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Quality of life and sexual function in women with genitourinary syndrome of menopause (GSM): effectiveness of local therapy with ultralow-concentration estriol vaginal gel

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ABSTRACT

Menopause is a natural phase in a woman's aging process defined as the absence of menstrual periods for 12 consecutive months with no further pathological or physiological causes. With "Genitourinary syndrome of menopause (GSM)" we usually describe the collection of symptoms resulting from changes to the internal and external genitalia and lower urinary tract. The most common symptoms are vaginal dryness, itching, irritation, and dyspareunia. GSM may have a significant impact on quality of life and sexual function of women affected. The aim of this review is to make a brief reflection about the use of ultralow-concentration estriol vaginal gel in the treatment of GSM symptoms and its impact on sexuality and quality of life of the patients.

Key words: menopause; postmenopause; genitourinary syndrome; estriol; quality of life.

SOMMARIO

La menopausa è una fase naturale del processo di invecchiamento di una donna definita come l'assenza di cicli mestruali per 12 mesi consecutivi senza ulteriori cause patologiche o fisiologiche. Con "Sindrome genitourinaria della menopausa (GSM)" di solito descriviamo l'insieme dei sintomi derivanti da alterazioni dei genitali interni ed esterni e delle basse vie urinarie. I sintomi più comuni sono secchezza vaginale, prurito, irritazione e dispareunia. La GSM può avere un impatto significativo sulla qualità della vita e la funzione sessuale delle donne colpite. Lo scopo di questa revisione è di proporre una breve riflessione sull'uso del gel vaginale a base di estriolo a bassissima concentrazione nel trattamento dei sintomi della GSM e il suo impatto sulla sessualità e sulla qualità della vita delle pazienti.

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INTRODUCTION

Menopause is a natural phase in a woman's aging process defined as the absence of menstrual periods for 12 consecutive months with no further pathological or physiological causes[1–7].

One of the main characteristic of this process is the decline of estrogens with consequent various metabolic and tissue changes, especially in the genital tract due to its particularly sensitivity to variation in the levels of sex hormones[1–3]. In fact, in women of childbearing age, vagina is made of thick layers of healthy cells, because of the circulating levels of estrogen which encourage the growth and development of these cells; therefore, vaginal epithelium remains multi-layered, and vaginal walls are elastic[1,2] while with the decline of estrogens, due to menopause, the vaginal epithelium progressively becomes thin, pale, dry and, as consequence, more susceptible to pain, trauma, and bleeding[1,3,8].

Vulvovaginal atrophy (VVA) is the name endorsed to define this collection of symptoms, that usually become more evident after few years from the beginning of menopause; dryness and dyspareunia are the most bothersome of them but a new term, more accurate and scientifically acceptable to better describe this collection of symptoms resulting in changes to the internal and external genital and lower urinary tracts is "genitourinary syndrome of menopause" (GSM)[9–12]. The clinical manifestations of GSM may include genital symptoms such as dryness, burning, and irritation; lack of lubrication, discomfort or pain during sexual intercourses and impaired sexual function. It is possible to observe also urinary symptoms such as urgency, dysuria and recurrent urinary tract infections, because of the reduction in estrogenic stimulation upon bladder[10,11,13,14]. Due to the embarrassment associated with the sensitive nature of the symptoms, GSM is often underdiagnosed[10,11]. However, it has been estimated that 10%–40% of postmenopausal women experience discomfort due to GSM and about 40% of women with this syndrome suffer from dyspareunia[11,15]. Symptoms of GSM have a negative impact on quality of life, social relationships and sexual activity. More specifically, the sexual sphere is particularly affected by the clinical manifestations of GSM and it is common to observe postmenopausal women suffering from female sexual dysfunctions (FSD)[15–18]. FSD is defined as a disorder relating to sexual desire, sexual arousal, orgasm, or dyspareunia. Different clinical conditions can compromise female sexual function, such as gynecological cancer[19–21], infertility[22,23] or pelvic organ prolapse[24–27].

The risk of sexual dysfunction for menopausal women grows with decrease in estrogen levels and ageing process[3,15–18]. It has been estimated that 9.7 million American women aged 50 to 74 years suffer from FSD and report diminished vaginal lubrication, pain and discomfort with intercourse, decreased arousal, and difficulty in achieving orgasm[18]. Nevertheless, literature about the relationship between GSM and FSD is still controversial: several studies underlined that sexual function is impaired by GSM but there are still few data on a significant association between these two conditions[16,17]. Therefore, further studies about this topic are needed.

Management of GSM is different according to symptoms' severity. Non-hormonal vaginal lubricants, moisturizers and regular sexual function are considered to be the treatment of choice for the symptoms of GSM[28,29]. For women with moderate to severe vulvovaginal symptoms who do not benefit from use of lubricants and moisturizers, estrogen therapy (ET) is generally recommended as a therapeutic standard[9]. Estrogen can be administered locally (cream, slow releasing vaginal ring, tablet) or systemically in the form of tablets, patches or transdermal gel[28,30]. Both forms of ET are effective in improving GSM. However, local ET is the most accepted therapy for GSM for the minor side effects compared to systemic therapy. According to the North American Menopause Society (NAMS), low-dose vaginal estrogens decrease vaginal pH, increase the number of vaginal lactobacilli, improve vaginal and urethral cytology, and prevent urinary symptoms[15,28,30,31].

In the last few years, a new ultralow-dose estriol vaginal gel formulation (0.005% estriol vaginal gel) that significantly enhances estriol delivery to vaginal tissue, has been developed. Thanks to this new formulation, it is possible to use much lower doses of estriol in the treatment of vaginal atrophy[2,3,32]. Many studies about this topic confirmed the effectiveness of these preparation in reducing the symptoms of GSM and improving sexual function. Delgado et al. investigated the pharmacokinetics, safety and effectiveness of ultra-lowdose estriol vaginal gel formulations which show a favorable tolerability profile and a very low systemic absorption of estriol[33]. Also a study by Cano et al. highlighted that 0.005% estriol vaginal gel is safe and effective in the treatment of postmenopausal vaginal

atrophy[34]. Recently, Caruso et al. evaluated the sexual function and QoL of 68 naturally postmenopausal women affected by GSM and treated with an ultralow-concentration estriol vaginal gel. Results underlined that estriol vaginal gel therapy significantly improves the trophism of the vaginal mucosa and the sexual health and QoL of women involved in the study[3]. Moreover, the application of 0.005% estriol gel to the vulvar vestibule seems to be effective in the management of postmenopausal dyspareunia, as evidenced by the study of Murina et al.[15].

Therefore, low doses of vaginal estrogen may be considered as the first choice for the initial treatment of postmenopausal genitourinary symptoms. Of course, treatment should be indicated taking into account the needs of each woman and the degree of severity of the symptoms.

In this sense, further studies are needed about this topic in order to improve the clinical management of postmenopausal women's health and to reduce the impact of the symptoms of GSM on QoL and sexual function of women affected.

METHODS

We lead a research on Pubmed and COCHRANE from 2010 to 2017 using the keywords "low-dose vaginal estrogens in menopause", "genitourinary syndrome menopause treatments", "local treatments menopause". Among a total of 1273 citations, we considered potentially eligible only 30 original studies, systematic reviews and meta-analysis, and National guidelines.

RESULTS

The Atrophy of the vaGina in womAn in posT – menopause in itAly (AGATA) study for the Italian Society for the Menopause (SIM) showed that the therapy should be started early, prior to the development of severe atrophic changes, and should be performed for a long term[35,36]. The intra-vaginal is preferred to the systemic administration of estrogens because safer and more effective[37]. Beside the proved clinical efficacy of many treatments, population-based studies seem to indicate that the management of VA is highly unsatisfactory[38]. In fact, this study, based on 913 patients, underlines that there is no clear indication to differentiate between hormonal and non-hormonal therapies, length of treatment is variable, and even the definition of cycle length is heterogeneous. Undoubtedly, the prescription is not performed on a long-term basis.

Treatment discontinuation was 84%, 63.1% and 55% among users of systemic hormone, intra-vaginal estrogens or local non-hormonal therapies, respectively. Treatment discontinuation of local therapies was performed in 132 cases (59.5%). Among these, 31.1% declared of having followed the physician indication and thus, to have discontinued the therapy in accordance to the physician prescription. 68.9% declared of having withdrawn from therapy spontaneously. The overall duration of local treatment varied from 1 month (14.4%) to more than 12 months (39.6%)[38].

Archer et al. in a phase 3, double-blind, placebo-controlled, multicenter study, randomized (1:1) 576 postmenopausal women with moderate–severe vaginal dryness as the most bothersome VVA symptom to estradiol cream 0.003% (15 µg estradiol; 0.5 g cream) or placebo (0.5 g cream)[39]. Treatments were applied vaginally once daily for 2 weeks followed by two applications/week for 10 weeks. They demonstrated that a very low-dose estradiol vaginal cream (0.003%/15 lg/application) met all three coprimary endpoints in postmenopausal women with VVA; it was efficacious in reducing the severity of vaginal dryness, decreasing vaginal pH, and improving the percentage of superficial cells while reducing parabasal cells on vaginal smears from baseline to final assessment when compared with placebo. Results also demonstrate that local low dose delivery of estrogen directly to the vagina, even at 15 µg/dose, is a highly effective mode of treatment for postmenopausal women experiencing VVA-associated vaginal dryness. The advantage of this approach is the lack of appreciable increase in systemic estrogen exposure: for this reason, it is feasible for those patients who are not able to take high systemic doses of estrogens[39].

The REJOICE phase 3 trial evaluated the efficacy of 4-, 10-, and 25-µg doses of low-dose vaginal soft gel capsule containing solubilized 17b-estradiol in 764 postmenopausal women (40–75 years) suffering from VVA, demonstrating that the vaginal soft gel capsule at doses of 4, 10, and 25 µg significantly increased superficial cells and reduced vaginal pH, parabasal cells, and severity of dyspareunia for a maximum of 12 weeks, with age, BMI, uterine status, pregnancy history, and vaginal birth status having little to no influence. Furthermore, the negligible

estrogen systemic levels make it a good tool to treat vaginal symptoms in estrogen-dependent breast cancer survivors, as the American Congress of Obstetricians and Gynecologists recently recommended[40].

On the opposite side of the matter, Lethaby et al., in a recent Cochrane, analyzed 30 RCTs (6235 women) comparing different intra-vaginal oestrogenic preparations (oestrogen ring, oestrogen tablets, oestrogen cream) with each other and with placebo[41]. They underline that there is no conclusive evidence of a difference in efficacy between the various intravaginal oestrogenic preparations when compared with each other. However, there is low-quality evidence that intravaginal oestrogenic preparations improve the symptoms of vaginal atrophy in postmenopausal women when compared to placebo. There is low-quality evidence that oestrogen cream may be associated with increase in endometrial thickness compared to oestrogen ring, but this may have been due to the higher doses used. However, there is no conclusive evidence of a difference in the overall body of evidence in adverse events between the various oestrogenic preparations compared with each other or with placebo. Women using intra-vaginal oestrogenic preparations who have postmenopausal bleeding should have endometrial investigation[41].

The recent EU REVIVE study, lead an online survey in four European countries; the Italian arm comprised 1000 participants from representative regions of Italy. Main outcome measures were perceptions, experiences and needs of Italian post menopause women in relation to sexual and vaginal health[42]. This analysis, based on the REal Women'sVIews of Treatment Options for Menopausal Vaginal ChangEs-Europe (REVIVE-EU) survey, was lead to achieve a deeper understanding of the VVA problem knowledge by Italian women after menopause, together with their experiences and needs in terms of sexual and vaginal health, as well as the current nature of their interactions with healthcare professionals. 44% of participants had experienced VVA symptoms in the past month. At the beginning of the survey, 575 (58%) of all those included participants with VVA symptoms were receiving VVA treatment. An overall ratio of 40% of current participants abandoned their medication at some point in the past. The most frequent reasons for this low compliance were the relief from VVA symptoms (23%), not consider symptoms bothersome enough (22%), the belief that symptoms would diminish with time (15%), the inability of treatment to reverse the vaginal changes (14%) and the price of the product (13%). In patients who completed or were currently taking an OTC medication, 60% reported overall satisfaction. These results demonstrated that, despite the commonness of VVA symptoms after menopause and its significant impact on quality of life and sexual enjoyment, this condition remains underdiagnosed and undertreated in Italy[42].

But, how to manage with patients who had had a breast cancer and are suffering from VVA due to aromatase inhibitor therapy?

Sulaica et al. summarized last literature evidences: hormonal and non-hormonal therapies are apparently prescribed to similar sets of patients, and length of treatment is not standardized. Indeed, there is no clear guideline that the physician can follow[43]. This study further highlights the need for additional clinical studies to answer the very important question of the long-term safety and efficacy of vaginal estrogen products in Breast Cancer survivors on Arhomatase Inhibitor (AI) therapy as well as a standardized clinical assay to detect ultra-low plasma E2 levels. Because of some efficacy observed with vaginal estriol as well as vaginal estradiol in small studies described here, comparison of these two agents in alleviating vaginal symptoms without compromising long-term safety should be performed systematically in randomized controlled trials. To accurately assess the problem, objective measures such as vaginal pH should also be evaluated for its utility and incorporation into future clinical trials. To ensure compliance to AI therapy, it is critical for clinicians to identify the barriers including adverse drug reactions, in fact a major barrier to AI compliance is the vaginal symptoms[43].

Mikkola et al. assessed the impact of VE use on the risk for cardiovascular mortality in a large cohort of post-menopausal women. Although several limitations, such as the absence of a placebo harm, the use of VE was associated with significant reductions in the risks of death from CHD and stroke[44].

DISCUSSION

The relationship between genitourinary symptoms and sexuality is complex: psychologic factors, interpersonal relationships, and sociocultural influences could play a role in sexual function.

Genitourinary atrophy can significantly impair

the quality of life (QoL) of postmenopausal women and may be underdiagnosed.

Several therapies, including vaginal lubricants and moisturizers, vaginal estrogen, and hormone and non-hormone systemic therapies, have demonstrated effectiveness depending on the severity of VVA symptoms[2,26].

The results of this review show on one side the effectiveness of local estrogen therapies in solving the VVA caused by menopause, demonstrating cellular changes (such as increased superficial cells and reduced vaginal pH, parabasal cells) involved in the reduction of severity of dyspareunia for a maximum of 12 weeks, with age, BMI, uterine status, pregnancy history, and vaginal birth status having little to no influence[41].

Furthermore, other studies have estimated that 40% of women receiving systemic estrogen do not obtain adequate relief from vaginal dryness[45].

Vaginal estrogen formulations are currently the first choice for the initial management of menopause-related vaginal atrophy symptoms[3].

Semisolid preparations for vaginal estrogen treatment include ointments, creams, and gels. A common feature of these preparations is the capability to adhere to surfaces for a therapeutic period. Gels can present several advantages over other vaginal drug delivery systems, such as higher bioavailability, safety, and versatility[2,3,45].

Choice and route of administration of therapy depend on the severity of symptoms, the effectiveness and safety of therapy for individual women, and women's preferences. On the other hand, when low-dose estrogen is administered locally to women with intact uterus, progestogen is not indicated[45].

Interestingly, the use of vaginal estrogens with correct counseling encouraging women to have regular sexual activity has been found to be beneficial in preventing vaginal atrophy[3].

In fact, women who participate in regular sexual activity have reported fewer symptoms of vaginal atrophy and show less evidence of atrophy on vaginal examination compared with sexually inactive women.

On the other side, this review underlined that, despite the commonness of VVA symptoms after menopause and its significant impact on quality of life and sexual enjoyment, this condition remains underdiagnosed and undertreated in Italy[42].

This is due, probably, to a lack of communication between physicians and their patients: the REVIVE survey underlined that, although 2/3 of Italian participants acknowledged that have discussed VVA with their health care practitioner (HCP), they still expect their HCP to initiate proactive discussion on symptoms (75%), a fact that very rarely happens. Maybe a higher training of gynecologists and general practitioners may solve the problem[42].

Regarding the therapeutic management of VVA, VVA treatments were administered mainly vaginally without prescription (OTC), although the efficacy and safety of minimally absorbed local vaginal estrogen as VVA therapy has been extensively proven, this is probably due to the fear of systemic effects of local estrogen. On this matter, especially to test the safety in women with an history of breast cancer, randomized controlled trials should be done and, to accurately assess the problem, objective measures such as systemic estrogen levels should also be evaluated.

DECLARATION OF INTEREST

The authors report no declarations of interest. The authors alone are responsible for the content and writing of the paper. No specific funding was obtained.

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