

REVIEW ARTICLE

Critical analysis of methods for assessing genitourinary syndrome of menopause used in clinical trials

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Abstract

Objective: The aim of the study was to determine the most used methods for assessing genitourinary syndrome of menopause by the latest studies on the subject, and to critically assess their differences and comparability.

Methods: A narrative review of the literature was conducted, employing the terms genitourinary syndrome, vaginal atrophy, urogenital atrophy, and atrophic vaginitis, to analyze methods used to assess treatment efficacy. Only controlled randomized clinical trials assessing improvement of genitourinary syndrome of menopause, conducted in the last 5 years, and considering all types of treatment, were selected.

Results: Of the 37 studies included, 24 combined both objective and subjective methods thereby ensuring reproducibility and efficacy of symptom relief of the treatment analyzed. The vaginal maturation index was the most used objective method, followed by vaginal pH. One study used histological and immunohistochemistry tests. Regarding subjective methods, the “Most Bothersome Symptom” and other questionnaires as the Female Sexual Function Index for sex life, the Verbal Rating Scale, among others, were used.

Conclusions: Despite the heterogeneity observed, particularly for subjective assessment of symptoms, there was a tendency to standardize methods and to use an objective method together with a subjective, which seems to be fundamental to guarantee reproducibility and comparability of results of each treatment analyzed. Histological and immunohistochemistry tests may be an option as an objective method in further studies, to better assess thickness, vascularization, among other parameters.

Key Words: Genitourinary syndrome – Menopause – Most bothersome symptom – Vaginal atrophy.

Genitourinary syndrome of menopause (GSM) is a group of signs and symptoms of the genitourinary tract secondary to the hypoestrogenism characteristic of the climacteric. The condition includes anatomic changes, thinning of the epithelium, increased density of connective tissue, and reduced blood vessels, leading to symptoms such as vaginal dryness, dyspareunia and bleeding after sexual activity, urinary incontinence, burning, irritation, discomfort, and higher incidence of infections.^{1,2} Unlike vasomotor symptoms, whose frequency and intensity diminish over time, vulvovaginal symptoms are generally permanent and progressive, requiring long-term therapy.³

The syndrome affects 15% of all climacteric women in the premenopausal phase⁴ and approximately 70% after

menopause.⁵ This prevalence may be even higher, given that the condition is underdiagnosed owing to the reluctance of women and health professionals to discuss the problem or because symptoms are merely attributed to aging, with little awareness of the role of hypoestrogenism or of treatment options available.^{6,7}

Hormone therapy with estrogen is the current treatment of choice.⁸⁻¹⁰ However, the demand for alternative methods to conventional hormone therapy rose dramatically.¹¹ Other options include ospemifene,¹² dehydroepiandrosterone,¹³ vaginal laser, water-based vaginal moisturizing gels, and, more recently, phytoestrogens.¹⁴ This has led to a need for trials assessing the efficacy of novel treatment approaches.¹¹

Objective measures available for assessing GSM include assessment of vaginal cytology and vaginal pH. Vaginal cytology, based on vaginal wall smears, quantifies parabasal, intermediate, and superficial epithelial cells. These yield a vaginal maturation index (VMI), expressed as a ratio of the percentage of each type of cell represented from left to right, respectively, and cervical maturation value, by multiplying the percentages in formulas to give a single value. Although different formulas are in use, typically the lower the value, the lower the proportion of intermediate and superficial cells, that is, the higher the degree of atrophy.^{15,16}

Received February 19, 2019; revised and accepted June 28, 2019.

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Funding/support: None reported.

Financial disclosure/conflicts of interest: None reported.

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OBJECTIVE

The purpose of this review is to evaluate evidence published in the past 5 years to determine the most commonly used objective and subjective methods for assessing GSM, and to critically assess their differences and comparability.

METHOD

Search strategy

A narrative review of the literature was conducted. Searches were carried out on the platforms PubMed, MEDLINE, and Google Scholar, employing the terms genitourinary syndrome, vaginal atrophy, urogenital atrophy, and atrophic vaginitis.

Eligibility criteria

The inclusion criteria were controlled randomized clinical trials assessing improvement of GSM using one or more methods (subjective or objective), conducted between January 2014 and December 2018, considering all types of treatment, written in English. We excluded studies performed before 2014, in languages other than English, or that assessed only the presence of adverse effects of interventions. One reviewer (J.V.H.) screened abstracts for type of study, methods of assessment used, and outcomes. Then applied the inclusion and exclusion criteria to the full text of selected studies.

Data extraction

From selected articles, we obtained the title, authors' surnames, publication year, description of methods used for assessing the improvement of GSM after interventions, duration of treatment, and outcomes. Data were organized classifying methods used in each study as "objective" and "subjective," for better analyses and comparison.

RESULTS

Study selection

The literature search using the descriptors initially retrieved 2,549 articles from the 2014 to 2018 period. After rejection of redundant (duplicated) articles and application of exclusion criteria, there were 37 articles for inclusion in the study (Fig. 1). The articles listed in order of publication are given in Table 1.

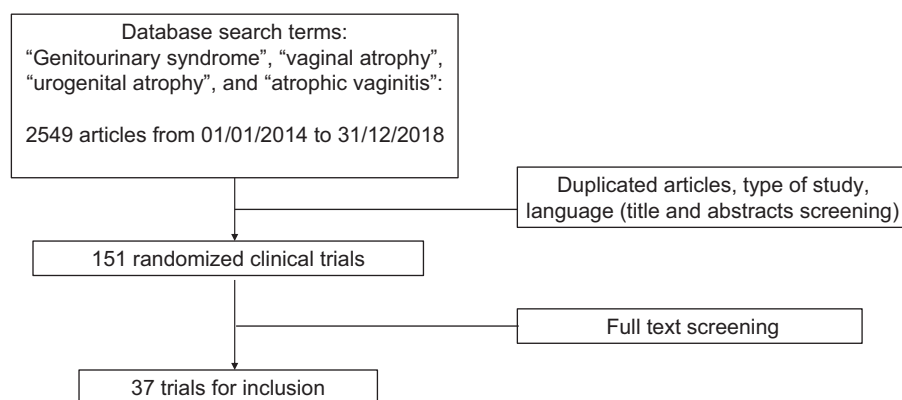


FIG. 1. Study selection.

TABLE 1. Methods used for subjective and objective analysis and classification of genitourinary syndrome of menopause

| Study Title | GSM assessment method | |
|--|--|--|
| | Subjective methods | Objective methods |
| Effect of fennel vaginal cream on sexual function in postmenopausal women: a double-blind randomized controlled trial. ²¹ | Female Sexual Function Index (FSFI) | pH and vaginal cytology (Vaginal Maturation Index) |
| A randomized, multicenter, double-blind, study to evaluate the safety and efficacy of estradiol vaginal cream 0.003% in postmenopausal women with vaginal dryness as the most bothersome symptom. ²² | Most bothersome symptom (MBS) | pH and vaginal cytology (Vaginal Maturation Index) |
| Effect of <i>Foeniculum vulgare</i> (fennel) on vaginal atrophy in postmenopausal women: a double-blind, randomized, placebo-controlled trial. ²³ | | Vaginal cytology (Vaginal Maturation Value and Index) |
| Impact of ospemifene on quality of life and sexual function in young survivors of cervical cancer: a prospective study. ¹² | The European Organization for Research and Treatment of Cancer (EORTC); Quality of Life Questionnaire (QLQ) | Vaginal health index (VHI) |
| The REJOICE trial: a phase 3 randomized, controlled trial evaluating the safety and efficacy of a novel vaginal estradiol soft-gel capsule for symptomatic vulvar and vaginal atrophy. ²⁴ | Most bothersome symptom (MBS) | pH and vaginal cytology (Vaginal Maturation Index) |
| Visual improvements in vaginal mucosa correlate with symptoms of VVA: data from a double-blind, placebo-controlled trial. ²⁵ | Visual physical examination with 1-4 scale for color, epithelial integrity, epithelial thickness, and vaginal secretions | |
| Combined data of intravaginal prasterone against vulvovaginal atrophy of menopause. ¹³ | Most bothersome symptom (MBS) | pH and vaginal cytology (Vaginal Maturation Index) |
| Monurelle Biogel vaginal gel in the treatment of vaginal dryness in postmenopausal women ²⁶ | Verbal Rating Scale (VRS), Female Sexual Function Index (FSFI), and Female Sexual Distress Scale-Revised (FSDS-R) | Vaginal health index (VHI), vaginal cytology (Vaginal Maturation Index) |
| Randomized, double-blind, placebo-controlled clinical trial for evaluating the efficacy of fractional CO ₂ laser compared with topical estriol in the treatment of vaginal atrophy in postmenopausal women. ²⁷ | Visual physical exam with 1-4 scale for color, epithelial integrity, epithelial thickness, and vaginal secretions | Vaginal cytology (Vaginal Maturation Index) |
| Efficacy of intravaginal dehydroepiandrosterone (DHEA) on moderate to severe dyspareunia and vaginal dryness, symptoms of vulvovaginal atrophy, and of the genitourinary syndrome of menopause. ²⁸ | Most bothersome symptom (MBS) | pH and vaginal cytology (Vaginal Maturation Index) |
| Vaginal testosterone cream vs estradiol vaginal ring for vaginal dryness or decreased libido in women receiving aromatase inhibitors for early-stage breast cancer: a randomized clinical trial. ²⁹ | Cancer Rehabilitation Evaluation System questionnaire; visual physical exam with 1-4 scale for color, epithelial integrity, epithelial thickness, and vaginal secretions | |
| Efficacy of erbium:YAG laser treatment compared to topical estriol treatment for symptoms of genitourinary syndrome of menopause. ³⁰ | Visual physical exam with 1-4 scale for color, epithelial integrity, epithelial thickness, and vaginal secretions | pH and vaginal cytology (Vaginal Maturation Index) |
| Pharmacokinetics of the fetal estrogen estetrol in a multiple-rising-dose study in postmenopausal women. ³¹ | | Vaginal cytology (Vaginal Maturation Index) |
| Comparison of <i>Pueraria mirifica</i> gel and conjugated equine estrogen cream effects on vaginal health in postmenopausal women. ³² | | Vaginal health index (VHI) and vaginal cytology (Vaginal Maturation Index) |
| An assessment of the safety and efficacy of a fractional CO ₂ laser system for the treatment of vulvovaginal atrophy. ³³ | Tolerance to dilator | Vaginal health index (VHI) |
| Efficacy of vaginally applied estrogen, testosterone, or polyacrylic acid on vaginal atrophy: a randomized controlled trial. ³⁴ | | Vaginal health index (VHI), vaginal cytology (vaginal maturation index), assessment of vaginal flora |
| Evaluation of efficacy and safety of conjugated estrogens/bazedoxifene in a Latin American population. ³⁵ | | Vaginal cytology (vaginal maturation index) |
| Oxytocin improves cytological and histological profiles of vaginal atrophy in postmenopausal women ³⁶ | | Vaginal histology and cytology (vaginal maturation index) |

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TABLE 1 (Continued)

| Study Title | GSM assessment method | |
|---|---|--|
| | Subjective methods | Objective methods |
| A randomized, double-blind, placebo-controlled phase 2 pilot trial evaluating a novel, vaginal softgel capsule containing solubilized estradiol. ³⁷ | Most bothersome symptom (MBS); Visual physical exam with 1-4 scale for color, epithelial integrity, epithelial thickness, and vaginal secretions | pH and vaginal cytology (Vaginal Maturation Index), assessment of vaginal flora |
| Pharmacokinetics and preliminary efficacy of two vaginal gel formulations of ultra-low-dose estriol in postmenopausal women. ³⁸ | | Vaginal cytology (Vaginal Maturation Value) |
| Effect of intravaginal dehydroepiandrosterone (DHEA) on the female sexual function in postmenopausal women: ERC-230 open-label study. ³⁹ | Female Sexual Function Index (FSFI) | |
| Effect of ospemifene on moderate or severe symptoms of vulvar and vaginal atrophy. ⁴⁰ | Assessment of symptom severity | |
| Effect of <i>Foeniculum vulgare</i> (fennel) vaginal cream on vaginal atrophy in postmenopausal women: a double-blind, randomized, placebo-controlled trial. ⁴¹ | | pH and vaginal cytology (Vaginal Maturation Index) |
| Effect of intravaginal Prasterone on sexual dysfunction in postmenopausal women with vulvovaginal atrophy. ⁴² | Female Sexual Function Index (FSFI) | |
| Low-dose 17- β -estradiol cream for vaginal atrophy in a cohort without prolapse: serum levels and vaginal response including tissue biomarkers associated with tissue remodeling. ⁴³ | Subjective assessment of symptoms | Vaginal cytology (Vaginal Maturation Index); |
| Intravaginally applied oxytocin improves postmenopausal vaginal atrophy. ⁴⁴ | Most bothersome symptom (MBS) | pH and vaginal cytology (Vaginal Maturation Index) |
| Nonhormonal treatment of vulvovaginal atrophy-related symptoms in postmenopausal women. ⁴⁵ | Subjective assessment of symptoms | pH and vaginal cytology (Vaginal Maturation Index); colposcopic assessment of atrophy Vaginal pH |
| Efficacy and safety of nonhormonal remedies for vaginal dryness: open, prospective, randomized trial. ⁴⁶ | Subjective assessment of symptoms | Vaginal pH |
| Prasterone has parallel beneficial effects on the main symptoms of vulvovaginal atrophy: 52-week open-label study. ⁴⁷ | Most bothersome symptom (MBS); Visual physical exam with 1-4 scale for color, epithelial integrity, epithelial thickness, and vaginal secretions | |
| The clinical relevance of the effect of ospemifene on symptoms of vulvar and vaginal atrophy. ⁴⁸ | | Vaginal health index (VHI) |
| Effects of sea buckthorn oil intake on vaginal atrophy in postmenopausal women: a randomized, double-blind, placebo-controlled study. ⁴⁹ | Visual physical exam with 1-5 scale for color, epithelial integrity, epithelial thickness, and vaginal secretions; Questionnaire and daily logbook of symptoms on scale of 1-3. | Vaginal health index (VHI), Vaginal cytology (Vaginal Maturation Index) |
| An alternative approach for the treatment of vaginal atrophy. ⁵⁰ | Visual Analogical Scale'' (VAS) | Vaginal health index (VHI) |
| Effects of glycine max (L.) Merr. soy isoflavone vaginal gel on epithelium morphology and estrogen receptor expression in postmenopausal women: a 12-week, randomized, double-blind, placebo-controlled trial. ⁵¹ | Classification of symptoms into none, mild, moderate, and severe | Vaginal cytology (Vaginal Maturation Value); Vaginal histology for analysis of estradiol receptor levels |
| Ultra-low-dose estriol and Lactobacillus acidophilus vaginal tablets (Gynoflor) for vaginal atrophy in postmenopausal breast cancer patients on aromatase inhibitors: pharmacokinetic, safety, and efficacy phase I clinical study. ⁵² | Symptoms diary and sexual health questionnaire | Vaginal pH and cytology (Vaginal Maturation Index); Analysis of vaginal flora |
| Ospemifene, a nonestrogen selective oestrogen receptor modulator for the treatment of vaginal dryness associated with postmenopausal vulvar and vaginal atrophy: a randomized, placebo-controlled, phase III trial ⁵³ | Most bothersome symptom (MBS) | Vaginal pH and cytology (Vaginal Maturation Index) |
| Assessment of ospemifene or lubricants on clinical signs of VVA ⁵⁴ | Most bothersome symptom (MBS) | Vaginal pH and cytology (Vaginal Maturation Index) |
| Ospemifene 12-month safety and efficacy in postmenopausal women with vulvar and vaginal atrophy. ⁵⁵ | | Vaginal pH and cytology (Vaginal Maturation Index) |

GSM, genitourinary syndrome of menopause.

Combined versus isolated assessment of GSM

Of the 37 articles included, 24 combined both objective and subjective methods thereby ensuring reproducibility and efficacy of symptom relief of the treatment analyzed,

including the VHI, used by 6 articles, which is a method that automatically comprises a subjective and objective method for assessing GSM. Five studies used a subjective method alone, whereas the remaining six employed an

TABLE 2. Subjective methods used in reviewed studies to assess presence and intensity of symptoms of genitourinary syndrome of menopause

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|--|
| Most bothersome symptom (MBS) |
| Female Sexual Function Index (FSFI) |
| Visual physical examination with 1-4 scale for color, epithelial integrity, epithelial thickness, and vaginal secretions |
| The European Organization for Research and Treatment of Cancer (EORTC) |
| Quality of Life Questionnaire (QLQ) |
| Verbal Rating Scale (VRS) |
| Female Sexual Distress Scale-Revised (FSDS-R) |
| Cancer Rehabilitation Evaluation System questionnaire |
| Tolerance to dilatator |
| Subjective assessment of symptoms |
| Subjective classification of symptom severity |
| Visual physical examination with 1-5 scale for color, epithelial integrity, epithelial thickness, and vaginal secretions |
| Questionnaire and daily logbook of symptoms on scale of 1-3 |
| Visual Analogical Scale (VAS) |
| Classification of symptoms into none, mild, moderate, and severe |
| Symptoms diary and sexual health questionnaire |

objective method only, namely, the VMI based on vaginal cytology.

Objective methods

The VMI was used in 25 articles, whereas pH was used in 21 articles, either alone or together with the visual scale in the physical examination (to calculate VHI). Three studies employed vaginal flora analysis and one additionally evaluated vaginal histology and immunohistochemical markers of estradiol receptors.

Subjective methods

The MBS was used in four studies. In the rest of the studies, a variety of other questionnaires suitable for the study population was used, including the Female Sexual Function Index for sex life and the Verbal Rating Scale. All the subjective methods used in studies reviewed are shown in Table 2.

DISCUSSION

The present study revealed predominant use of the VMI and pH as objective methods for assessing GSM in studies on novel alternative treatments. Subjective GSM assessment methods proved heterogeneous. Weber et al¹⁶ also found this disparity, noting that the broad range of signs and symptoms included and definition difficulties contributed to this lack of standardization.

The GSM should include in its criteria the presence of specific vaginal symptoms, atrophic signs on physical examination, and cytologically determined atrophy. However, consensus on the best manner to classify each aspect is lacking, given there are different ways of interpreting the maturation index, many techniques and body sites adopted for measuring vaginal pH, as well as a broad range of symptoms attributed to hypoestrogenism and atrophy. In addition, there are at least seven different subjective assessment systems, including questionnaires and symptom scales for assessing vaginal atrophy signs on the physical examination.¹⁶

Despite these differences, the studies showed a tendency to standardize, at least for objective methods, with predominant use of the VMI and vaginal pH, and the additional use of a subjective method in most of the trials reviewed. This is important in light of the weak correlation between the VMI and severity of signs on physical examination or symptoms. Davila et al⁵⁶ showed that scores for vaginal atrophy symptoms had no significant correlation with maturation values. Only a moderate negative correlation was observed between the VHI and the maturation value. Lower maturation values were found among women with greater degree of atrophy as measured by the VHI. Simon et al²⁵ found that changes in vaginal pH showed a consistent correlation with percentage of superficial and parabasal cells; subjective intensity of vaginal dryness and dyspareunia; and with parameters of the physical examination of the VHI (vaginal color, epithelial integrity, thickness of the epithelial surface, and secretions).

In the present review, one study employed histological and immunohistochemical methods to assess the extent of changes in the vaginal epithelium. Recently, Al-Saqi et al collected vaginal biopsies to analyze the degree of atrophy based on the percentage of superficial and parabasal cells, revealing a weak correlation with the VMI. The authors found no difference in the percentage ratio of superficial cells on cytology and histology, and highlighted that the histological investigation of vaginal biopsies, given they involve parameters such as number of cellular layers in the epithelium, degree of cell maturity, glycogen levels, among others, may represent a more sensitive technique for assessing the effects of the treatment tested in the study.³⁶ Gaspar et al³⁰ performed vaginal biopsies in six patients before and after treatment with Erbium: YAG laser and also observed additional effects such as increased thickness, increase in the number of blasts and fibrillar components of the extracellular matrix, and improved vascularization.

Summarizing the most used methods, although there is still heterogeneity in evaluation of GSM treatments' efficacy, this review may help researchers to select the assessment methods to use in further trials, to ensure comparability to prior studies, or to bring additional information to those already published. As a limitation of the review, is important to cite the use of only three searching platforms made by only one researcher and reviewer.

CONCLUSIONS

The results revealed heterogeneity in methods, particularly for subjective assessment of symptoms, although there was a tendency to standardize methods used, facilitating the comparison of studies. The importance of using an objective method of assessing atrophy together with a subjective method for improved assessment of symptom relief was evident and seems to be fundamental to guarantee reproducibility and comparability of results of each treatment analyzed in further studies. In addition, histological and immunohistochemistry tests may be an option as objective methods, to better assess thickness, vascularization, among other

parameters, as well as the effects of the treatments tested on the vaginal epithelium.

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