



A Review of the Genitourinary Syndrome of Menopause

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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 introduce new terminology and discuss the importance of this syndrome. Moreover, we comment the necessity of active treatment in postmenopausal women.

Keywords: Genitourinary syndrome of menopause; Menopause; Vulvovaginal atrophy

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 hypoestrogenism 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 sequelae as a consequence of the hypoestrogenism of menopause [1-3].

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

50% of postmenopausal women have GSM symptoms during and after menopause [4,5]. These symptoms are manifested in approximately 15% of premenopausal women and in 40% to 54% of postmenopausal [1].

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Symptoms and Signs

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

Vulvovaginal symptoms and sexual dysfunction

The postmenopausal women (45% to 63%) reported that they had experienced vulvovaginal symptoms, most commonly vaginal dryness. Other symptoms included dyspareunia, vaginal irritation, itching sensation, vaginal tenderness, and vaginal bleeding or spotting during intercourse (Table 1) [6]. 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 [6], around 20% of postmenopausal women had severe urgency and almost 50% had Stress Urinary Incontinence (SUI). In particular, urge UI is more prevalent after menopause than before, and its prevalence increases with time in women with estrogen 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 still below estimated. Some women believe that their symptoms are a necessary part of the aging process. Social, religious and cultural beliefs play a very important role in the fact of feeling uncomfortable expressing everything related to the

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 Tissue itching of the vulva or vagina | Fragility, Fissures, Petechiae |
| Dysuria | Urethral eversion or prolapse |
| Urinary frequency and urgency | Loss of hymeneal remnants |
| | Prominence of urethral meatus |
| | Introital retraction |
| | Recurrent urinary tract infections (UTIs) |

genitourinary system. For this reason health professionals may keep a proactive attitude to look for signs and symptoms. Additionally, a comfortable climate should be established, allowing an adequate education, counselling and treatment [9,10].

Many tools to try to study the real prevalence of GSM as well as their impact on the quality of life of affected women have been developed. 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. Explained below:

It involved a questionnaire designed to measure the disease-specific quality-of-life impact of vulvovaginal symptoms in postmenopausal women.

Applied to the population, we objected that more than 50% of the women had at least 1 vulvovaginal symptom in the last week and 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 and 75% reported being affected in their sex life by these symptoms.

Treatment

The principal therapeutic goal in the GSM is to relieve symptoms and restore the normal urogenital fisiology [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 moisturizers and lubricants, estrogenic 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 attached table on how to choose a lubricant over another (Table 2). Vaginal moisturizers rehydrate dry mucosal tissue and are absorbed into the skin and adhere to the vaginal lining, thereby mimicking natural vaginal secretions [14]. 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. [4], although they are effective, are not as effective as local estrogen therapy since vaginal moisturizers do not show a reduction in urinary symptoms or asymptomatic bacteriuria. Moreover they do not eliminate the need to use vaginal lubricants during intercourse [15].

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, hormonal therapy 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 estrogen 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: 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. They produce an improvement in sexual satisfaction, in the lubrication and increases vaginal discharge and sensitivity [4]. 2006 Cochrane review about local estrogenic therapy for the VVA, analysed 30 randomized studies with 6235 postmenopausal women comparing the different estrogenic preparations among them (cream, ring and vaginal tablets) with placebo. Results indicated significant findings favouring the cream, ring, and tablets when compared to placebo and nonhormonal gel [16,17].

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

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 | Use a vaginal moisturizer with acidic pH and osmolality below the WHO ideal recommendation of 380 mOsm/kg. | Rehydrate vaginal tissues and lower vaginal pH to minimize infection (e.g. bacterialvaginosis). |
| Dyspareunia (painful intercourse) caused by urogenital atrophy | Use a vaginal lubricant with acidic pH matched to vaginal pH and with osmolality below the WHO ideal recommendation of 380 mOsm/kg. | Lubricate dry vaginal tissues without causing irritation and maintain or lower vaginal pH. |
| Urogenital atrophy as a result of cancer treatment when HRT is contraindicated, or in combination with topical estrogen 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. 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 380 mOsm/kg. | Rehydrate vaginal tissues and lower vaginal pH to minimize infection. 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 380 mOsm/kg. | Reduce the risk of irritating/ damaging the vaginal or rectal epithelium. |

also positioned; there is no need to add a progestogen for endometrial protection [18].

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

Selective estrogen-receptor modulators (SERMs)

Ospemifene: Is an oral non-estrogen drug, with an estrogen 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 November 20, 2014 [20] ospemifene as treatment of moderate to severe symptomatic VVA in post-menopausal women who are not candidates for local vaginal estrogen 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 estrogen-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 demonstrate ospemifene to be an effective and safe treatment for dyspareunia

associated with postmenopausal vulvar and vaginal atrophy.

TSEC: Combination of selective Estrogen- 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 estrogen 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 nm to 400 nm), visible (400 nm to 800 nm), near-infrared (800 nm to 3,000 nm), mid-infrared (3,000 nm to 30,000 nm), and far-infrared (>30,000 nm) regions of the electromagnetic spectrum [22].

In 2014, the FDA approved the use of fractional micro ablative CO₂ Laser therapy for genitourinary surgery [4,9]. The currently available data on the effects of fractional laser and Radio Frequency (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

CO₂ laser: MonaLisa Touch, which was developed in Europe by DEKA, and is now distributed in the United States by Cynosure, is a CO₂ 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 CO₂ laser at a wavelength of 10,600 nm. This treatment approach enables a deeper secondary thermal effect and controlled heating of the target mucous membrane of the vaginal wall. Review of collated

Table 3: Level of evidence of GSM treatments [4].

| 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 systemic estrogens | |
| Symptom improvement | I-A |
| Vaginal laser for trophic improvement and symptoms | I-A |

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. 6.5.3. Conclusions:

- The main difference between the two lasers is that the CO₂ laser is ablative and the Er:YAG laser is non ablative.
- 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.
- There are no contraindications to vaginal laser therapy except for its high cost. 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 week). 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 and 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 et al. [26] in 2011 was the first to demonstrate that fractional CO₂ 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 estrogen 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. 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].

Lifestyle modifications

Modify the factors that increase the estrogenic decrease like smoking, or factors that can enhance them as a Body Mass Index (BMI) > 27 kg/m² 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 stimulation [1]. 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 estrogen 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 legwear 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.

- 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 estrogen therapy is contraindicated. Significant differences have been found in the decrease in pH and a 20% increase in vaginal maturation index when 300 microg 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 [29].
- 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 [30].

- 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 epithelium [1]. 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 the latest terminology instated to increase awareness and reduce social stigma of the genitourinary sequelae and sexual dysfunction associated with postmenopausal hypoestrogenism [1].

It is an inclusive term that includes several urological, sexual and external genital tract sequels as a consequence of the hypoestrogenism of menopause. There are many studies that support the high prevalence of this syndrome in the menopausal population, but at the same time it is underdiagnosed and under-treated.

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 estrogens may begin. When estrogen therapy is contraindicated, new treatments that have recently appeared as ospemifene and the vaginal laser therapy may be a therapeutic option.

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