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SM Journal of Gynecology and Obstetrics

Review Article

A Review of the Genitourinary Syndrome of Menopause

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Article Information

Received date: Mar 04, 2018
Accepted date: Mar 14, 2018
Published date: Mar 22, 2018

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Keywords Genitourinary syndrome of menopause; Menopause; Vulvovaginal atrophy

Abstract

The Genitourinary Syndrome of Menopause (GSM) is the last terminology accepted that describes various menopausal symptoms and signs. It includes genital (burning, dryness or pain), sexual (lack of lubrication, discomfort), but also urinary symptoms (urgency, dysuria, and recurrent urinary tract infections).

In this review we explain this terminology and discuss the importance of this syndrome. Moreover, we comment the necessity of active treatment in postmenopausal women.

Introduction

The Genitourinary Syndrome of Menopause (GSM) is a chronic and progressive vulvovaginal, sexual and lower urinary tract condition. It is characterized by symptoms which are secondary to a clinical state of hypoestronism after the establishment of menopause [1].

In 2014 the International Society for the Study of Women's Sexual Health (ISSWSH) and the North American Menopause Society (NAMS) established the nomenclature of "genitourinary syndrome of menopause", previously known as "atrophic vaginitis or urogenital atrophy". The current term is inclusive and wide, and includes several urological, sexual and external genital tract sequels as a consequence of the hypoestronism of menopause [1-3].

It is defined as a collection of symptoms and signs associated with the decrease of oestrogens and other steroid hormones. It produces changes in major and minor lips, clitoris, vestibule/introits, vagina, urethra and bladder.

Postmenopausal women (50%) have GSM symptoms during and after menopause [4,5] (related to low oestrogen levels).

Symptoms and Signs

Women may present all or some of these symptoms and signs, and should not be explained by another diagnosis.

These symptoms are manifested in approximately 15% of premenopausal women and in 40-54 % of postmenopausal [1].

Vulvovaginal symptoms and sexual dysfunction: Postmenopausal women (45 to 63 %) reported that they had experienced vulvovaginal symptoms, most commonly vaginal dryness [6]. Other symptoms included dyspareunia, vaginal irritation, itching sensation, vaginal tenderness, and vaginal bleeding or spotting during intercourse [6] (Table 1). Similar digits are published in a Korean study [7]; 49% of postmenopausal women had experienced vulvovaginal symptoms including vaginal dryness and dyspareunia.

Urological symptoms: In a study by Robinson and Cardozo, around 20% of postmenopausal women had severe urgency and almost 50% had Stress Urinary Incontinence (SUI). In particular, Urge Urinary Incontinence (UUI) is more prevalent after menopause than before, and its prevalence increases with time in women with oestrogen deficiency [6].

A European study, with 3000 women between 55 and 77 years old, analyses the different aspects of urogenital aging. 30% suffer urogenital atrophy symptoms. 60% of them make efforts to relieve these symptoms [8].

GSM, Quality of Life and Diagnosis

The impact of GSM on quality of life is not adequately estimated yet as women on occasions believe that the symptoms of the GSM are a natural step in the aging process. Additionally, some other patients feel uncomfortable and are reluctant to express their real symptoms related to their

Table 1: Genitourinary syndrome of menopause: Symptoms and signs.

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

genitourinary system due to certain social, religious or cultural beliefs. For this reason, health professionals may keep a proactive approach when looking for the specific signs and symptoms of the GSM. Moreover, such professionals should always be keen to create a comfortable atmosphere between the patient and themselves, allowing an adequate health education, counseling and treatment [9].

Many tools have been developed to study the real prevalence of GSM as well as its impact on the quality of life of affected women. Some of the main studies are:

- 2008: REVEAL the Revealing Vaginal Effects at MidLife study.
- 2010: VIVA: Vaginal Health; Insights, Views and Attitudes.
- 2011: Healthy Women online survey en EEUU.
- 2011: CLOSER: Clarifying vaginal atrophy´s impact On Sex and Relationships.
- 2013 REVIVE: Real Women´s Views of Treatment Options for Menopausal Vaginal Changes.
- 2014 DIVA: Day to Day Impact of Vaginal Aging Questionnaire.
- 2014 VSQ: Vulvovaginal Symptoms Questionnaire.

The VSQ questionnaire was designed to measure the prevalence of the GSM symptoms and their effects in the quality of life in postmenopausal women.

Once the questionnaire was applied to the population, it was concluded that more than 50% of the women participating in the questionnaire had at least 1 vulvovaginal symptom in the last week. More than 10% of the postmenopausal women suffer 5 or more symptoms. Among women with symptoms, 40% experienced emotional impact and 33% experienced impact on their lifestyle, lastly, 75% reported being affected by these symptoms in their sex life [10].

Treatment

The principal therapeutic goal in the GSM is to relieve symptoms and restore the normal urogenital physiology [4]. According to the practice guideline of menopause treatment of Endocrine Society, women without personal history of hormone-dependent cancer, who have GSM symptoms and want to relieve it, but persist despite the use of moisturizes and lubricants, oestrogenic vaginal hormonal therapy is recommended [11].

Lubricants and vaginal moisturizers

The NAMS establish as first-line therapies for women with symptomatic vulvovaginal atrophy, lubricants and vaginal moisturizers [12]. In the same direction, the Society of Obstetrician and Gynaecologist of Canada (SOGC) [13], publishes in its clinical guidelines that vaginal moisturizers used regularly (at least twice weekly), may provide an effective non hormonal approach to alleviating symptoms of vaginal atrophy.

The regular use of vaginal gels/ foams/ lotions, may decrease the pH to premenopausal levels but does not improve vaginal maturation and the use of lubricants may reduce friction during intercourse [9].

Several lubricants are available. Data do not demonstrate the superiority of one over another [12]. Water-based or silicone-based lubricants are preferable since they are easier to remove by washing, while greasy or oily derivatives are more difficult to wash.

The World Health Organization (WHO) recommends the use of additional lubricants with condoms for women in the menopause and postmenopausal [14].

See table 2 below which indicates several criterion to follow in order to choose the appropriate lubricant.

Vaginal moisturizers rehydrate dry mucosal tissue and are absorbed into the skin and adhere to the vaginal lining, thereby mimicking natural vaginal secretions [14,15]. Used regularly (at least twice weekly), may provide an effective non hormonal approach to alleviating symptoms of vaginal atrophy. However, the studies are small, not double-blind, and limited to 12 weeks. According to Palacios et al, although they are effective, are not as effective as local oestrogen therapy since vaginal moisturizers do not show a reduction in urinary symptoms or asymptomatic bacteria. Moreover they do not eliminate the need to use vaginal lubricants during intercourse [4].

Hormone Therapy (HT)

It is the GSM standard treatment. Both oral and topical administrations are effective in the improvement of the GSM. In the risk / benefit balance, HT should always be individualized and reviewed with the patient. The least possible dose should be applied.

Systemic treatment: There are many publications supporting the systemic indication of hormone therapy for GSM treatment. Systemic HT fails to resolve vaginal symptoms in 10% to 15% of women, and additional low-dose vaginal oestrogen may be needed [6]. This is sufficient reason not to recommend the use of systemic hormonal therapy in women with only genitourinary symptoms [4].

Local treatment: As low-dose vaginal oestrogen produces very low serum levels of oestrogen. Thus, this treatment is considered to have a lower risk of adverse effect than commonly used doses of systemic oestrogen therapy. In addition, a low-dose of vaginal oestrogen improves sexual satisfaction, lubrication and increases vaginal discharge and sensitivity [4].

2006 Cochrane review about local oestrogenic therapy for the VVA, analysed 30 randomized studies with 6235 postmenopausal women comparing the different oestrogenic preparations among them (cream, ring andvaginal tablets) with placebo. Results indicated significant findings favouring the cream, ring, and tablets when compared to placebo and non-hormonal gel [16,17].

Evidence shows that the use of local oestrogens is safe and there is no need to add a progestogen for endometrial protection when topical oestrogens are used in the recommended doses (there is insufficient data on long-term for endometrial safety) [4], as indicated in the clinical guidelines of the International Menopause Society and the North American Menopause Society published [4,11].

The European Menopause and Andropause Society (EMAS) are also positioned in this sense; there is no need to add a progestogen for endometrial protection [18].

In women with history of hormonal gynaecological cancer, non-hormonal lubricants and moisturizers should be considered first line. When these are not effective, vaginal oestrogens can be used at the lowest dose required and always after being informed [18].

Selective Oestrogen-Receptor Modulators (SERMs)

Ospemifene: Is an oral non-oestrogen drug, with an oestrogen agonistic effect on vaginal epithelial tissue and on bone and neutral/antagonist on breast [19]. First oral non-hormonal alternative drug for genitourinary syndrome for GSM. Published studies have shown improvement in vaginal maturation index, vaginal pH, vaginal dryness, and dyspareunia [1,20]. Follow-up at one year has shown no effect on the endometrium.

Ospemifene is the only SERM approved by the US Food and Drug Administration (FDA) for treatment of moderate to severe dyspareunia associated with VVA secondary to menopause [4,19].

The European Medicine Agency (EMA) approved on 20th November 2014 [20] ospemifene as treatment of moderate to severe symptomatic VVA in post-menopausal women who are not candidates for local vaginal oestrogen therapy. In conclusion, daily use of ospemifene 60mg orally offers an oral and well tolerated therapeutic alternative in postmenopausal women with GSM [4].

Regarding ospemifene and breast cancer, the FDA does not recommend it if there is risk or history of breast cancer or oestrogen-dependent neoplasms [19]. However, EMA reports that there are no clinical data on the concomitant use of ospemifene with oncology therapies for early or advanced breast cancer, and recommends to use ospemifene only after completion of treatment, including adjuvant therapy in breast cancer.

There is a recent meta-analysis published on ospemifene in 2014 [21], which objective was to analyse the efficacy and safety of the drug for treating dyspareunia associated with postmenopausal vulvar and vaginal atrophy. The study reveals that ospemifene 60mg per day is superior to placebo in reducing parabasal cells, increasing superficial cells, decreasing vaginal pH, and reducing dyspareunia during short-term therapy. It produces an increase in the endometrial line, but based on endometrial biopsies, no cases of endometrial hyperplasia or carcinoma were reported. This meta-analysis demonstrates ospemifene to be an effective and safe treatment for dyspareunia associated with postmenopausal vulvar and vaginal atrophy.

TSEC: Combination of selective oestrogen-receptor modulators with an equine conjugated (CEE). It is a new alternative developed to improve menopausal symptoms and to prevent osteoporosis. It maintains the benefits of oestrogen therapy in the relief of vasomotor symptoms and VVA, and antagonizes its effects on the endometrium and breast [4].

Laser therapy

Laser therapy has a therapeutic role in various medical conditions and most recently has gained interests a non-hormonal treatment for genitourinary syndrome of menopause and as a non-invasive option for Stress Urinary Incontinence (SUI).

The word "LASER" is an acronym for "light amplification by stimulated emission of radiation," operate in the ultraviolet (157-400 nm), visible (400-800 nm), near-infrared (800-3,000 nm),

Table 2: How to choose a lubricant.

Symptom or Situation	Recommendation	Rationale
Urogenital atrophy, elevated vaginal pH, experiencing pain in daily life due to extreme dryness	Vaginal moisturizer with acidic pH and osmolality below the WHO ideal recommendation of 380mOsm/kg	Rehydrate vaginal tissues and lower vaginal pH to minimize infection (e.g. bacterial vaginosis)
Dyspareunia (painful intercourse) caused by urogenital atrophy	Vaginal lubricant with acidic pH matched to vaginal pH and with osmolality below the WHO ideal recommendation of 380mOsm/kg	Lubricate dry vaginal tissues without causing irritation and maintain or lower vaginal pH
Urogenital atrophy as a result of cancer treatment when HT is contraindicated, or in combination with topical oestrogen if still experiencing discomfort from atrophy	For daily comfort, use a paraben-free vaginal moisturizer with acidic pH and osmolality below the WHO ideal recommendation of 380mOsm/kg.	Rehydrate vaginal tissues and lower vaginal pH to minimize infection.
	For sexual intercourse or for use with vaginal dilators, use a paraben-free vaginal lubricant with acidic pH matched to vaginal pH and osmolality below the WHO ideal recommendation of 380mOsm/kg.	Lubricate dry vaginal tissues without causing irritation and maintain or lower vaginal pH
		Avoid potential endocrine disruptor (i.e. paraben preservatives)
Trying to conceive and needing a lubricant	At ovulation, use a sperm-friendly lubricant	Lubricant is pH-matched and iso-osmotic to semen
Rectal/anal sex	Use a rectal lubricant that is condom-compatible with osmolality below the WHO ideal recommendation of 380mOsm/kg and a pH matched to rectal pH	Reduce the risk of condom damage and resulting pathogen transmission, without irritating/damaging the rectal epithelium
Vaginal or rectal examination	Use a lubricant that is pH-matched for the vagina or rectum and has osmolality below the WHO ideal recommendation of 380mOsm/kg	Reduce the risk of irritating/damaging the vaginal or rectal epithelium

mid-infrared (3,000-30,000 nm), and far-infrared (> 30,000nm) regions of the electromagnetic spectrum [22].

In 2014, the FDA approved the use of fractional micro ablative CO_2 Laser therapy for genitourinary surgery [4,9].

The currently available data on the effects of fractional laser and Radiofrequency (RF) on the skin, and additional information reported in almost 20 peer-reviewed publications on GSM-related symptoms, unequivocally demonstrate the following vaginal changes: Thickening of glycogen enriched postmenopausal epithelium, neovascularization, and neocollagenesis in the lamina propria, increased lactobacilli counts, reduced pH, vaginal wall tightening, and improved urination control with minimal risk of short- and long-term complications [22].

Types of laser [23]**:**

CO_2 laser: MonaLisa Touch, which was developed in Europe by DEKA, and is now distributed in the United States by Cynosure, is a CO_2 laser designed to stimulate and promote the regeneration of collagen fibres and to restore hydration and elasticity within the vaginal mucosal. It is a fractionated laser in a non-continuous mode.

ER-YAG laser: Emits laser energy in the mid-infrared region. This laser has 10 to 15 times the affinity for water absorption than the CO_2 laser at a wavelength of 10,600nm. This treatment approach enables a deeper secondary thermal effect and controlled heating of the target mucous membrane of the vaginal wall.

Review of collated evidence from the studies (level of evidence IV) to date suggests that laser therapy is effective in the treatment of GSM [23]. The lack of randomized controlled trials made it difficult to undertake a meta-analysis. In all the published trials reviewed, 224 women have been studied a clear improvement of the symptoms is shown on them. A study of efficacy cannot be done because the parameters studied in the several studies are different. The evidence reviewed shows that laser therapy can be used for the treatment of GSM symptoms and does not show any adverse effects. However, patients were followed up for a maximum of 3 months except in the study by Gambacciani et al [24] (the patients were followed up for only 12 weeks). There does not appear to be sufficient evidence of its long-term efficacy and other effects. Another recent review is the one signed by Gambacciani Palacios [25] suggest that laser treatment for the restoration of vaginal function might improve the quality of life of millions of women. Cohort prospective studies show that the procedure is effective and safe, if appropriately applied, and no serious adverse effects have been reported. Gaspar [26] in 2011 was the first to demonstrate that fractional CO_2 laser induces a significant improvement in the symptoms and signs of vaginal atrophy. Salvatore et al. [27] conducted a follow-up pilot study in 50 postmenopausal women with symptoms suggestive of GSM who were dissatisfied with previous local oestrogen therapies or who were non responders. A key finding was that three laser applications improved the most bothersome GSM symptom in this 12week follow-up study. Vaginal dryness improved in 86%, vaginal burning in 90%, vaginal itching in 80% and dysuria in 74%. The dyspareunia improved in 100%. EMAS's position on the use of laser therapy is that it is a new therapeutic strategy, but long-term studies are needed to explore efficacy and safety before drawing definitive conclusions [28].

Laser treatment may be appropriate for women who cannot or do not want hormonal treatment as well as for women who refuse long-term use of moisturizers and lubricants. There are no contraindications to vaginal laser therapy except for its high cost. Data from vaginal procedures suggest that they are safe and well tolerated, with no major adverse effects or side effects. Further long-term efficacy and safety data should be collected before fully embracing this expensive new technology [23,29], (Table 3).

Table 3: Level of evidence of GSM treatments.

Treatment	Level of Evidence
Lifestyles	II-2B
Obesity	III-C
Exercise	III-C
Smoke	II-3B
Vaginal moisturizers 2-3 a/w	I-A
Lubricants	II-2B
Homeopathy	III-D
Phytoterapy	III-D
Local and systemicoestrogens	
Symptom improvement	I-A
Vaginal laser for trophic improvement and symptoms	I-A

Lifestyle Modifications

Modify the factors that increase the oestrogenic decrease like smoking, or factors that can enhance them as a Body Mass Index (BMI) > 27kg/m^2 or no physical exercise (resulting in a decrease in genitourinary vascularization) [4].

Increased sexual activity is advised for maintaining robust vaginal muscle condition. There is a positive link between sexual activity and maintenance of vaginal elasticity and pliability as well as lubricative response to sexual stimulation1. Women who have sex or masturbation have fewer symptoms associated with vaginal atrophy.

Use of vaginal dilators can increase vaginal function, help relaxation and can be progressively adjusted to different sizes 4. For women in whom oestrogen therapy is contraindicated, the use of dilators may improve vaginal function [15].

Stress reduction therapy and psychological counseling may benefit women with non-organic causes of vaginal dryness [1].

Cessation of smoking can help relieve symptoms [1]. Wearing looser undergarments and leg wear may improve air circulation, discouraging growth of microorganisms [1].

Treatment should be individualized, and consists of guiding and advising on vulvar hygiene, and lifestyle modifications (avoid overly perfumed products, use of unadjusted cotton underwear, drying of the perineal area after bathing or smoking cessation). Women with recurrent UTIs should be instructed in the consumption of red fruit juices [8].

Homeopathic Remedies

There is no proven efficacy on the vaginal epithelium and treatment of GSM [1].

Some substances are

Aloe-vera, Marigold, Dong quai, Lavender chamomile or Green tea, but there is not enough evidence for its recommendation.

Innovative treatments

Although the vagina has previously not been considered an androgen-dependent organ, innovative animal studies suggest, that androgens may have a direct effect on estradiol-independent structure and vaginal function [10].

A phase I/II pilot study examining the use of vaginal testosterone in patients with breast cancer and vaginal atrophy, where oestrogen therapy is contraindicated. Significant differences have been found in the decrease in pH and a 20% increase in vaginal maturation index when 300μg per day are used for 28 days [4].

A randomized double-blind controlled trial conducted in Stockholm reported that application of oxytocin gel produced healthier and more normalized vaginal epithelium [30].

A recent randomized, double-blind, placebo controlled phase III trial showed that daily intravaginal application of 0.5% dehydroepiandrosterone increased superficial cell percentage and decreased parabasal cell in the vaginal epithelium, decreased vaginal pH, and decreased sexual pain [31].

Some vitamins such as vitamin E and D have been used for GSM therapy; vitamin D may help generate keratinocyte proliferation and differentiation in the vaginal epithelium1. The vagina is lined with stratified squamous epithelium, so vitamin D may increase the proliferation and differentiation of the epithelium.

Conclusion

"Genitourinary syndrome of menopause" is an inclusive term that includes several urological, sexual and external genital tract sequels as a consequence of the hypoestronism of menopause. First line of treatment includes lubricants and vaginal moisturizers as well as regular sexual activity. If this treatment fails, the first pharmacological line with local oestrogens may begin. When oestrogen therapy is contraindicated, new treatments that have recently appeared as ospemifeme and the vaginal laser therapy may be a therapeutic option.

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Citation: Ibarra Vilar P, Marín Sánchez MP, Ñíguez Sevilla I, Marín Pérez AM and Nieto Díaz A. A Review of the Genitourinary Syndrome of Menopause. SM J Gynecol Obstet. 2018; 4(1): 1028.

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