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Systematic Review

Treatment of vulvar pain caused by atrophy: a systematic review of clinical studies

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Background: The signs and symptoms of the genitourinary syndrome of menopause are well established, and there is extensive knowledge with high scientific evidence about the response that vaginal and urinary tissues present to various treatments. However, this does not usually apply to the vulva in general, or any of its structures in particular, since it is included in the term vulvovaginal. The aim of this review is to improve knowledge about the vulva and to improve symptoms in women who experience vulvar pain associated with atrophy. *Methods*: The study was registered at PROSPERO (registration number CRD42020172102). We also assessed the quality of evidence for each outcome of interest according to the GRADE criteria. *Results*: We systematically reviewed eight studies: four with ospemifene, a pilot study with prasterone, a study using a combination of estrogens and androgens, another study that used CO_2 laser surgery and another with application of 0.005% estriol gel to the vulvar vestibule. Meta-analysis was not possible due to the heterogeneity and small sample size of the included studies. Ospemifene orally, at a dose of 60 mg daily for a time period of between 60 days and 20 weeks, report preliminary data showing improvements of vulvar and vestibule trophism. Prasterone showed in an open-label prospective survey, improve in the vulvoscopic results and dyspareunia, in women that used vaginal prasterone. The combination of estriol and testosterone propionate 2% for 12 weeks showed an improve of Vulvar pain due to atrophy (VPA) and dyspareunia in a descriptive prospective survey. A retrospective analysis of 79 postmenopausal women presenting vulvar pain who were treated with CO_2 laser or laser plus ospemifene, showed that vestibular dryness was significantly lower in the ospemifene + laser group compared with the laser treatment group (–87% vs –34%, respectively). Finally, we also included a prospective open-label survey using for a 12-week treatment period, a fingertip to apply 0.25 g of vaginal gel containing 25 μg of estriol to the vulvar vestibule daily for three weeks and then twice weekly for up to 12 weeks. Dyspareunia improved or was cured (score $\leq$1) by week 12 in 81.4% of patients. *Discussion*: All the therapeutic strategies show improvement in vulvar pain, but not all are papers with the same scientific evidence. The best quality studies are those carried out with ospemifene since they are randomized and placebo controlled studies. However, the improvement demonstrated by prasterone, estriol, the combination of estrogens and androgens, as well as the CO_2 laser, although they do not have high-quality studies, should not be ruled out since they promise good results and the user profiles they represent, allow more women to be reached. We propose a therapeutic strategy where the patient expresses her preferences, based on previous experiences and treatments already carried out. In addition, we believe that correctly informing patients about VPA can help a better therapeutic response. More investigation about the vulvar treatments is needed.

Keywords

Vulvar atrophy; Vulvar pain; Sexual health; Genitourinary syndrome of menopause

1. Introduction

Estrogen and androgen deficiencies are considered to be the main pathophysiological mechanisms underlying the genitourinary syndrome of menopause (GSM). The signs and symptoms of the genitourinary syndrome of menopause are well established, and there is extensive knowledge with high scientific evidence about the response that vaginal and urinary tissues present to various treatments. However, this does not usually apply to the vulva in general, or any of its structures in particular, since it is included in the term vulvovaginal [1, 2].

In fact, recently there has been a growing awareness of the importance of the pathology of the vulva, particularly with regard to vulvar pain due to atrophy (hereafter VPA), due to the psychological and sexual repercussions for the affected women [3]. In this regard, it is thus necessary to increase existing anatomical knowledge of the vulva. One of the more important points is to know the distribution of estrogen and androgen receptors. Studies on the labia majora have shown that androgen receptors seem to be particularly abundant in epidermal keratinocytes and in dermal fibroblasts. Androgen receptors are also abundant in the epidermis, especially in the keratinocytes, and in the dermis of the labia minora and vestibule, where they are more numerous than in the vagina [4].

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All of this will help us to establish a more specific diagnosis and the most effective treatments for the vulva. Although there are other causes of vulvar pain, in this review we refer to that caused by atrophy [5, 6].

The objective of this systematic review is to analyze the therapeutic options to improve quality of life of women with VPA. We must make an adequate diagnosis, rule out other pathologies that can also lead to persistent vulvar pain such as vulvodynia and, specifically, suspect those women who do not respond to conventional treatment with local or systemic estrogens.

2. Methods

The study was registered at PROSPERO (registration number CRD42020172102).

2.1 Systematic review strategies

We searched the Scientific Information Web of Knowledge (MEDLINE, Pubmed, Scopus, and Cochrane databases) for all articles (in any language) published in peer-reviewed journals up to December 2020 using the search strategy described in **Supplemental Material 1**. The search criteria were applied to each database and combined with the available database-specific filters. Other publications were identified by manually searching through a reference list of papers highlighted by the search, as well as key reviews. Press reports published in peer-reviewed journals and reports available online prior to publication were also considered.

The PICOS (Population, Intervention exposure, Comparators, Outcomes, Study Design) criteria were developed *a priori* to guide the scope of the review, along with the procedures, selection, and synthesis of the literature search. The selection criteria were as follows: (Population) perimenopausal or postmenopausal women affected by vulvar pain due to atrophy (Interventions) any type of vulvar treatments; (Comparators) placebo or no treatment; (Outcome) primary outcomes: efficacy for treating vulvar pain; (Study Design) clinical studies. Any complete article that met the inclusion criteria was reviewed in detail. Other related papers are for reference purposes only.

We have also reviewed the grey literature, like Spanish guides [7].

To select only the relevant studies, we examined both the titles and abstracts of all citations identified by the literature search. We included all studies that investigated the specific theme of vulvar pain or vulvar symptoms due to atrophy. Duplicate studies, surveys that include perimenopausal women, or those with vulvar pain not caused by atrophy were excluded.

We synthesized the evidence according to PRISMA guidelines [8].

2.2 Outcomes

The primary outcome was the efficacy for treating vulvar pain. The secondary outcome was the security of each treatment.

2.3 Data extraction and risk of bias assessment

NM, LB and SS designed the research study. SS extracted the relevant data on the main characteristics of the eligible studies to obtain a summary, which were narratively described and compared for analysis. LB and NM made a cross-checked data to ensure accuracy. SS analyzed the data.

We assessed the risk of bias of the eligible studies using the Cochrane tool for clinical trials, which takes into account the evaluation of five possible sources of bias (selection, performance, detection, attrition and report bias) [9]. For observational studies, we adapted the ROBINS I tool, focusing on the evaluation of the impact of the confounding variables, selection bias, outcome measures, and attrition [10].

2.4 Data synthesis

We described the synthesis of the evidence following the PRISMA guidelines. We developed a narrative synthesis of the findings and effect estimates from the included studies focusing on the outcomes of interest, to explore the association between the treatment and the outcomes of interest.

We made explicit judgements on the certainty of the evidence for each outcome of interest according to GRADE criteria [11]. Quality will be classified as high, moderate, low or very low, based on several factors (including risk of bias, inaccuracy, inconsistency, lack of directionality and publication bias).

3. Results

This is the first systematic review to evaluate the effectiveness of treatments for vulvar atrophy and VPA by analyzing these separately from treatments for vaginal atrophy and vulvodynia caused by conditions other than atrophy. Our review has identified seven publications involving 779 postmenopausal women with vulvar pain due to atrophy. All the therapeutic strategies used have been effective in treating vulvar atrophy and/or VPA.

Tables 1 (Ref. [12–18]), 2 (Ref. [12–18]), 3 (Ref. [12–18]) display a summary of the main characteristics of the selected studies (study design, population, intervention, objective and main results).

As shown in Fig. 1 (PRISMA Flowchart), the literature search strategy identified 289 articles. Of these, 282 were excluded at various stages of the search. Finally, we systematically reviewed eight studies: one of the articles describes an ad hoc study of a RCT with ospemifene [12], three are prospective cohort studies that also use ospemifene [13–15], one is a pilot study with prasterone [16], another study was conducted in Spain using a combination of estrogens and androgens [17], a study was included that used CO_2 laser surgery [18], and a descriptive study was included with application of 0.005% estriol gel to the vulvar vestibule [19].

Meta-analysis was not possible due to the heterogeneity and small sample size of the included studies.

Table 1. Systematic review of randomized clinical trials and prospective studies for treating vulvar atrophy and vulvar atrophy pain. Summary of findings.

Authors	Study design	Population	Intervention	Objective	Main results
Goldstein *et al.*, 2019 [12]	RCT (NCT02638337)	631 postmenopausal women with moderate-severe VVA. 59.7 ± 6.6 Ospemifene 59.8 ± 7.2 Placebo	Ospemifene 60 mg daily, 12 weeks (n = 313) 2º objective n = 154 Placebo (n = 314) 2º objective n = 150	Primary: efficacy on bothersome symptom Secondary: changes in vulvar-vestibular images	Improvements in vulvoscopy images and symptomatology
Alvisi *et al.*, 2018 [13]	Prospective cohort study	20 postmenopausal women undergoing elective vaginal surgery	Ospemifene 60 mg daily, weeks (n = 11) Control group with no treatment (n = 9)	Primary: changes induced on epithelial thickness, glycogen content proliferation index, collagen content, and type I/III collagen ratio in vulvar and vaginal tissue	Improvement of various morphological and physiological features of both vaginal and vulvar vestibule epithelium
Murina *et al.*, 2018 [14]	Prospective cohort study	55 Postmenopausal women with moderate-severe VVA	Ospemifene 60 mg daily, 60 days	Primary: vulvar vestibule effect Secondary: sensitivity of vestibular nerve fibers	Efficacy in dryness, burning, dyspareunia and vestibular trophic score Efficacy in current perception threshold testing obtained from the vulvar vestibule
Goldstein *et al.*, 2018 [15]	Prospective cohort study	8 Postmenopausal women with Dyspareunia (vulvodynia)	Ospemifene 60 mg daily, 20 weeks	Primary: vulvoscopic changes Secondary: pain changes	Improvements in vulvoscopy images and pain
Goldstein *et al.*, 2020 [16]	Prospective cohort study	16 postmenopausal women with vulvodynia	Prasterone (DHEA) 6.5 mg vaginal insert daily, 20 weeks	Primary: Vestibular changes Secondary: Pain changes	Improvement in vestibular images and pain
Nohales *et al.*, 2020 [17]	Prospective cohort study	29 postmenopausal women with vestibulodynia and VVA symptoms	Estriol 50 mcg + testosterone 2% daily, 12 weeks	Primary: effect on vulvar discomfort symptoms	Differential diagnosis between vulvodynia an VVA (vulvovaginal atrophy) nsufficiently or poorly treated
Murina *et al.*, 2016 [18]	Prospective cohort study	33 patients with vestibular atrophy and vestibulodynia	Three sessions of vestibular Fractional CO_2 laser application	effectiveness and safety	Efficacy and safety

RCT, randomized control trial; DHEA, Dehydroepiandrosterone; VVA, vulvovaginal atrophy.

Most of the studies were considered to be of low to medium quality, primarily because they are not RCTs, or because of the small sample size or high dropout rates (see Tables 2,3).

All studies included heterosexual patients.

Among the described treatments was the use of ospemifene orally at a dose of 60 mg daily for a time period of between 60 days and 20 weeks [12–15]. These studies report preliminary data showing improvements of vulvar and vestibule trophism [20].

Prasterone showed in an open-label prospective survey, improve in the vulvoscopic results and dyspareunia, in women that used vaginal prasterone [16]. The combination of estriol and testosterone propionate 2% for 12 weeks showed an improve of VPA and dyspareunia in a descriptive prospective survey [17]. In both cases, these followed the indications of the international consensus for the use of androgenic preparations [21]. A prospective study with 33 women who presented VPA showed improvements with the use of CO_2 laser treatment [18]. This technology has been introduced in recent years as a therapeutic alternative for GSM and has been shown to improve dyspareunia and sexual function, although studies of the efficacy of laser in GSM are of limited quality due to a lack of randomization, masking, and/or control groups [21]. A retrospective analysis of 79 postmenopausal women presenting vulvar pain who were treated

Table 2. Quality of studies included in the systematic review.

Authors	RCT	Random	Allocation	Blind	Time from menopause	Drop out (%)	Adverse effects
Golsdtein *et al.*, 2019 [12]	Yes	Yes	Yes	Yes	Not described (median age: 60 years)	10.9	26.3% hot flushes
Alvisi *et al.*, 2018 [13]	No	No	No	No	In months: 190 ± 89 (ospemifene) vs 213 ± 72 control	Not described	Not described
Murina *et al.*, 2018 [14]	No	No	No	No	Not described	5.5 (hot flushes)	21% hot flushes
Goldstein *et al.*, 2018 [15]	No	No	No	No	Not described	Not described	Non-serious, the % of hot flushes is not described
Goldstein *et al.*, 2020 [16]	No	No	No	No	Not described	31.25	Not observed
Nohales *et al.*, 2020 [17]	No	No	No	No	12.6 years average (1–41)	6.9 (adverse effects)	20.7% hair growth, 17.2 % irritation/acne
Murina *et al.*, 2016 [18]	No	No	No	No	Not described	32.4	Not observed

RCT, randomized control trial.

Table 3. Certainty evaluation of studies.

Nº of studies	Study design	Risk of bias	Inconsistency	Indirect evidence	Inaccuracy	Other considerations	Certainty
1 [12]	RCT	Low	No	Low	Low	None	⨁⨁⨁◯ MODERATE
6 [13–18]	Prospective cohorts	High	No	High	High	None	⨁◯◯◯ VERY LOW

RCT, randomized control trial.

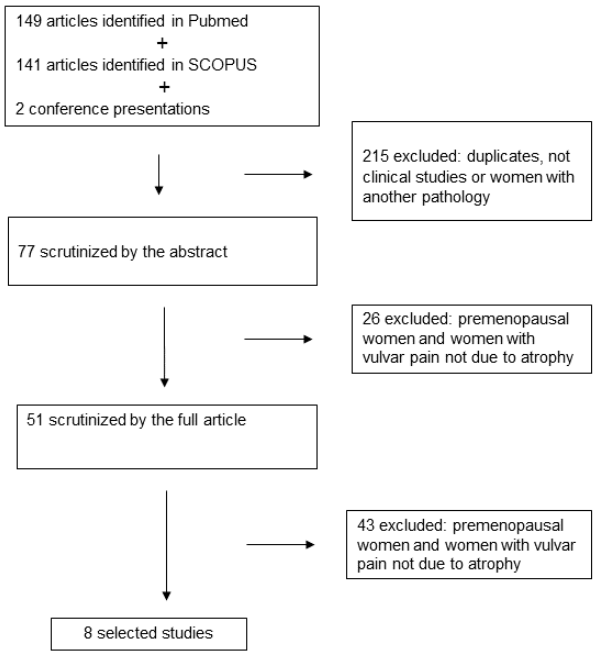

Fig. 1. Prisma Flowchart.

with CO_2 laser or laser plus ospemifene, showed that vestibular dryness was significantly lower in the ospemifene + laser group compared with the laser treatment group (–87% vs –34%, respectively) [18]. An open-label survey was included using for a 12-week treatment period, a fingertip to apply 0.25 g of vaginal gel containing 25 μg of estriol to the vulvar vestibule daily for three weeks and then twice weekly for up to 12 weeks. Dyspareunia improved or was cured (score $\leq$1) by week 12 in 81.4% of patients, the patients also showed a statistically significant reduction in vestibular atrophy and cotton swab test at the end of treatment [19].

Different alternatives can improve vulvar pain associated with atrophy: estriol, ospemifene, prasterone, CO_2 laser, testosterone alone or in combination with topical estrogens. These treatments are effective in improving vaginal symptoms.

We propose a therapeutic strategy where the patient expresses her preferences, based on previous experiences and treatments already carried out. In addition, we believe that correctly informing patients about VPA can help a better therapeutic response [7].

Further research is needed to find which treatment shows a superior effect on the vulva. The answer probably lies in the combination of different treatments.

4. Discussion

VPA is the symptom of GSM that causes the most discomfort and has the greatest impact on general, psychological, and sexual health along with the quality of life of the affected women [22].

In 2015, the International Society for the Study of Vulvovaginal Disease, International Society for the Study of Women's Sexual Health, and International Pelvic Pain Society adopted a new vulvar pain and vulvodynia terminology that acknowledges the complexity of the clinical presentation and pathophysiology involved in vulvar pain and vulvodynia, and incorporates new information derived from evidence-based studies conducted since the last terminology published in 2003 [23].

Based on the important repercussions of VPA for women's sexual life and with the aim of promoting sexual health, health services should ensure diagnostic and therapeutic in-

terventions related to sexuality [2–6]. VPA is caused by the post-menopausal decline of estrogens and androgens [24]. The fundamental differences between this condition and the pain caused by vaginal atrophy lie in the greater involvement of androgens and the effects on the innervation of the vulvar structures. The vestibule is the vulvar structure most affected by hormonal deficiencies and is the one that has the greatest impact on post-menopausal dyspareunia [18].

VPA should be distinguished from other vulvodynia, particularly in women who do not show adequate response to local or systemic menopausal hormone therapy (MHT). The management of vulvar pain due to atrophy is currently a challenge in our daily clinical practice. Relatively few studies have helped to develop tools to improve the pain suffered by these women, and the impact on their quality of life or sexual experience is severe [22].

Most studies have considered the vulva and vagina in general, few studies have considered the vulva independently of the vagina. This is important, because we already know that they are different structures, with different concentrations of receptors and that they may not respond the same to treatments.

A different physiopathology has been observed for the vulva in comparison with the vagina. Thus, as with the vagina, vulvar manifestations of GSM depend on the duration of hypoestrogenism, but also largely on hypoandrogenism. This is due to the fact that estrogens and androgens act on specific receptors which are found in varying quantities and concentrations in the epithelium, stromal tissue, muscle fibers and blood vessels of all vulvar structures [2–6].

There are tools that can help us to make a good diagnosis of vulvar atrophy and VPA, for example the Vulvar Health Index (VuHI) [22]. With this index we can assess the severity of the atrophy as well as the improvement that occurs with the treatments.

The main limitation of this review is the inability to conduct a metanalysis due to the heterogeneity of the reviewed studies. Most studies fail to specifically define the severity of VPA, whilst the criteria used to determine degrees of severity do not include VPA scores or the ability of this condition to alter patterns of sexual functioning. Other important limitations to consider are the small sample size of most of the studies, along with dropout rates and follow-up failures. The studies also differed in terms of outcome measurement, which hindered a pooled analysis. With the exception of one RCT using ospemifene, the quality of the studies was generally low or very low.

Thus, there is a need for high-quality trials with more participants to provide us with better grades of recommendation.

In conclusion, this systematic review reveals specific therapeutic alternatives for the treatment of vulvar atrophy and VPA, including oral ospemifene, local androgens, local estrogens, DHEA and CO_2 laser therapy. Although it would seem that all of these are shown to be effective and safe, the quality of evidence is very low with only a single trial with random, blinded allocation of ospemifene and placebo has been realized.

Abbreviations

VPA, vulvar pain due to atrophy; GSM, Genitourinary syndrome of menopause; MHT, menopausal hormone therapy.

Author contributions

NM, LB and SS designed the research study. SS extracted the relevant data on the main characteristics of the eligible studies to obtain a summary, which were narratively described and compared for analysis. LB and NM made a cross-checked data to ensure accuracy. SS analyzed the data. All authors contributed to editorial changes in the manuscript. All authors read and approved the final manuscript.

Ethics approval and consent to participate

Not applicable.

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Conflict of interest

The authors declare no conflict of interest.

Supplementary material

Supplementary material associated with this article can be found, in the online version, at https://ceog.imrpress.com/EN/10.31083/j.ceog4804128.

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