Genitourinary syndrome of menopause – is the problem solved?
State of the art 2018

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Abstract

Vulvovaginal atrophy accompanied by lower urinary tract dysfunction related to low levels of estrogen and androgens is labeled as genitourinary syndrome of menopause (GSM). Although this condition affects most postmenopausal women worldwide, it seems to be underdiagnosed and undertreated. Women should be properly advised to choose an adequate treatment modality to improve their quality of life, sexual relationships and social activity. The aim of this article is to increase knowledge of GSM. The current treatment options, both hormonal and non-hormonal, are reviewed. Topical estrogen therapy still remains the gold standard, but the demand for individually tailored therapy is growing. New treatment modalities are continuously included in clinical practice. They should consider the whole personality of a woman as well as cultural and social factors. Further studies on GSM and on the effectiveness of various treatment options are necessary to achieve this purpose.

Key words: menopause, vulvovaginal atrophy, androgens, estrogens, SERMs, laser, RF devices.

Introduction

Vulvovaginal atrophy (VVA) accompanied by lower urinary tract dysfunction (LUTS) related to low levels of estrogen and androgens is labeled as genitourinary syndrome of menopause (GSM). The signs and symptoms of VVA – vaginal dryness, irritation, burning and dyspareunia – are the most bothersome for postmenopausal women. The GENISSE study revealed presence of GSM in 70% of participants. The most prevalent signs were vaginal dryness (93.3%), reduced lubrication (90%) and dyspareunia (81.6%), markedly decreasing quality of life [1]. However, as it was shown in the AGATA study, there is great confusion about the therapy of VVA. The treatment is heterogeneous and inadequate. The discontinuation rate is almost 40%. Women spontaneously withdraw from treatment due to the lack of efficiency (46.6%), messiness (24.3%), difficulty in application (7.8%) and vaginal discharge (1.9%). The absence of clear therapeutic standards based on well-controlled clinical studies leads to heterogeneity of the treatment schedules.

Inadequate prescribed products in terms of type, time schedule and length of administration make the therapy insufficient and decrease a patient’s compliance. In fact, VVA remains practically untreated [2]. These problems seem to affect women all over the world. The European REVIVE study (REVIVE-EU) showed that 47% of participants were not aware of the VVA condition, 8.1% were not aware of the cause of VVA and only 39.9% directly attributed VVA to the menopause. The European women mostly suffered from vaginal dryness (70%), vaginal irritation (32.7%), dyspareunia (29%) and vaginal tenderness (14.3%). A great impact of VVA symptoms on sexual satisfaction was reported by 72% of participants. More than 60% of women in the survey discussed these problems with their HCP (health care professional), but about 50% had to initiate this conversation themselves. Satisfaction with treatment was reported by approximately 45% of women and the OTC personal lubricants and moisturizers were the most common agents. The therapy was discontinued by 39.2% of participants, mainly because the symptoms were not bothersome enough to continue treatment (18.4%), the medication was not sufficiently effective (18.3%), or due to relief from VVA symptoms. The main worries related to vaginal hormonal agents were concerns about adverse effects (AE) (55.7%) and a fear of possible carcinogenesis [3]. The pan-Asian REVIVE survey gave evidence that GSM is underdiagnosed and undertreated in Asia. Only 25% of women discussed their VVA symptoms with a health care professional and only 24% were HCP-initiated. Moreover, only 21% of the participants were clinically diagnosed with GSM by HCP. The most common rea-
son for not discussing GSM symptoms with a HCP was the belief that these symptoms were a natural part of aging (49%) and would diminish over time without treatment. Among women who have ever been treated 52% abandoned therapy because they felt improved or cured. The users of GSM treatment reported a high degree of concern mostly related to hormonal therapy and its safety in long-term use (58%) [4]. The VIVA-LATAM study revealed the lack of knowledge of postmenopausal vaginal atrophy in women of Latin America. Across Latin America there are huge differences between countries in health care access and standards. Some country-specific differences between surveyed populations of women were confirmed in this study. For instance, fewer responders in the Brazilian cohort were concerned about the health of their vagina (31% [64% overall]) and their sexual health (27% [51% overall]). More women from Columbia associated VVA with a symptom of the menopause (54% [45% overall]). For women from China urinary incontinence constituted the major problem (75% [60% overall]). Nevertheless, overall 71% of the participants did not know vaginal atrophy to be a chronic condition and only 6% attributed vaginal dryness, itching, burning or dyspareunia directly to VVA. Overall 64% of the surveyed population believed that vaginal discomfort could limit the comfort of their everyday activities, including sex, and 56% considered that the condition could also decrease the comfort of sexual satisfaction of their partners. Despite the availability of many treatment modalities, 34% of women with severe vaginal symptoms do not believe in the possibility of effective therapy. However, 52% of women were aware of the existence of some form of local hormonal treatment [5]. Similar studies from other countries and world regions show that despite cultural differences, the GSM is underdiagnosed and undertreated. Women need more information, more education and wider access to treatment modalities to improve their sexual functions and postmenopausal quality of life [6].

Androgens

During menopause, estrogen synthesis in the ovaries ceases rapidly, but this process is not directly accompanied by a parallel decrease of the androgen blood levels. The androgens decrease progressively throughout adult life, but a lower sex hormone-binding globulin (SHBG) concentration in the menopause period allows the free testosterone level to be kept stable [7]. Androgens act by activation of the intracellular androgen receptors (AR), which are localized in the vaginal tissues, vestibule, clitoris, labia, bladder, urethra and pelvic muscles [8]. AR stimulation could involve the genomic pathway, through androgen response elements (AREs) on the DNA, resulting in mRNA expression of specific androgen-responsive genes leading to changes in cellular metabolism or non-genomic signaling related to the cytoplasmic and membrane-associated receptor activation [9]. After menopause dehydroepiandrosterone (DHEA) becomes the main source of the androgens and estrogens synthesized in peripheral tissues. The blood concentration of DHEA declines continuously from the third decade of life and leads to a decrease in the peripheral synthesis of sex steroids after menopause. This, in consequence, causes the constellation of perimenopausal signs and symptoms, such as hot flushes, sexual dysfunction, VVA, bone and muscle loss, cognition disorders and many others. An intracrinological enzymatic system unique to humans maintains under control intracellular transformation of DHEA into active sex steroids. The UGT enzymes (the uridine diphosphate [UDP]-glucuronosyltransferase family), involved in the glucuronidation pathway, maintain the sex steroids serum level within the normal postmenopausal range. Thus, activation of the sex hormone specific tissue receptors is strongly limited [10, 11]. Intravaginal 0.5% (6.5 mg) DHEA has no significant effect on serum estrogens and androgens levels. The serum E2 concentration 12 weeks after intravaginal administration of prasterone was about 19% below the postmenopausal value [12]. Contrarily, long-term local treatment with low doses of E2 could increase the serum estradiol level with possibly systemic estrogenic effects [13]. A recent review of 12 randomized controlled trials of intravaginal prasterone versus placebo revealed safety and high effectiveness of DHEA in VVA therapy. At the 52-week follow-up of daily treatment of 0.5% prasterone (6.5 mg) a significant improvement in desire, arousal, lubrication, orgasm, sexual satisfaction and pain scores was observed [14]. Cytological analysis showed a significant decrease in parabasal vaginal epithelial cells with simultaneous increase in superficial layer and vaginal secretion [15]. In any case, where an impact of DHEA on endometrium was analyzed, a proliferative effect was found [16]. A comparison of intravaginal 6.5 mg prasterone with 0.3 mg conjugated estrogens and 10 μg estradiol showed at least equal efficacy of DHEA as vaginal estrogens [17]. The most commonly reported AE were vaginal discharge (5.71%) and abnormal cervical smear (in 2.1% of women: low-grade squamous intraepithelial lesions [L-SIL] and atypical cells of undetermined significance [ASC-US]) [18].

Low-dose vaginal estrogens

Low-dose vaginal estrogens constitutes the gold standard of VVA therapy. In the statement of the North American Menopause Society (NAMS), this treatment is preferred over systemic estrogen therapy due to its safety and effectiveness [19]. The wide range of FDA-approved products help patients to choose the most
suitable, accepted and convenient form. The optimal treatment should involve the lowest dose of vaginal estrogen which makes the therapy effective. Estrogen vaginal creams, inserts and rings are available in the USA. The vaginal cream, applied 0.5-1.0 g daily for 2 weeks, followed by 0.5-1.0 g 1-3 times weekly, contains estradiol-17β or conjugated estrogens (conjugated estrogens are not available on the European market). It provides additional vaginal moisturizing but the lack of a dosing unit increases the risk of exceeding the proper dose. Vaginal tablets (10 mg estradiol) support more controlled dosing of E2. Vaginal softgel capsules with estradiol-17β (4, 10 and 25 mg doses) are a novel promising option for VVA treatment. Two randomized, single-dose, two-way cross-over trials comparing the pharmacokinetics of a solubilized estradiol softgel capsule with a vaginal estradiol tablet in postmenopausal women at 10 mg and 25 mg doses established the safety, patient's satisfaction and good tolerance of the softgels. Serum levels of estradiol, estrone and estrone sulfate were significantly lower than those found with the estradiol 10 mg vaginal tablet [13]. A recent randomized, multicenter, double-blind study showed the effectiveness of a very low-dose estradiol vaginal cream (0.003%) applied twice a week in the treatment of vaginal dryness [20]. Mueck et al. in a clinical review revealed the efficacy of ultra-low doses of estradiol (0.03 mg/l) in combination with Lactobacillus acidophilus in restoring vaginal mucosa and microflora in ageing menopausal women [21]. Santen compared various doses of estrogens in local vaginal therapy and their concentration in the urine. He noted that the estrogen blood level did not exceed the postmenopausal value (< 20 pg/ml) during long-term administration of low-dose estrogens (e.g. 10 mg vaginal tablets). The intermediate and high-dose-estrogen regimens (25 mg and higher estradiol agents) maintained the plasma estrogen concentration within the premenopausal range [22]. There are two vaginal rings available releasing different estrogen doses, both applied for 90 days. The lower-dose ring contains 2 mg of estradiol-17β and is dedicated for the treatment of VVA only. The higher-dose ring with 12.4 mg of estradiol acetate provides a systemic hormone level adequate to the GSM and vasomotor symptoms therapy [19]. According to the NAMS and National Institute for Clinical Excellence (NICE), low-dose vaginal estrogens improve the vaginal maturation index, increase the number of vaginal lactobacilli and decrease vaginal pH [23]. The treatment should be continued as long as needed to relieve symptoms (NICE 2015). Moreover, the NAMS and NICE do not recommend the protection of endometrium with progesterone while treated with low-dose vaginal estrogens. However, monitoring of the endometrium is recommended in women with high risk of endometrial cancer and when higher doses of estrogen than usual are used in the therapy [19, 24] (NICE 2015). Currently animal studies are ongoing to evaluate the impact of estetrol (E4) (a weak estrogen produced exclusively by the human fetal liver during pregnancy) on vaginal tissue. Estetrol does not increase the level of hepatic-derived coagulation factors and thus should not increase the risk of thrombosis. The biological effect of E4 is mediated by nuclear ER-α activation and it was found to increase vaginal epithelial proliferation and lubrication in ovariectomized mice [25].

**Selective estrogen receptor modulators**

Estrogen receptor agonist antagonists (ERAAs), previously called selective estrogen receptor modulators (SERMs), are nonsteroidal agents that selectively stimulate or inhibit estrogen receptors in different tissues. Ospemifene is the only ERAA approved by the FDA for the treatment of GSM. The effectiveness of ospemifene 60 mg taken orally in the therapy of GSM was confirmed in 3 double-blind clinical trials. A significant improvement in dyspareunia and vaginal dryness was noted on the Likert scale after 12-week follow-up. Cytological examination revealed an improvement in the vaginal maturation index and a decrease in vaginal pH at weeks 12 and 52 [26-28]. Post hoc analysis of safety data pooled from six phase 2 and 3 RCTs revealed AE, mild and moderate in severity. The most commonly reported AE were hot flush (8.5% vs. 3.3% for placebo), urinary tract infection (6.5% vs. 4.8%), headache (5.4 vs. 5.9%), nasopharyngitis (5.4% vs. 3.1%), muscle spasm (4.4% vs. 1.4%), vaginal discharge (4.4% vs. 0.4%), and vulvovaginal candidiasis (4.3% vs. 0.5%). Discontinuation due to AE occurred in 7.6% of women treated with ospemifene versus 3.8% with placebo, and hot flushes were the most common reason. No detrimental impact on the breast, bone, and cardiovascular system was observed in women treated with ospemifene 60 mg compared to placebo [29]. Moreover, the short- and long-term studies did not reveal any case of endometrial carcinoma and < 1% of patients experienced endometrial hyperplasia [30, 31]. Ospemifene is an optional treatment of dyspareunia in women who have not achieved benefits from personal lubricants and are not willing to use low-dose vaginal estrogens. Although ospemifene received marketing authorization in the UK, there is no clear NICE recommendation for administration of this medication in VVA treatment [32]. A positive effect on the genitourinary system was established for bazedoxifene 20 mg in combination with conjugated estrogens 0.45 mg approved by the FDA for the therapy of vasomotor symptoms and in prevention of postmenopausal osteoporosis [33]. The efficacy of these agents in the treatment of VVA was confirmed in the SMART-3 trial. A significant improvement in the vaginal maturation index, vaginal dryness, and decreased pH as compared to placebo were observed [34].
Lubricants and moisturizers

Women with vaginal dryness can benefit from using personal lubricants and moisturizers, especially for relief of pain during intercourse. A vast range of lubricants and moisturizers are available as OTC products. Lubricants are applied into the vagina before sexual intercourse, as they act rapidly, giving short-term relief from vaginal dryness. It seems that water-based lubricants are the most beneficial and acceptable by women with vaginal dryness. In contrast, the aim of vaginal moisturizers is to rehydrate mucosal tissue, so they should be applied regularly. Moisturizers adhere to the surface of the vaginal epithelial tissue, mimic natural secretion and maintain vaginal moisture due to epithelial hydration and acidifying the vaginal environment. In order to keep water in the vaginal lining the moisturizers contain either plant-based or synthetic polymers. Both lubricants and moisturizers also contain a wide range of additional ingredients such as humectants, emollients and preservatives to provide appropriate viscosity, pH buffering, alter water activity and prevent bacterial contamination [35]. All these excipients have an impact on osmolarity values and pH. The World Health Organization (WHO) recommends the use of lubricants and moisturizers for women in the menopause and post-menopause [36]. In adult women the normal vaginal pH range is 3.8-4.5, but many lubricants and moisturizers exceed these limits. Lubricants with too high or too low pH may be unacceptable for women. Moreover, additional ingredients can cause mucosal irritation, burning and vaginal discharge. Widely used glycols and microbicides can cause inflammation of vaginal mucosa and alter the vaginal microbiome. Animal studies showed exfoliation of the epithelial cells and mucosal damage caused by nonoxynol-9 [37, 38]. Furthermore, nonoxynol-9 can promote sexual transmission of HIV and other sexually transmitted diseases due to damage of the epithelium. In summary, the WHO recommends the use of lubricants and moisturizers with osmolarity under 380 mOsm/kg, but the upper limit of 1200 mOsm/kg can be acceptable. The pH of lubricants should lie in the range of vaginal pH. The contents of glycerol should not exceed 9.9% mass fraction and the use of nonoxynol-9 is not recommended [36].

Laser devices

Although several trials have revealed positive laser therapeutic effect on GSM symptoms, the use of laser devices remains controversial. The limitations of these studies include short follow-up, small cohorts and lack of a control group. The mechanism of action on vaginal mucosa is different for CO2 and erbium: YAG lasers. The mechanism of action on vaginal epithelium with cell proliferation in the basal layer as well as increased glycogen storage in the intermediate and superficial cells was noted. Structural changes in the epithelium were accompanied by formation of new blood capillaries penetrating inside newly connective tissue papillae, supporting fibroblasts for enhanced collagen synthesis. These changes in the mucosal structure result in collagen remodeling leading to vaginal rejuvenation [39]. Histological findings have been confirmed by clinical observations. Objective assessment revealed improvement in the VHI (Vaginal Health Index) as well as in the VMI (Vaginal Maturation Index) and MV (Maturity Value) [40]. An increased amount of Lactobacillus in the vaginal microflora resulting in decreased pH of the vaginal fluid was also reported [41]. Positive subjective evaluation of the therapy was also reported in several trials. Significant improvement in vaginal dryness, itching, burning and dyspareunia compared to baseline was noted [42, 43]. A review of six articles concerning sexual functions in women suffering from GSM treated with CO2, laser revealed statistically significant improvement in FSFI (Female Sexual Function Index) for each single domain and the overall score compared to the entry [44]. Moreover, the out-of-pocket expenses associated with the therapy do not affect patients’ satisfaction [45]. The real mechanism of action of the lasers in GSM treatment remains unclear. Probably the beneficial effect is a combination of morphological and biochemical changes in the epithelium assisted by the expression of specific cytokines involved in the anti-inflammatory process. Becorpi et al. observed a significant decrease in the levels of pro-inflammatory cytokines, such as IL-2 and IL-7, as well as inflammatory factors of cell-mediated immunity, in particular RANTES, GM-CSF, and eotaxin, showing the ability of laser therapy to inhibit an inflammatory reaction. On the other hand, they noted an increased concentration of some cytokines and growth factors, such as IL-8, CTACK, LIF, and M-CSF, which are usually involved in inflammatory processes but also stimulate cell proliferation and migration. The authors suggest that increased levels of these molecules could be a consequence of the vaginal tissue repair and remodeling after laser therapy [46]. Recent research has concentrated on novel treatment protocols. Mothes et al. introduced an innovative dual-phase protocol for pulsed ablative erbium: YAG laser treatment of GSM. The aim of the first, ablative phase is to create small canals in the superficial layer of the vaginal epithelium. This phase is followed immediately by the second phase, which induces hyperthermia that irritates collagen fibers in the lamina propria, stimulating neo-collagenesis. The authors observed significant improvement in VHI and vaginal pH after treatment assisted by high patients’ satisfaction [47]. Athanasiou et al. evalu-
ated the efficacy of additional (extra 4th and extra 5th) CO₂ laser sessions for the management of GSM. They observed significant improvement after the 5th session as compared to the 3rd one in all GSM symptoms. This study could indicate possible dose-dependent effectiveness of GSM treatment [48]. Conversely, the efficacy of the therapy does not seem to be dependent on the power of the device (30 W vs. 40 W) [49]. Recently Gaspar et al. released a pilot study concerning the treatment of urinary symptoms with an intraurethral erbium: YAG laser. The authors observed a reduction of the quantity of leaked urine by 42% and an improvement by an average of 40% at 6-month follow-up [50].

**Radiofrequency devices**

Radiofrequency (RF) devices generate an electrical field resulting in creation of heat delivered to a tissue. At local temperature of 40-45°C the inflammation cascade is initiated and fibroblasts are stimulated to produce collagen, leading to the skin tightening [51]. RF devices have FDA clearance for use in dermatological and surgical procedures (hemostasis and coagulation) but they are not approved for GSM treatment. Observational studies based on the VLQ (Vaginal Laxity Questionnaire), FSFI (Female Sexual Function Index) and FSDS (Female Sexual Distress Scale) revealed improvement in vaginal laxity, arousal, orgasm and sexual satisfaction at 6-month follow-up, but this improvement diminished at 12 months [52, 53]. The multicenter RCT study VIVEVE showed improvement in vaginal laxity in 43% of participants in the treated group at 6 months based on VLQ; however, similar improvement was reported in 19.6% of patients in the sham group. Although the difference between the groups was significant, the placebo effect was greater than expected. Women in the active group had significantly greater improvement in the overall FSFI scale compared to controls. The AE included vaginal discharge, vaginal discomfort and feeling “hot”. AEs were reported in both groups, without a significant difference [54]. RF devices work in general in non-ablative mode. However, recently a pilot study evaluating microablative fractional radiofrequency in the treatment of GSM was performed as a proposal of a new therapeutic option. The procedure is performed with a vaginal pen with 64 microneedles inserted into the vagina under direct vision using a vaginal speculum lightly touching the mucosa. A significant improvement was seen in sexual functions and health-related quality of life. All patients stopped using lubricants after treatment. In the satisfaction questionnaire 100% of participants stated that they were satisfied or very satisfied and 92.6% felt cured or much better. The limitations of this study were the small number of patients and short follow-up. Further studies are required to establish the long-term effectiveness of this procedure [55].

Long-term, well-designed prospective randomized and comparative trials are needed to assess the therapeutic potential of laser devices in the treatment urogenital dysfunctions. The preliminary observations are promising but currently there is insufficient evidence to promote this therapy in stress urinary incontinence or vaginal laxity [56]. Several other issues should be determined, e.g. ablative versus non-ablative technology, the optimal depth of micro-ablation, and the temperature of the energy. The understanding of the mechanism and physiology of rejuvenation seem to be fundamental in the development of novel treatment protocols. A meta-analysis of 14 studies involving 542 participants showed the improvement of quality of life, reduction of GSM symptoms and positive structural changes in the vaginal mucosa. However, the body of evidence was assessed as “low” or “very low” [57].

In July 2018 the FDA released a safety communication against use of energy-based devices to perform vaginal rejuvenation [58]. This warning was supported by the statement of the International Society for the Study of Vulvovaginal Disease (ISSVD) and the International Continence Society (ICS) highlighting the complexity of postmenopausal sexuality not limited to vaginal mucosa disorders [59]. Further studies are necessary to establish the indications for use of energy-based devices in the therapy of vaginal atrophy and for treatment of vulvodynia, lichen sclerosus and urinary incontinence [60].

**Conclusions**

GSM constitutes a complex of signs and symptoms that in a very individual manner negatively affects the life of postmenopausal women. Its impact on the quality of life could be modified by cultural, social and psychological factors. Therefore, the therapy must be individually tailored. Among many treatment modalities none is good for all. Every treatment option has its restrictions, contraindications, more or less serious adverse effects and a limited period of improvement or cure. Thus, the problem of GSM so far has remained unsolved. Further research on vaginal biology and physiology as well as on the influence of different therapeutic modes on vaginal tissue is required. At the other end of this spectrum, studies concerning GSM therapy should consider the whole personality of a woman and not concentrate only on the vagina.

**Disclosure**

The authors report no conflict of interest.
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