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REVIEW ARTICLE

Recent Advances in the Management for Genitourinary Syndrome of Menopause

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ABSTRACT

Menopausal women suffer from various symptoms related to genital tract and urinary tract. These symptoms are due to low estrogen level at this stage of life. Although this is commonly termed as vulvovaginal atrophy or atrophic vaginitis, it does not reflect the presence of underlying urinary symptoms. So, to encompass full spectrum of symptoms, a broad term like genitourinary syndrome of menopause (GSM) is being used more recently in place of vulvovaginal atrophy or atrophic vaginitis. It describes various symptoms and signs of menopause which include genital symptoms, such as dryness, irritation and burning, urinary symptoms like urgency, dysuria, and recurrent urinary tract infection (UTI) and sexual symptoms like lack of lubrication and discomfort or pain. Wide range of treatments are available which include nonhormonal black cohosh, a phytoestrogen, lubricants or moisturizers for symptom relief, vaginal estrogen therapies, systemic hormonal therapies (HTs), tissue-specific estrogen complex [combination of selective estrogen receptor modulators (SERM) and estrogen] besides newer therapies. These newer therapy include laser, radiofrequency (RF), and magnetic therapy. As the GSM have negative impact, awareness, recognition and appropriate treatment of GSM will improve the quality of postmenopausal women.

Keywords: Genitourinary syndrome of menopause, Menopause, Vulvovaginal atrophy.

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INTRODUCTION

Vulvovaginal atrophy or atrophic vaginitis was the term commonly used until recently to describe the symptoms and signs related to genitourinary system following menopause. Although atrophic vaginitis signifies inflammation or infection of vagina, it does not form a primary change associated with menopause. In addition, it does not reflect the underlying lower urinary tract symptoms, which are related to menopause. Besides all of the above, the words vulva and vagina are not commonly used in social discussion or media.[1] Therefore, the Board of Directors of the International Society for the Study of Women's Sexual Health and the Board of the North American Menopause Society (NAMS) emphasized the introduction of a new terminology in place of terms like vulvovaginal atrophy and atrophic vaginitis in a terminology consensus conference which was organized in 2013. The term GSM was finally approved in 2014.

The GSM narrates various menopausal symptoms and signs related to changes in the vulva, vagina, and lower urinary tract as well. The genital symptoms of GSM include dryness, burning, and irritation, and sexual symptoms include lack of lubrication, discomfort or pain, and urinary symptoms include dysuria, urgency, and recurrent UTI. With the increasing life expectancy, women spend considerable period of life in postmenopausal period. Hypo-estrogenic state of this period causes many health problems. Of these problems, vasomotor symptoms like hot flushes and night sweating often get better over the time, whereas genitourinary symptoms which are chronic, rarely resolve of its own and rather worsen, if left untreated.[2]

Although these manifestations are not a deathly illness, they worsen and have deep impact on the quality of life (QOL) of postmenopausal women. It affects not only their self-esteem but also intimacy with their partners negatively.[3] Moreover, GSM may appear following surgical menopause, use of gonadotropin-releasing hormone agonists, because of cancer treatments like chemotherapy, pelvic radiation, or endocrine therapy.[4] So, taking care of postmenopausal women with genitourinary symptoms has evolved as an important problem in our society.

PREVALENCE OF GSM

Vulvovaginal Symptoms and Sexual Dysfunction

In a study by Iosif and Bekassy,[5] 15% reported itch, discharge, whereas 38% reported dyspareunia and vaginal dryness. Stenberg et al,[6] in a cohort study, reported that

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among 59% sexually active women, 43% had vaginal dryness and 10% had sensation of vaginal burning. In cohort surveys of Western populations, 45 to 63% of postmenopausal women mention experiencing vulvovaginal symptoms, vaginal dryness being most common; other symptoms included were vaginal irritation, dyspareunia, itching sensation, and vaginal spotting during intercourse.[3,7,8] In a Korean study, 49% of postmenopausal women had experienced similar symptoms.[9] Levine et al[10] reported that vulvovaginal symptoms were four times more common in postmenopausal sexually active women. Among them with vulvovaginal symptoms, 40% also had overall sexual dysfunction, 34% arousal difficulties, 24% lack of desire, whereas 19% had orgasm difficulties. The Study of Women's Health Across the Nation in the USA reported vaginal dryness to be an important factor associated with pain, arousal, masturbation, physical pleasure, and emotional satisfaction.[11]

Dysfunction of Lower Urinary Tract

Iosif and Bekassy[5] in their study showed that 29.2% had varied degrees of urinary incontinence. Among them, 11.8% of the women reported stress incontinence, 7.9% urge incontinence, 9.5% had mixed incontinence, and 13% had recurrent UTI. They also reported that 48.8% had lower genital tract problem. Stenberg et al,[6] in a population-based cohort study, reported that 73% of the women experienced urinary incontinence of which 33% were of severe degree; 31% experienced urge incontinence of which 14% were severe. In a study by Robinson and Cardozo,[12] the proportion of severe urge incontinence and stress incontinence were 20 and 50% respectively. The study by Hyun et al[13] revealed intrinsic sphincteric dysfunction as a result of altered connective tissue due to hypo-estrogenic state as the prime cause of urinary incontinence in postmenopausal women, whereas anatomical change was the most common responsible factor for urinary incontinence in premenopausal women. Studies have shown that bacteriuria was associated with 15 to 20% of women aged 65 to 70 years, and 20 to 50% of women aged > 80 years.[14,15]

ETIOPATHOLOGY OF GSM

The hypo-estrogen levels after menopause are directly related to these symptoms. During reproductive life, estrogen receptors are commonly present in the vagina, vulva, urethra, bladder trigone, musculature of the pelvic floor, and endopelvic fascia. But with menopause, their levels decline, which may be restored by treatment with estrogen. Due to hypo-estrogenic state following menopause, the content of collagen, hyaluronic acid, and the levels of elastin reduce. This leads to thinning of the epithelium, altered smooth muscle cell function, increase in connective tissue density, and fewer blood vessels. All these lead to reduce vaginal elasticity, increased vaginal pH, vaginal flora change, and reduced lubrication, which in turn predispose the postmenopausal women to increased vaginal irritation and trauma.[16,17] Due to its common embryological source, i.e., urogenital sinus, in both genital tract and lower urinary tract, hypo-estrogenic state of menopause is responsible for lower urinary tract symptoms, such as dysuria, urgency, frequency, nocturia, urinary incontinence, and recurrent UTI.[12]

MANAGEMENT OF GSM: THE PRIMARY FOCUS OF TREATMENT IN GSM IS TO RELIEVE SYMPTOMS

Currently available treatments can be classified into nonhormonal and hormonal. Nonhormonal includes black cohosh which is a phytoestrogen, lubricants or moisturizers for symptom relief, whereas HT consists of local use of estrogen (vaginal cream, tablets, ring), systemic use of estrogen (oral and transdermal), and tissue-specific estrogen complex (combination of SERM and estrogen). However, advancement in the management of GSM includes laser, RF, and magnetic therapy. ·

Local Treatment

Nonhormonal Treatment

According to NAMS, the nonhormonal lubricants, i.e., water-, silicone-, or oil-based, are the first-line treatment during intercourse for postmenopausal women who suffer from vulvovaginal symptoms. Besides that, long-acting, locally active moisturizing agents can decrease pH of vaginal to premenopausal levels, but they do not ameliorate the vaginal maturation index.[4] The Society of Obstetricians and Gynecologists of Canada guidelines also affirm that regular topical application of vaginal moisturizers is equally effective to that of vaginal estrogen applied topically for alleviating vulvovaginal symptoms, such as itching, irritation, and dyspareunia. So, it should be recommended to women who wish to avoid the application of estrogen because of health concerns.[18]

Hormonal Treatment

Short-term application of local estrogen preparations can ameliorate clinical picture of GSM when nonhormonal treatment fails. In the presence of vasomotor symptoms, application of systemic estrogen works better, whereas genitourinary symptoms respond better to local application of estrogen.[4] Usually, application of vaginal estrogen is safe to use for symptomatic relief of GSM, but it is

admonished in women with undiagnosed bleeding either from vaginal or uterine. Its use is controversial in women with neoplasia of breast and endometrium, which are estrogen-dependent.[19]

Systemic Treatment

- Systemic treatment with estrogen or combination of estrogen and progestogen relieves both menopausal symptoms and vulvovaginal symptoms. However, its use to relieve sexual dysfunction in terms of improving libido, arousal is not evidenced by current research.[20]
- Selective ER modulators: Systemic estrogen has stimulatory effects on endometrium and breast, predisposing to malignancy in long-term use. So, use of SERMs was introduced. SERMs have positive effects on targeted tissues, but very little negative influence on other tissues. Of SERMs, the only drug which is approved for the treatment of moderate-to-severe dyspareunia is ospemifene. It has a positive impact on vaginal tissue in postmenopausal women. Its main use is to prevent postmenopausal osteoporosis.[21,22]
- Bazedoxifene (BZA) and conjugated estrogens (CEs): The combination of BZA (20 mg) and CE (0.45 or 0.625 mg) is a tissue-selective estrogen complex. It has been designed to alleviate vasomotor and dyspareunia, but has no positive effect on vagina. It also averts bone loss while being invulnerable for the endometrium and breast.[23,24]

Newer Treatment Modalities

Laser Treatment

A beam of photons with specific wavelength is generated by Laser equipment. Biological tissues, i.e., blood, melanin, and water absorb and react to this beam. This is of two types, i.e., micro-ablative CO_2 laser and nonablative Vaginal erbium:yttrium aluminum garnet smooth laser (VEL). The CO_2 laser uses the ablative approach. It generates high temperature in the tissue by creating micro-thermal zone (MTZ), which are basically minute holes that are made in the vaginal wall. These MTZs induce shrinkage of tissue, but are not as effective as in initiating neogenesis of collagen. The VEL produces collagen hyperthermia up to 65°C in the epithelium and lamina propria, resulting in breaking of the intermolecular crosslinks that stabilize collagen's triple-helix structure, causing rapid contraction of the collagen fibers. This in turn results in shrinkage and greater tissue rigidity and also initiates neocollagenesis *in vivo*. As it increases the density of the connective tissue, stimulating collagen remodeling and neo-angiogenesis, leading to sub-urethral reinforcement, it is useful for the correction of mild-to-moderate stress urinary incontinence and vaginal canal tightening with subsequent improvement of sexual gratification. The treatment protocol for vaginal tightening and stress urinary incontinence is nicknamed as IntimaLase and IncontiLase respectively. Similarly, the treatment protocol for the pelvic organ prolapse and vaginal atrophy is called ProlapLase and RenovaLase. The IntimaLase protocol involve two 8 to 10 minute sessions at 4- to 6-week interval, whereas IncontiLase involves two 15-minute sessions with the same interval. The protocol for treatment of ProlapLase follows the same principle as that of vaginal tightening and incontinence, but only difference is in the treatment intensity (duration) and the major area treated, i.e., the prolapsed part of the vaginal wall. The ProlapLase protocol requires 3 to 5 sessions at 4- to 6-week interval.

The RenovaLase is based on a concept of milder hyperthermia. Here, the mucosa is warmed up to 45°C. This causes the stimulation of cell proliferation via heat shock protein activation, an increase of collagen production, and anti-inflammatory action as well. This protocol consists of three sittings at intervals of 3 weeks.[25]

Radiofrequency Wave

It is another treatment option designed on the principle of bulk heating of tissue to reach the required temperature in collagen for shrinkage and neocollagenesis. However, RF heats the epithelium to a higher temperature, making treatment unpleasant. Moreover, RF needles require local anesthesia.[25]

Functional Magnetic Stimulation

It has performed well for treatment of all types of urinary incontinence. This causes faster regeneration of muscles and other tissues of pelvic floor, resulting in stronger pelvic floor muscles. It does not require insertion of unpleasant electrode. During the therapy, patients sit dressed in a comfortable chair and a treatment is carried out twice or thrice a week for twenty minutes. As it does not come in contact with the skin directly, the treatment is not painful or uncomfortable and has no side effect.[25]

CONCLUSION

The GSM is a broad term that encompasses lower urinary tract symptoms and vulvovaginal symptoms related to hypo-estrogenic state. Very few women relate symptoms to menopause or hypo-estrogenic state, whereas most women consider them as part of normal and avoid consulting a gynecologist for that. Although a varied range of accomplished treatment options are available from nonhormonal local application to noninvasive laser

treatment including local and systemic HT, many women are still diffident to accept HT because of its concern of adverse effects including cancer.

However, since the GSM may have a considerable adverse impact on the QOL of postmenopausal women, they should be made aware of these problems and treated appropriately.

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