to 53 [1]. Time of onset of menopause depends on many factors, such as a woman’s social status, nutrition, lifestyle (smoking), and body weight.

The climacteric syndrome is characterized by the presence of symptoms in the climacteric period manifested by the vasomotor, emotional and vegetative or metabolism disorders. The urogenital disorders including various types of the
urinary incontinence refer to the “local” manifestations of the climacteric syndrome at the level of the lower parts of the genitourinary tract.

The urogenital atrophy or urogenital disorders (UGA, UGD) are the second common “markers” of the onset of menopause and indication for hormone therapy prescription. Despite the large number of the scientific researches for over 20 years until present, the disputes about the form of hormone replacement therapy (local or system) in the development of UGD symptoms, its safety, duration, possible alternative treatments have not been completed.

In the English literature from the 1990s of the 20th century, the term “vulvovaginal atrophy” was adopted. In 2012, a conference was held to reach the consensus about the replacement of the term “vulvovaginal atrophy” with the term “genitourinary syndrome of menopause” (GSM).

In the experts’ opinion, from a medical point of view GSM is more accurate, universal and acceptable to the clinicians, researchers, teachers, patients, and mass media. The need for a new term is due to that the word “atrophy” means something finally lost, and the word “vagina” barely survives in the mass media. The experts hold up as an example the replacement of the adopted term “impotence” on a more neutral term “erectile dysfunction”. In addition, the term “vulvovaginal atrophy” does not include the urinary abnormalities (pollakiuria, nocturia, urinary urgency, urinary incontinence, dysuria, recurrent infections of the urinary tracts, etc.). The respective NAMS and ISSWSH commissions have already formally approved the new terminology in 2014.

There is no harmonious term in the Russian language, which would begin with the word “genital”, and the term “urogenital disorders” is ordinary for us, including both vaginal and urinary symptoms.

The term “genitourinary syndrome of menopause”, GSM will be presented and discussed at the leading institutions for obstetrics and gynaecology. From our point of view, the terminology adopted in Russia may not be changed or may be changed with the term “urogenital syndrome, UGS”.
GSM or UGS (synonyms) is a set of the vaginal and urinary symptoms associated with the development of atrophic and dystrophic processes in the oestrogen-dependent tissues and structures of the lower third of the genitourinary tract: bladder, urinary tract (urethra), vagina, ligamentous apparatus of the small pelvis and muscles of the pelvic floor. The term “urogenital atrophy” (UGA) or “urogenital disorders” is a synonym of GSM or UGS.

The symptoms related to the atrophy of vagina (vaginal atrophy) and urinary disorders (cystourethritis atrophy) are marked in the clinical picture of UGS in the climacteric period. Very often, the patients with symptoms of UGS do not call for help and find them as the natural symptoms of aging [4].

**The symptoms of the vaginal atrophy include:**
- dryness, pruritus, burning in the vagina;
- dyspareunia;
- recurrent vaginal discharges;
- contact bloody issues;
- colpoptosis;
- sexual frustration.

**The urinary disorders at UGS include:**
- pollakiuria (urination more than 8 times per day);
- nocturia (more than one episode of urination per night);
- urgent uriesthesia;
- urgent urinary incontinence;
- stress urinary incontinence;
- recurrent infections of the urinary tracts.

The data about the prevalence of UGS symptoms practically do not reflect the real situation. Therefore, in the study by Barlow D. H. et al. [3], which includes 2,045 British women at the age of 55-85, the urogenital symptoms were found in every second woman, but only 11 % of the patients focused the doctor’s attention on the presence of these symptoms.
According to a number of authors [2, 4], UGS incidence varies from 3 % in the perimenopause and 60 % in the postmenopause with duration longer than 5 years. Unlike the vasomotor symptoms of the climacteric syndrome, often levelled over time, UGS has a progressive nature, and with its significant impact on the sexual health and quality of women life, is almost not corrected without treatment. The lowering sexual activity, progressing with age, is observed in 70 % of women with UGS. More than 30 % of women reported about the dyspareunia and/or dryness in the vagina and associated the decline in sexuality with these symptoms.

The highest UGS incidence and severity are observed in smoking women as well as in patients receiving treatment for breast cancer [2].

The appearance of UGS symptoms is associated with dystrophic changes in oestrogen-dependent tissues of the urogenital tract, and is based on the peculiarities of embryogenesis. The urinary and genital tracts are shown to have a common origin from the intermediate mesoderm of the early embryo. The upper three-quarters of the vagina are formed from the mesoderm, the distal vagina and vulva are formed from the endoderm, and the epithelium of the vulvar lips has ectodermal origin.

The population and density of receptors for sex steroids in the structures of the urinary tracts and vagina are different, which seems to be the result of thin tissue differentiation during the embryogenesis, but it may also explain the alternative response of the various structures to hormone replacement therapy.

Relatively recently, using the immunological and immunocytochemical methods in all structures of the urogenital tract, the localization of α- and β-oestrogen receptors (ERα, ERβ), progesterone receptors (A and B), androgen receptors was revealed. It is found that the receptors for sex hormones are located in the basal and parabasal cells of the vaginal epithelium, vascular smooth muscle cells, lower third of the vagina, skin and striated muscles of perineum, urothelium, vascular endothelium of the vagina, bladder and urethra walls [6, 7]. The oestrogen receptors have the biggest density; these receptors being located in the ectoderm
derivatives are likely to play a dominant role in the development of vulvar diseases.

In 2008, the study results were published, greatly extending our understanding about the reception of the urogenital tract; in the biopsy material of the vaginal wall, a large group of steroidal nuclear receptors of ERR oestrogen-related receptors, including three isoforms (ERRα, ERRβ, ERRγ), is isolated [5].

The authors have shown that ERα content is not significantly different in the patients in the perimenopause and postmenopause, unlike ERβ, the level of which is reduced in the postmenopause. It is shown that the oestrogen therapy does not significantly affect the level of ERβ receptors [5]. The assumption was made about ERRα and ERα co-expression in the vaginal epithelium, as well as in the tissues that are sensitive to oestrogens. The level of mRNA of ERβ, ERRα, and ERRγ was found to be reduced in the biopsy material of the vaginal wall in the postmenopausal women, which may explain the clinical effect of isoflavones and natural components of hormone replacement therapy in the development of the vaginal atrophy. The presence of the oestrogen receptors in the region of autonomic and sensory neurons of the vagina and vulva explains the beneficial effects of oestrogen therapy. It is shown that in contrast to the density of androgen receptors, the density of receptors to oestrogens decreases in the direction from the vagina to the skin of the external genitalia.

The progesterone receptors (PR) function as the transcriptional activators of the progesterone stimulated genes in response to progesterone. PR of type A plays a minimal role, which can inhibit the activity of PR of type B. The different isoforms pf PR can be presented in different cells of the body.

The receptors to androgens are the least studied among the marked receptors of the urogenital tract. Their density is known to change during the life, with its decrease in the menopause and increase during the therapy [10].

**The main elements of UGS pathogenesis are as follows:**

- blood supply disturbance of the bladder wall, urinary tract, vaginal walls, development of detrusor ischemia, urinary tract, vagina, reduced transudation;
• the proliferation disorder of the vaginal epithelium and urinary tract, reducing the synthesis of glycogen, changing nature of vaginal secretion (disappearance of Lactobacillus, pH increase), possible accession of the secondary infection;
  • changes in collagen synthesis and metabolism in the ligamentous apparatus of small pelvis, loss of elasticity, brittleness. As a consequence, the colpoptosis and violation of the mobility and position of the urinary tract, development of stress urinary incontinence;
  • reduction of the amount of α- and β-adrenoreceptors in the urinary tract, cervix and bottom of the bladder;
  • altered sensitivity of the muscarinic receptors to acetylcholine, decreased sensitivity of myofibrils to noradrenaline, reduction of muscle volume and contractile activity of myofibrils, their atrophy;
  • decreased blood supply and oxygenation of the vaginal wall, reduced transudation leads to dyspareunia symptoms.

The appearance of symptoms of the vaginal atrophy are due to the changes in the vulva and vagina, characterized by thinning of the mucous membranes, reduction of blood flow and secretion. The length of the vagina can be reduced, often in the absence of sexual encounters. The elasticity and folding of the vagina are reduced, and petechias appear on the mucous membranes. The change of the cell composition of the vaginal mucosa leads to impaired microbiocenosis. Disappearance of the intermediate cells of the vaginal epithelium results in reduced glycogen synthesis and altered vaginal secretion (disappearance of Lactobacillus, increased pH), contributing to the accession of the secondary infection.

The increase in the incidence of bacterial vaginosis was reported in the perimenopausal women, as compared with the postmenopausal women, that is due to the prevalence of the latter species of lactobacilli in the biocenosis—Atopobium vaginae, providing a protective effect. Unfortunately, often the detection of Atopobium vaginae leads to prescription of antibacterial therapy, which is certainly irrational in the postmenopausal patients [12]. The prevalence of Lactobacillus
iners and Lactobacillus crispatus subspecies was detected in the biotope of the vagina in healthy women in the postmenopause.

The UGS diagnostics occurs based on the patient’s complaints, past history, examination findings, and extended colposcopy and vulvoscopy. If it is necessary, the Ph of the vaginal contents and the value of the maturity of the vaginal epithelium (VMVE) are determined, and the comprehensive microbiological examination of vaginal discharge is conducted. To determine the intensity of the vaginal atrophy symptoms, the five-point scale by D. Barlow is used, where 0 means no symptoms, and 5 means severe symptoms.

The hormonal drugs include the systemic hormone therapy and local oestrogens (17β-estradiol, estradiol acetate, estradiol hemihydrate, conjugated oestrogens, oestrone as vaginal creams, rings, tablets). The only selective modulator of oestrogen receptors is approved in the United States, recommended for the treatment of moderate and severe dyspareunia – ospemifene. At present, the assessment of lasofoxifene efficacy, bazedoxifene combination with conjugated oestrogens and dehydroepiandrosterone intravaginal form is performed. It is shown that efficacy of the cream containing testosterone in relieving the vaginal atrophy symptoms is not more than that of a placebo.

The pathogenic significance of the hormone replacement therapy in the treatment of urogenital disorders is uncontroversial. The numerous studies, the first of which were performed in the middle of the 20th century, confirmed the safety and positive impact of the local estriol-containing agents on the state of the urogenital tract during the hormone-dependent processes [8, 9]. The works by O. Al-Baghdadi et al. (2009) show that the local forms of oestrogen in the treatment of urogenital disorders are more effective than the systemic menopausal hormone therapy (MHT) [2]. The meta-analysis of 34 randomized, placebo-controlled studies involving over 7,000 women showed different efficacy of oestrogen therapy of UGR symptoms depending on the oestrogen type and method of administration. Systemic estradiol or conjugated oestrogen agents were shown to be ineffective in correcting urogenital atrophy, and their prescription is
contraindicated in a part of women in the postmenopause (level of evidence B).

With regard to the non-drug treatment, its efficacy is similar to placebo. High efficacy of local oestrogen, estriol in particular, was found in the treatment of atrophic changes in the urogenital tract (level of evidence A). Topical estriol agents have minimum systemic absorption, the positive effect of treatment comes quickly in 2-3 weeks. The long-term follow-up (up to 24 months) showed no negative impact of topical dosage forms of oestrogens on the endometrium [13]. In the cases of oestrogen deficiency, the most optimal way of treatment is a hormone replacement therapy.

However, there are some situations where the alternative treatment options are required:

- contraindications to MHT;
- dryness in the vagina even when MHT is administered systemically;
- dryness in the vagina, which is not associated with oestrogen deficiency.

At present, the only non-hormonal moisturizing gel with the liposomal structure for vaginal administration, Muvagel, was offered. Its ingredients: Hyaluronic acid 0.1 %, mallow and chamomile extracts, **vegetable phospholipids of soy and red clover**.

Hyaluronic acid has a moisturizing and regenerative action for the integrity of the vaginal mucosa. The anti-inflammatory action is characteristic of mallow and chamomile extracts. Soy isoflavones have an effect similar to that of the oestrogen. The synergistic effect of soy isoflavones and red clover extract recover the vaginal mucosa tissues and increase production of collagen and hyaluronic acid. The liposomes promote quick penetration of the active substances in the epithelial cells. The indications for use of the product include mild and moderate vaginal atrophy.

References


**Authors:**
Vera Yefimovna Balan, Doctor of Medicine, professor. – Head of the outpatient department of SFIH “MRSRIOG” of MH of the RF
Larisa Anatolyevna Kovaleva, Candidate of Medical Science – Assistant of the Department of Obstetrics, Gynaecology, Perinatology and Reproductive Medicine of SFEI “The First MSU named after I. M. Sechenova