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Review Article

The Recent Review of the Genitourinary Syndrome of Menopause

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The genitourinary syndrome of menopause (GSM) is a new term that describes various menopausal symptoms and signs including not only genital symptoms (dryness, burning, and irritation), and sexual symptoms (lack of lubrication, discomfort or pain, and impaired function, but also urinary symptoms (urgency, dysuria, and recurrent urinary tract infections). The terms *vulvovaginal atrophy* and *atrophic vaginitis*, which were generally used until recently, had a limitation because they did not cover the full spectrum of symptoms and did not imply that the symptoms are related to a decreased estrogen level in menopause. Since the GSM may have a profound negative impact on the quality of life of postmenopausal women, women should be made aware of these problems and treated with an appropriate effective therapy. Thus, in this review we introduce new terminology and discuss the importance of comprehension of GSM and the necessity of active treatment of this syndrome in postmenopausal women. **(J Menopausal Med 2015;21:65-71)**

Key Words: Genitourinary syndrome of menopause, Menopause, Vulvovaginal atrophy

Introduction

The genitourinary syndrome of menopause (GSM) is a new term that describes various menopausal symptoms and signs associated with physical changes of the vulva, vagina, and lower urinary tract. The GSM includes not only genital symptoms (dryness, burning, and irritation) and sexual symptoms (lack of lubrication, discomfort or pain, and impaired function), but also urinary symptoms (urgency, dysuria, and recurrent urinary tract infections [UTI]) (Table 1).[1]

The terms *vulvovaginal atrophy* and *atrophic vaginitis* were widely used until recently, but they have been considered to be inadequate for referring to the constellation of symptoms and signs associated with the genitourinary system after menopause. The term *vulvovaginal atrophy* mentions the vulva and vagina only, and these words are not used comfortably in general social discussion and in the media. The term *atrophic vaginitis* implies a state of inflammation or infection, which is not a primary component of menopausal changes. In addition, a limitation of the terms *vulvovaginal atrophy* and *atrophic vaginitis* is that they do not take into account the symptoms of the lower urinary tract, which are among the most important symptoms related to menopause.[1]

Therefore, the Board of Directors of the International Society for the Study of Women's Sexual Health (ISSWSH) and the Board of the North American Menopause Society (NAMS) have acknowledged the necessity of new terminology instead of the terms *vulvovaginal atrophy* and *atrophic vaginitis*, and a terminology consensus conference was held in 2013. The ISSWSH and NAMS Boards finally formally approved the term GSM in early 2014.

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Table 1. Genitourinary Syndrome of Menopause (GSM): symptoms and signs

Symptoms	Signs
Genital dryness	Decreased moisture
Decreased lubrication during sexual activity	Decreased elasticity
Discomfort or pain during sexual activity	Labia minora resorption
Post-coital bleeding	Pallor, erythema
Decreased arousal, orgasm, desire	Loss of vaginal rugae
Irritation, burning, or itching of the vulva or vagina	Tissue fragility, fissures, petechiae
Dysuria	Urethral eversion or prolapse
Urinary frequency and urgency	Loss of hymenal remnants
	Prominence of urethral meatus
	Introital retraction
	Recurrent urinary tract infections

Supportive findings: vaginal pH > 5, increased parabasal cells on maturation index, and decreased superficial cells on wet mount or maturation index
Note: adopted from[1]
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In this review, we introduce the new terminology and discuss the importance of comprehension of GSM and its active treatment in postmenopausal women.

Prevalence of GSM

1. Vulvovaginal symptoms and sexual dysfunction

In recent large cohort surveys in Western populations, 45% to 63% of postmenopausal women reported that they had experienced vulvovaginal symptoms,[2] most commonly vaginal dryness; other symptoms included dyspareunia, vaginal irritation, itching sensation, vaginal tenderness, and vaginal bleeding or spotting during intercourse.[2~4] Similarly, in a Korean study, 49% of postmenopausal women had experienced vulvovaginal symptoms including vaginal dryness and dyspareunia.[5]

These symptoms are directly related to the reduced circulating estrogen levels after menopause. Estrogen receptors (ERs; both α and β) are present in the vagina, vulva, musculature of the pelvic floor, endopelvic fascia, urethra, and bladder trigone during reproductive life; their levels decline with menopause and may be restored by estrogen treatment.[6] As a result of estrogen deficiency after menopause, anatomic and histologic changes occur in female genital tissues, including reduction in the content of collagen and hyaluronic acid and in the levels of elastin, thinning of the epithelium, alterations in the function of smooth muscle cells, increase in the density of connective tissue, and fewer blood vessels. These changes reduce elasticity of the vagina, increase vaginal pH, lead to changes in vaginal flora, diminish lubrication, and increase vulnerability to physical irritation and trauma.[6,7]

These vaginal discomforts negatively sexual function in postmenopausal women. Levine et al.[8] reported that postmenopausal sexually active women with sexual dysfunction were nearly four times more likely to have vulvovaginal symptoms than those without sexual dysfunction. Among women with vulvovaginal symptoms, 40% also reported overall sexual dysfunction, 24% lack of desire, 34% arousal difficulties, and 19% orgasm difficulties.[8] The Study of Women's Health Across the Nation (SWAN) in the USA reported that women with sexual dysfunction considered vaginal dryness to be an important factor associated with masturbation, pain, arousal, physical pleasure, and emotional satisfaction.[9]

2. Lower urinary tract dysfunction

The female genital tract and lower urinary tract share a common embryonic origin, both arising from the urogenital sinus.[10] As estrogen plays an important role in the function of the lower urinary tract throughout the premenopausal period, estrogen deficiency after menopause causes lower urinary tract symptoms, such as dysuria, urgency, frequency, nocturia, urinary incontinence (UI), and recurrent UTI.[10]

In a study by Robinson and Cardozo,[10] about 20% of

postmenopausal women had severe urgency and almost 50% had stress UI (SUI). In particular, urge UI is more prevalent after menopause than before menopause, and its prevalence increases with time in women with estrogen deficiency. Since ERs are present in the trigone of the bladder and in the squamous epithelium of both the proximal and distal urethra, estrogen may increase the sensory threshold of the bladder and urethral closure pressure.[10] The study by Hyun et al.[11] suggested that the major cause of UI in postmenopausal women was the intrinsic sphincteric dysfunction related to altered connective tissue following estrogen deficiency, while the anatomical change was the most responsible factor of UI in premenopausal women.

The incidence of UTI rises dramatically in elderly women. Studies have shown that 15% to 20% of women aged 65 to 70 years and 20% to 50% of women aged > 80 years have bacteriuria.[12,13] Postmenopausal and premenopausal women may have different risk factors for UTI. While sexual intercourse is the most common cause among younger women, UI, anatomic changes such as a cystocele, increased residual urine and diabetes are the risk factors for recurrent UTI in older women.[12] Lack of awareness of the association between recurrent UTIs and GSM may result in multiple unnecessary courses of antibiotic therapy, antibiotic prophylaxis, and altered patterns of antimicrobial drug resistance.[1,14]

GSM and Quality of Life (QOL)

The Korean postmenopausal population was 5.26 million in 2000 (22.5% of total female population). In 2030, the postmenopausal population will be 13.15 million, comprising nearly half of the entire female population.[15] Therefore, appropriate care of these postmenopausal women will be one of the most important issues in our society.

Low-estrogen state in the postmenopausal period causes many health problems. In contrast to vasomotor symptoms that are often improved over time, genitourinary symptoms are chronic, and rarely resolved spontaneously and often progress if left untreated.[16] Although these symptoms are not life-threatening, they are progressive and may have a profound impact on the QOL of postmenopausal women by negatively affecting self-esteem and intimacy with their partners.[3]

The recently published Clarifying Vaginal Atrophy's Impact on Sex and Relationships (CLOSER) study found that vaginal discomfort had a direct, negative impact on the intimacy of both partners (women, 58%; men, 78%) and resulted in a loss of libido (64% and 52%, respectively). Overall, 38% of women and 39% of their male partners reported that vaginal symptoms had a worse-than-expected impact on their intimate relationships.[17] In the REalWomen's VIews of Treatment Options for Menopausal Vaginal ChangEs (REVIVE) survey, women reported that their vaginal symptoms negatively affected enjoyment of sexual activity (59%), sleep (24%), and overall enjoyment of life (23%).[4]

Furthermore, GSM may also occur in induced hypoestrogenic states including surgical menopause, use of gonadotropin-releasing hormone (GnRH) agonists, hypothalamic amenorrhea, or because of cancer treatments like chemotherapy, pelvic radiation, or endocrine therapy.[18] Since the genitourinary symptoms related to an abrupt menopause in these patients tend to present in relatively younger women and cause greater sexual dysfunction and poorer QOL outcomes, the management of their menopausal symptoms has become an increasingly important issue.

Treatment of GSM

The primary goal of treating GSM is to relieve symptoms. For women with vulvovaginal symptoms unrelated to sexual activity, first-line therapies include long-acting vaginal moisturizers and a short course of low-dose vaginal estrogen. For women with vulvovaginal symptoms related to sexual activity, stepwise treatment is required.[17] Currently available treatment options include non-hormonal vaginal lubricants to be used during intercourse, long-acting vaginal moisturizers, systemic hormonal therapies (oral and transdermal), and low-dose vaginal estrogen therapies (e.g., vaginal creams, intravaginal tablets, or intravaginal rings).[7,17] Although there are still insufficient data on the use of local estrogen in the management of lower urinary tract symptoms, such therapy has been described in some studies.[12,19,20] Black cohosh, which has been most commonly

used phytotherapy as a hormone substitute in western countries, also has been studied widely for the treatment of menopausal symptoms. However, its effect on genitourinary symptoms is still controversial, and a recent Korean study reveals that black cohosh does not exert estrogenic effects on the vaginal atrophy.[21]

Systemic Treatment

1. Hormone therapy (HT)

HT using estrogen only or estrogen plus progestogen is effective for the management of menopausal symptoms, including vulvovaginal symptoms. When systemic HT is needed to treat other menopausal symptoms, vaginal symptoms are generally satisfactorily resolved as well. However, systemic HT fails to resolve vaginal symptoms in 10% to 15% of women, and additional low-dose vaginal estrogen may be needed.[18,22] Since a significant effect of HT on sexual interest, arousal, and orgasmic response is not supported by current evidence, HT is not recommended as the sole treatment of sexual function, including diminished libido.[22] Moreover, systemic HT may worsen or provoke stress incontinence.[23,24]

2. Selective ER modulators (SERMs)

Because of concerns about the potential stimulatory effects of systemic estrogen on breast and endometrial tissues and long-term adverse effects, SERMs have been developed with the aim of positive effects on targeted tissues with minimal negative effects on other tissues.[25]

Several studies have investigated the use of SERMs for treatment of vulvovaginal symptoms in menopausal women. While raloxifene and tamoxifen have no estrogen agonist effect on the vagina, lasofoxifene and ospemifene show a positive impact on vaginal tissue in postmenopausal women.[25,26] Although several studies have found that lasofoxifene resulted in significant improvements in vaginal pH and vaginal maturation index, clinical development of this SERM is on hold.[18]

Ospemifene is the only SERM approved by the US Food and Drug Administration (FDA) for treatment of moderate to severe dyspareunia. Ospemifene is an oral non-estrogen drug with an estrogen agonistic effect on vaginal epithelial tissue.[18,27] Published studies have shown improvement in vaginal maturation index, vaginal pH, vaginal dryness, and dyspareunia with daily use of ospemifene 60mg orally.[27~29]

3. Bazedoxifene (BZA) and conjugated estrogens (CEs)

The combination of BZA a SERM for the prevention and treatment of postmenopausal osteoporosis, and CE is a tissue-selective estrogen complex (TSEC) which is intended to provide clinical benefits of each of the two components.[30] BZA/CE has been designed to relieve vasomotor and vulvovaginal symptoms and to prevent bone loss while being safe for the endometrium and breast. Studies revealed that BZA (20 mg) / CE (0.45 or 0.625 mg) significantly improved vulvovaginal symptoms and dyspareunia, although BZA alone did not have positive vaginal effects.[30,31]

Local Treatment

1. Non-hormonal treatment

A number of over-the-counter vaginal lubricants (water-, silicone-, or oil-based) and moisturizers are commonly used for the treatment of postmenopausal women with vulvovaginal symptoms. The North American Menopause Society[18] stated that the first-line treatment for women with vulvovaginal symptoms includes non-hormonal lubricants during intercourse and a regular use of long-acting vaginal moisturizers. In general, lubricants may be used during sexual intercourse to reduce of friction-related irritation of atrophic tissue.[32]

In addition, long-acting vaginal moisturizing agents can decrease vaginal pH to premenopausal levels, although they do not improve the vaginal maturation index.[18] Two recent studies have reported that vaginal hyaluronic acid-based moisturizers as effective in relieving vulvovaginal symptoms as topical vaginal estrogen, and may be considered as an alternative to estrogen-based treatment.[33,34] The guidelines of The Society of Obstetricians and Gynecologists of Canada (SOGC) also state that vaginal moisturizers applied on a regular basis have an efficacy equivalent to that of topical vaginal estrogen for relieving vulvovaginal symptoms such

as itching, irritation, and dyspareunia, and should be offered to women wishing to avoid the use of estrogen because of health concerns.[35] In Korea, a vaginal hyaluronic acid-based moisturizer, *Hyallin*®, has been recently developed and is now available on prescription. However, since few clinical studies have been conducted on the long-term safety and efficacy of these non-hormonal products, further studies are needed.

2. Hormonal treatment

Systemic estrogen therapy is preferred if vasomotor symptoms are also present, whereas local vaginal estrogen therapy (estrogen tablets, creams, or a vaginal ring) is preferred when genitourinary symptoms are the only complaint.[17] Local estrogen preparations as short-term therapy can improve clinical signs and symptoms of GSM that does not respond to non-hormonal treatment.[18]

Studies of the effectiveness of vaginal estrogen have reported subjective outcomes, including improvement in vulvovaginal symptoms and lower urinary tract symptoms such as dysuria, urinary urgency, frequency, nocturia, SUI, and UTI.[18,32] These studies have also demonstrated objective outcomes including decrease in vaginal pH, increases in the number of vaginal lactobacilli, favorable shifts in vaginal and urethral cytology, improved gross vaginal mucosal appearance, and favorable changes in urine culture results.

However, women have a variety of concerns about vaginal estrogen treatments, ranging from the inconvenience of vaginal administration to safety concerns regarding estrogen-related neoplasm. In general, low-dose vaginal estrogen is considered to have a lower risk of adverse effect than commonly used doses of systemic estrogen therapy because it produces very low serum levels of estrogen.[18] A 2006 Cochrane review found no reports of increased risk of venous thromboembolism associated with the use of low-dose vaginal estrogen.[36] In addition, the serum estradiol levels remained within the normal postmenopausal level and endometrial hyperplasia or adenocarcinoma was extremely rare.[32] Although vaginal estrogen therapy is generally safe for most symptomatic women with GSM, the treatment is contraindicated in some women with undiagnosed vaginal or uterine bleeding and controversial in women with estrogen-dependent neoplasia (e.g., breast cancer or endometrial cancer).[18]

Conclusion

The GSM is a comprehensive term that includes vulvovaginal symptoms and lower urinary tract symptoms related to low estrogen levels. The terms *vulvovaginal atrophy* and *atrophic vaginitis*, which were in general use until recently, had a limitation because they did not cover the full spectrum of symptoms and did not imply that the symptoms were related to decreased estrogen levels in menopausal state. Actually, only a few women attributed symptoms to menopause or hormonal changes, most women do not consult a gynecologist about their symptoms, considering them to be part of normal aging.[37] Also a number of women are still unwilling to take HT due to the concern of adverse effects including cancer.[5]

However, since the GSM may have a profound negative impact on QOL of postmenopausal women, women should be made aware of their problems and treated with an appropriate effective therapy. Vaginal estrogens effectively relieve common vulvovaginal symptoms and have additional effects on urinary symptoms such as urinary urgency, frequency or nocturia, SUI, and recurrent UTIs. Non-hormonal moisturizers are also a useful alternative for minor atrophy-related symptoms and for patients at risk of estrogen-related neoplasm.

Conflict of Interest

No potential conflict of interest relevant to this article was reported.

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