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Hyaluronic Acid in Postmenopause Vaginal Atrophy: A Systematic Review

Carlos Campagnaro M. dos Santos, MsC,[1] Maria Laura R. Uggioni,[1] Tamy Colonetti, PhD,[1] Laura Colonetti,[1] Antonio José Grande, PhD,[2] and Maria Inês Da Rosa, PhD[1]

ABSTRACT

Background: The decline in postmenopausal serum estrogen concentration results in several changes in the vulvovaginal and vesicourethral areas, resulting in the genitourinary syndrome of menopause, including symptoms such as vaginal atrophy.

Aim: To evaluate the effects of hyaluronic acid in vaginal atrophy.

Methods: A search strategy was developed using the following terms: "Hyaluronic Acid vaginal gel," "vaginal estrogens," "Vaginitis, Atrophic," and "Postmenopause." This strategy was used in major databases such as MEDLINE, EMBASE, Scopus, Cochrane library, Web of Science, Virtual Health Library (BVS), Congress Abstracts, and Gray Literature (Google Scholar and British Library) for studies published until June 2020.

Outcomes: A systematic review was carried out to assess the results of atrophic vaginitis/vaginal dryness, dyspareunia, vaginal pH, and cell maturation of the studies found by the search strategy.

Results: A total of 833 studies were identified, 528 studies were directed for reading titles and abstracts, and 515 were excluded for not meeting the selection criteria. A total of 13 studies were selected for reading the full text. 5 primary studies involving 335 women met the criteria and were included. The studies were published between the years 2011 and 2017. It was not possible to perform meta-analysis owing to the substantial heterogeneity present in the studies. The results presented suggest that treatment with hyaluronic acid, when compared with the use of estrogens, does not present a significant difference in the results obtained for the outcomes: epithelial atrophy, vaginal pH, dyspareunia, and cell maturation.

Clinical Translation: Hyaluronic acid appears to be an alternative to non-hormonal treatments for the signs of vaginal atrophy and dyspareunia.

Strengths & Limitations: The analysis of the studies in this systemic review suggests that hyaluronic acid has efficacy similar to vaginal estrogens for the treatment of the signs of vaginal atrophy and dyspareunia. However, the included studies measured the data in different ways, causing the performance of meta-analysis to be impaired.

Conclusion: The comparisons presented suggest that hyaluronic acid has a profile of efficacy, safety, and tolerability comparable with vaginal estrogens for the treatment of symptoms of vaginal atrophy. It is a possible alternative for women who cannot use hormonal treatment. **dos Santos CCM, Uggioni MLR, Colonetti T, et al. Hyaluronic Acid in Postmenopause Vaginal Atrophy: A Systematic Review. J Sex Med 2020;XX:XXX–XXX.**

Key Words: Postmenopause; Hyaluronic Acid; Vaginal Atrophy; Systematic Review

INTRODUCTION

Menopause is a natural phenomenon, defined as absence of menstruation over a period of 12 months, typically occurs between the ages of 49 and 52 years, as a result of the complex hormonal changes that accompany the reduction in ovarian follicles.[1,2]

The decline in circulating estrogen induces symptoms that affect women's well-being and health, causing them insomnia,

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night sweats, mood disorders, reduced bone mass, hot flushes, and vaginal dryness.[3]

The decline in postmenopausal serum estrogen concentration results in several changes in the vulvovaginal and vesicourethral areas, resulting in the genitourinary syndrome of menopause (GSM).[4] Changes in hormone levels lead to loss of cell proliferation in the vaginal squamous epithelium. This causes connective tissue damage, which promotes inflammatory infiltration of leukocytes and macrophages, leading to causing further damage to the blood vessels that permeate the affected tissue, reducing vascular supply, as well as the production of vaginal fluids.[5] Estrogen maintains the thickness of the scaly vaginal epithelium in multilayers, conveying its normal coloration, roughness, and moisture. With lower levels of estrogen, connective tissue proliferation increases, elastin becomes fragmented, and collagen is subject to hyalinization.[6,7] The GSM main symptoms are vulvovaginal dryness; decreased vaginal lubrication during sexual activity; dyspareunia, including vulvar or vaginal pain; vulvar or vaginal bleeding; decreased arousal, orgasm or sexual desire; vulvovaginal burning, irritation or itching; vaginal discharge; and urinary tract symptoms, such as altered urinary frequency, urethral discomfort, recurrent urinary tract infections, among others.[8,9]

Because it is essential for maintaining the mechanical integrity of tissues, hyaluronic acid (HA) presents itself as an effective alternative for GSM treatments, redirecting to the fact that its clinical manifestations cause serious tissue alterations.[10] HA can adhere to the vaginal wall and bind to a large amount of water, releasing these molecules into the tissue, causing it to be hydrated. This hydration gives through the migration of water and electrolytes into the vaginal dermal vasculature, causing vasodilation and increasing the blood supply to the mucosa. Gel adhesion remains for up to 3 days until the peeling of epithelial cells occurs.[11–13] HA may be a good alternative for women who cannot use exogenous estrogens or who seek more efficient nonhormonal treatments.[14]

This study aimed to evaluate the effects of HA for the improvement of vaginal atrophy compared with the use of vaginal estrogen (estriol) in gel or another type of vaginal hormone or placebo.

MATERIALS AND METHODS

We performed a systematic review following the PRISMA statement guidelines.[15] The review protocol was registered at PROSPERO (International prospective register of systemic reviews, http://www.crd.york.ac.uk/prospero; CRD42019145639).

Search Strategy

A search strategy was developed using the following terms: "Hyaluronic Acid," "Hyaluronic Acid vaginal gel," "Vaginal estrogens," "Vaginitis, Atrophic," and "Postmenopause", as keywords that were queried in Medical Subject Headings (ie, MeSH and EMTREE) to query for possible synonyms A sensitive filter was created by combining these different synonyms to identify studies using the Boolean operators "OR" and "AND," such as MEDLINE, EMBASE, Scopus, Cochrane library, Web of Science, Virtual Health Library (BVS), Congress Abstracts and Gray Literature (Google Scholar and British Library) for studies published until June 2020. The search was limited to human studies and had no language restrictions. Reference lists of all primary studies were reviewed to identify additional relevant citations.

Box 1. Inclusion criteriaP (Participants): postmenopausal/climacteric women;I (Interventions): hyaluronic acid use;C (Comparisons): use of vaginal estrogens or other hormones or placebo;O (Outcomes): atrophic vaginitis/vaginal dryness, dyspareunia, vaginal pH, and cell maturation;S (Study type): Randomized controlled trials (RCTs)

Study Selection

2 reviews authors independently assessed all studies identified from the database searches by screening titles and abstracts using the review management Website Covidence (http://www.covidence.org). We separated potential studies, which presented the inclusion criteria for full-text reading (Box 1). A third review author resolved any disagreements in the selection of included studies.

Studies that included postmenopausal or climacteric women who used HA, compared with women who were in the same condition but who used vaginal estrogen (estriol) gel or who used of another type of hormone via vaginal or placebo, whose main result was to evaluate the improvement of atrophic vaginitis (vaginal dryness).

Studies that included female smokers, those using anticoagulants (such as heparin), topical or injectable hormone, vaginal infection, history of cancer (such as the breast), thrombotic disease, hypertension, or diabetes, as well as participants, were excluded. As also women who used intravaginal medication in the last 30 days before the survey.

Data Extraction

2 investigators independently extracted data from the primary studies. The final decision to include or exclude studies in this systematic review was made concerning to the study project registered in PROSPERO. Any disagreements about the inclusion or exclusion of studies were resolved by consensus. If there was no consensus, a third reviewer selected the conflicting articles. The data extraction form consisted of author, year, country, patients, methods, intervention information, and results from each included study.

Study Quality Assessment

All included studies were assessed for their methodological quality. The Cochrane Collaboration's risk of bias tool was used

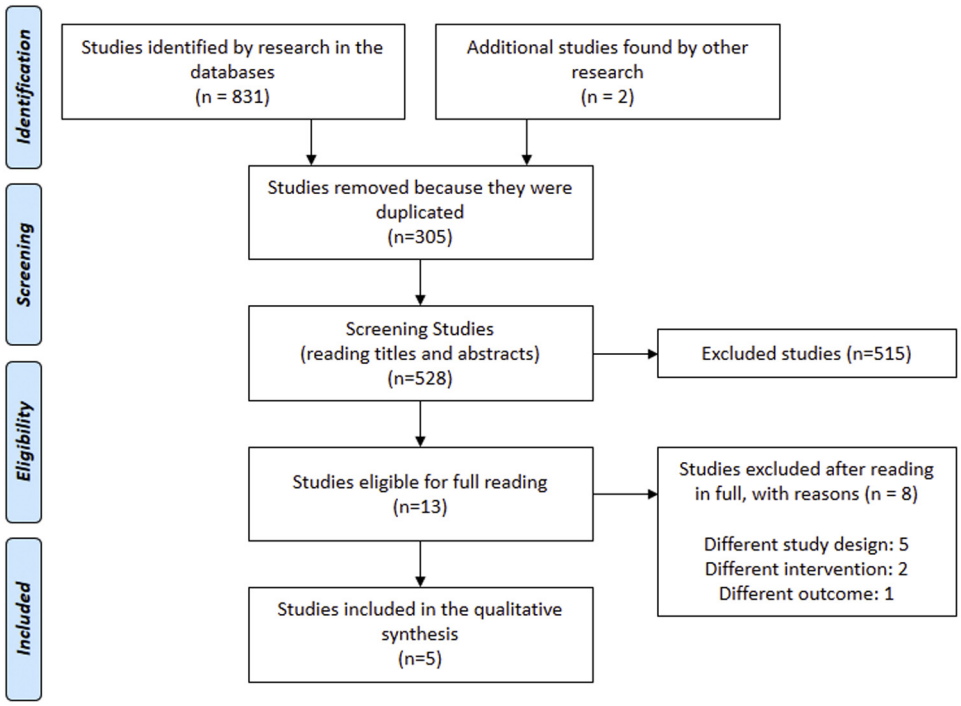

Figure 1. Flow diagram of included studies. Figure 1 is available in color online at www.jsm.jsexmed.org.

(RevMan 5.4). The criteria consist of 7 items: random sequence generation, allocation concealment, blinding of participants and researchers, blinding of outcome assessment, incomplete outcome data, selective outcome reporting, and other sources of bias.

Data Synthesis and Statistical Analysis

It was not possible to perform meta-analysis owing to the substantial heterogeneity present in the studies included in this review. When heterogeneity presents values greater than 75%, one can question the validity of combining the presented results, and it is not recommended to be performed. The analyses of the included studies, concerning to patient populations, interventions, comparators, outcome measures, and study designs, were carried out descriptively in the results and the discussion.

RESULTS

The search identified a total of 833 studies; 305 studies were duplicates. A total of 528 studies were screened for titles and abstracts. Of these, 515 were excluded for not meeting criteria for study design; population studied; intervention; or outcomes because they were protocol study. A total of 13 studies were analyzed in full text. From these studies, 8 full articles were excluded because they were protocol studies. In the end, 5 primary studies met the criteria and were included in the qualitative synthesis. The study selection process is summarized in Figure 1.

The 5 included studies[14,16–19] were published between the years 2011 and 2017, involving a total of 335 women in the menopause or postmenopause period, aged between 45 and 70 years. The studies evaluated as the main outcome of the use of HA was to improve the symptoms of vaginal atrophy. Improvements in vaginal pH, dyspareunia, and cell maturation were also evaluated. The assessment of vaginal atrophy was performed using the visual analog scale, where the severity of symptoms was measured before and after treatment, the scales evaluated the symptoms from 0 to 10 (0 = asymptomatic; 10 = severe symptom). The improvement of dyspareunia was assessed by means of the quality of life questionnaires answered by the women who participated in the study, the pH was measured by an indicator band inserted in the vagina, while the vaginal maturation was measured by means of cytologic examinations performed before and after the intervention.

The general characteristics of the included studies are described in Table 1.

Risk of Bias

For the evaluation of random sequence generation, only the study by Duque-estrada et al (2017)[19] did not present information on this selection bias, being judged as high risk of bias. As for the assessment of allocation concealment, the studies by Ekin et al (2010)[16] and Grimaldi et al (2012)[14] did not present all the information clear, resulting in an unclear risk of bias, and the study by Duque-Estrada et al (2017)[19] did not present enough information, resulting in a high risk of bias. As for the blinding of participants and professionals and the blinding of the evaluation of outcomes, the studies by Chen et al (2013),[17] Jokar et al (2016),[18] and Duque-Estrada et al (2017)[19] did not present information about they were classified as high risk of bias,

Table 1. General characteristics of the included studies

Author, y (design; country)	Age (mean ± SD)	n total (n per group)	Time of menopause (mean ± SD)	Menopause age (mean ± SD)	Description of HA	Description of estrogen or placebo	Follow-up
Ekin et al, 2010[16] (RCT; Turkey)	HA: 52.95 ± 4.80	42 (HA: 21; Estrogen: 21)	HA: 4.67 ± 3.13 y	-	HA sodium salt 5 mg, vaginally in tablets, once a d for 8 wk	Estradiol tablets via vaginal (Vagifem), 25 mg; 1x/d for 14 d and then 2x/wk	8 wk
	Estrogen: 51.86 ± 4.35		Estrogen: 5.29 ± 3.03 y				
Chen et al, 2013[17] (RCT; China)	HA: 54.05 ± 4.27	133 (HA: 67; Estrogen: 66)	HA: 4.44 ± 3.71 years	-	Intravaginal gel with HA, 5 g every 3 d for 3 wk (10 doses)	Estriol in vaginal cream; 0.5 g for 3 d (10 doses)	30 d
	Estrogen: 54.41 ± 4.60		Estrogen: 5.58 ± 5.45 years				
Jokar et al, 2016[18] (RCT; Iran)	HA: 56.4 ± 5.47	56 (HA: 28; Estrogen: 28)	-	HA: 47.71 ± 5.26 y	Vaginal cream with HA, 5 mg/d for 8 wk	Conjugated estrogen vaginal cream (Premarin); 0.625 mg/d for 14 d + 2x/d for 6 wk	8 wk
	Estrogen: 51.92 ± 4.31			Estrogen: 46.2 ± 4.16 y			
Duque-Estrada et al, 2017[19] (RCT; Brazil)	HA: 56.7 ± 5.7	68 (HA:35; Estrogen: 33)	-	-	Vaginal cream with HA (Lubrinat), once a d, twice a wk for 3 consecutive wk	Estradiol in vaginal cream (Colpotrofine), for a period of 3 wk, every d	3 wk
	Estrogen: 55.2 ± 5.5						
Grimaldi et al, 2012[14] (RCT; Italy)	Total sample: 57.4 ± 13.7	36 (HA:18; Estrogen: 18)	-	-	Vaginal gel with HA (Fillergyn), tea tree oil, methylsulfonylmethane, gelling agents with bioadhesive capacity, preservatives and water. Each application consisted of about 2.5 mL, the use was performed every d for 4 consecutive wk	Placebo, similar to the vaginal gel of the intervention group, composed of tea tree oil, methylsulfonylmethane. Each application consisted of about 2.5 mL, use was made every day for 4 consecutive wk.	30 d

HA = hyaluronic acid; RCT = randomized clinical trial.

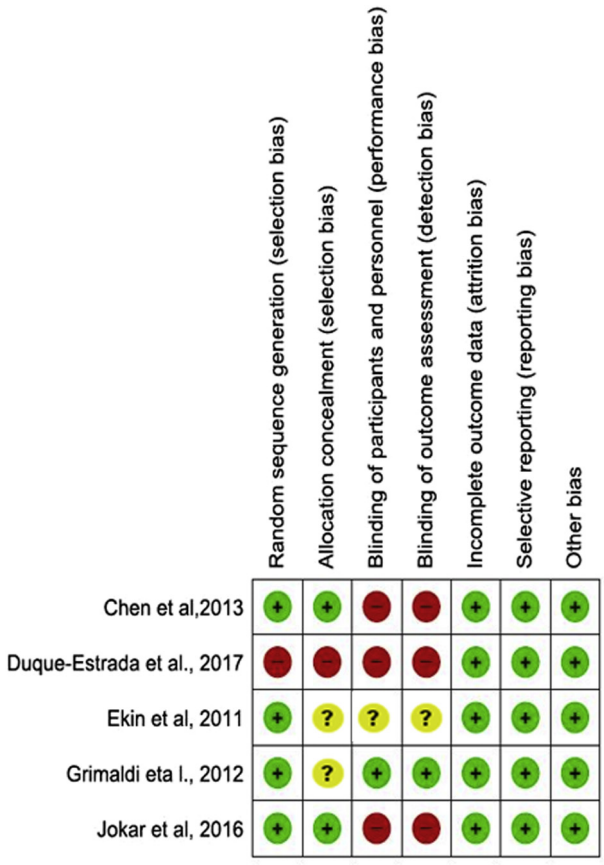

Figure 2. Risk of bias assessment. Figure 2 is available in color online at www.jsm.jsexmed.org.

whereas the study by Ekin et al (2010)[16] was classified as unclear risk of bias. For items about incomplete results, selective reports, and other biases, all studies had a low risk of bias (Figure 2).

Primary Outcome

Improved Vaginal Atrophy

The study by Ekin et al (2010)[16] compared treatments for vaginal epithelial atrophy. In which, before treatment, the group that received the estrogenic formulation had 1 woman (4.8%) with mild epithelial atrophy and 20 women (95.2%) with moderate epithelial atrophy. The group that used the formulation with HA, before the treatment, had 16 women (76.2%) with moderate epithelial atrophy and 5 women (23.8%) with severe epithelial atrophy. At the end of treatment, the group that received estrogen was composed of 3 women (14.3%) without epithelial atrophy and 18 women (85.7%) with mild epithelial atrophy. The group that received HA, at the end of treatment, had 2 women (9.5%) without epithelial atrophy, 18 women (85.7%) with mild epithelial atrophy, and 1 woman (4.8%) with moderate epithelial atrophy. For this analysis, the intragroup comparison showed significant differences, after both treatments in the vaginal epithelial atrophy outcome ($P < .001$).

In the study by Chen et al (2013),[17] the results for vaginal atrophy were demonstrated by means ± SD of the percentage of women who did not have vaginal atrophy, at the beginning of the study, in the group that used HA (group A), the value was 49.17 ± 23.90%, whereas for the group that used the estrogenic formulation (group B), it was 53.53 ± 27.67%. At the end of the study, the values found for group A was 84.44 ± 20.60%, whereas group B was 89.42 ± 17.21%. There was no significant difference between groups ($P = .3082$).

In the study by Duque-Estrada et al,[19] the results for vaginal atrophy were demonstrated through analyses that compared the treatment before and after, through the perception of dryness of the patients themselves. When starting the research, the group that used HA, the percentage of women who had a lot of dryness was 54.3%; with moderate dryness was 42.9%; with little dryness, the value was 2.9%; and without dryness, it was 0%. For the group that used estrogen, the percentage of women who had a lot of dryness was 57.6%; with moderate dryness was 42.4%; with little dryness, the value was 0%; and without dryness, it was 0%. The score at the end of the time of use was represented by the sum of the categories that represented a mild decrease, a moderate decrease, and a lot of decreases. For the group that used HA, the sum represented the value of 97 ± 1, and the group that used estrogen, the value was 100, the comparison between the 2 groups did not show any significant difference ($P = .786$).

In the study by Grimaldi et al (2012),[14] both treatments significantly reduced vaginal atrophy ($P < .001$), with HA being more effective than a placebo. Consequently, vaginal dryness was also reduced ($P < .001$), with the mean ± SD of the vaginal dryness visual analog scale, which ranges from 0 (without symptoms) to 10 (maximum symptom), before the start of the study for HA was MD 7.46 (SD 0.23) and for the placebo group, it was MD 7.14 (SD 0.29). At the end of the study, the mean ± SD for the AH group was 3.73 ± 0.57 and for the placebo group MD 4.88 (SD 0.36). However, no statistically significant difference was observed when comparing the 2 groups. The results demonstrate that in the placebo group, a large majority of low or moderate atrophy scores of 66.6% and 33.3% of the scores were assessed as good or excellent. In the group that used HA gel, the analysis showed that the score of the evaluation of good or excellent was 72.2% compared with 27.7% of the evaluation of poor or moderate.

In the study by Jokar et al (2016),[18] the analysis for vaginal atrophy was not performed independently of the analysis of symptoms derived from vaginal atrophy. Therefore, there is no specific description of this study for this outcome.

Secondary Outcome

Vaginal pH

In the study by Ekin et al (2010),[16] vaginal pH decreased significantly in both groups after treatment ($P < .01$), with the most prominent decrease in the group that received the estrogenic formulation. In the group that received estrogen, 19

women (90.5%) had a vaginal pH of 5.5−6.49 and 2 women (9.5%) had a vaginal pH higher than 6.49. In the end, this group had 3 women (14.3%) with a pH less than 5.0 (considered ideal) and 18 women had a pH between 5.0 and 5.49 ($P < .001$). While the group that used HA had 15 women (71.4%) with a pH between 5.5 and 6.49 and 6 women (28.6%) with a pH higher than 6.49 before treatment. At the end, this group had 15 women (71.4%) with vaginal pH between 5.0 and 5.49 and 6 women (28.6%) with pH between 5.5 and 6.49 ($P < .001$).

In the study by Chen et al (2013),[17] vaginal pH also shows improvement in both groups that used the intervention. The results of this study for vaginal pH were described as mean ± SD at the beginning of the study, but at the end of the study, the PD was not described. Group A, which used the formulation with AH, obtained a mean ± SD of 5.63 ± 1.04 when starting the study, whereas group B, which used the formulation with estrogen, obtained a mean ± SD of 5.61 ± 0.98 when starting the study. At the end of the study, group A obtained an average of 5.30 ($P < .05$) and group B obtained an average of 4.87 ($P < .05$).

In the study by Jokar et al (2016),[18] vaginal pH decreased significantly in both groups after treatment ($P < .01$). Before treatment, the group receiving estrogen had 13 women (46.4%) with a vaginal pH higher than 6.49, 3 women (10.7%) with a vaginal pH between 5.5 and 6.49, 1 woman (3.6%) with a pH between 5.0 and 5.49, and 11 women (39.3%) with a pH less than 5.0. In the end, this group had 4 women (14.3%) with a vaginal pH higher than 6.49, 6 women (21.4%) with a vaginal pH between 5.5 and 6.49, 6 women (21.4%) with pH between 5.0 and 5.49, and 12 women (42.9%) with pH less than 5.0. The group that used HA, had before the treatment, 10 women (35.7%) with a vaginal pH higher than 6.49, 3 women (10.7%) with a vaginal pH between 5.5 and 6.49, 4 women (14.3%) with a pH between 5.0 and 5.49, and 11 women (39.3%) with a pH lower than 5.0. At the end, the group that used HA had 2 women (7.1%) with vaginal pH higher than 6.49, 2 women (7.1%) with vaginal pH between 5.5 and 6.49, 7 women (25.1%) with a pH between 5.0 and 5.49, and 17 women (60.7%) with a pH less than 5.0. This shows that the population with a pH less than 5.0 was more prominent in the group that used HA. There was a statistical difference when comparing the improvement of the groups before and after the treatment ($P < .001$); however, the value of comparison between the 2 groups had no significant difference ($P = .463$).

The studies by Grimaldi et al (2012)[14] and Duque-Estrada et al (2017)[19] did not perform an analysis of vaginal pH. Therefore, there is no description of these studies for such an outcome.

Dyspareunia

In the study by Ekin et al (2010),[16] the results found by the authors show that both groups showed improvement in the assessed symptoms; however, the group that received estradiol had a significant improvement in the dyspareunia outcome. Before the intervention, the group that received the estrogenic formulation had 12 women (57.2%) with moderate dyspareunia and 9 women (42.8%) with severe dyspareunia. The group that received HA had 1 woman (4.8%) with mild dyspareunia, 13 women (61.9%) with moderate dyspareunia, and 7 (33.3%) with severe dyspareunia. After the intervention, it was observed in the group that used estrogen had 9 women (42.8%) without symptoms of dyspareunia, and 12 women (57.3%) with mild symptoms, whereas the group that used HA had 3 women (14.2) without symptoms of dyspareunia, 16 women (76.1%) with mild symptoms, and 2 women (9.5%) with moderate dyspareunia.

The results in the study by Chen et al (2013)[17] for the dyspareunia outcome were described as mean ± SD of the percentage of patients who reported pain improvement at the time of sexual intercourse. Group A, which used the formulation with AH, obtained a mean ± SD of 24.33 ± 31.78% of women who did not report the presence of dyspareunia when starting the study, whereas group B, which used the formulation with estrogen, obtained a mean ± SD of 26.64 ± 35.62% of women who did not report dyspareunia when starting the study. At the end of the study, group A obtained a mean ± SD of 56.96 ± 41.47% of women who did not report dyspareunia and group B obtained a mean ± SD of 62.33 ± 43.80% of women who did not report dyspareunia. reported dyspareunia. The comparison between groups showed no statistically significant difference ($P = .2551$).

In the study by Jokar et al (2016),[18] the analysis for dyspareunia was not performed independent of the analysis of the symptoms derived from vaginal atrophy. Therefore, there is no specific description of this study for this outcome. The studies by Grimaldi et al (2012)[14] and Duque-Estrada et al (2017)[19] did not analyze dyspareunia.

Cell Maturation

In the study by Ekin et al (2010),[16] vaginal maturation values also improved significantly in both groups after 8 weeks of treatment ($P < .001$), while the average maturation value was significantly higher in the group that received the estrogenic formulation than in the group that received the formulation with HA. The group that received estrogen had a mean ± SD of 4.38 ± 0.80 before the intervention and 71.19 ± 12.96 after the intervention ($P < .001$), wheraes the group that received HA had a mean ± SD of 4.14 ± 0.85 before the intervention and 44.40 ± 9.32 after the intervention ($P < .001$).

In the study by Jokar et al (2016),[18] cell maturation was assessed by performing a vaginal and cervical Pap smear, the rate and type of cells (parabasal, medial, and superficial) were determined. The degree of maturation was made as per the following index: absence of estrogenic effect (absent) = 0−25; low (mild) estrogenic effect = 26−49; moderate (moderate) estrogenic effect = 50−75; and high (severe) estrogenic effect = 76−100.

Thus, the group that received Premarin before the study had 10 women (35.7%) with no maturation, 14 women (50%) with mild maturation, 4 women (14.3%) with moderate maturation, and no women with severe maturation (considered ideal for this study). After using the estrogenic formulation, the group did not have women with no maturation or with mild maturation, 25 women (89.3%) with moderate maturation, and 3 women (10.7%) with severe maturation. The group that used HA, before its application, had 3 women (10.7%) with no maturation, 25 women with mild maturation, and no women in the groups of moderate and severe maturation. At the end of the study, this group did not present women with no maturation, 1 woman (3.6%) with mild maturation, 25 women (89.3%) with moderate maturation, and 2 women (7.1%) with severe maturation. The results for vaginal cell maturation indicated that there was an improvement in maturity in both groups ($P < .01$). The comparison between the groups showed a significant difference ($P = .018$).

In studies by Grimaldi et al (2012),[14] Chen et al (2013),[17] and Duque-Estrada et al (2017),[19] no analyses of cell maturation were performed. Therefore, there is no description of these studies for such an outcome.

The measured outcomes analyzed in this study are summarized in Table 2.

DISCUSSION

This review aimed to assess the effects of HA for the treatment of vaginal atrophy compared to the use of vaginal estrogen gel or another hormone or placebo vaginally. Vaginal atrophy is addressed in all included studies, but the studies also evaluate other vaginal parameters, which fit as symptoms derived from menopause genitourinary syndrome (GSM). The definition of GSM comprises genital symptoms (dryness, burning, itching, irritation, bleeding), sexual symptoms (dyspareunia and other sexual dysfunctions), and urinary symptoms (dysuria, frequency, urgency, recurrent urinary infections).[20] For this, the improvement of epithelial atrophy, vaginal pH, dyspareunia, and cell maturation was evaluated. The results presented suggest that HA treatment, when compared with the use of vaginal estrogens, does not present a significant difference from the results obtained for the evaluated outcomes. The studies included in this review include parameters related to clinical symptoms, such as pH, cell maturation, and epithelial atrophy, which are indicators of vaginal health as a whole. The main clinical symptom assessed was dyspareunia, addressed in only 2 studies.

The study by García et al (2019)[21] evaluated the effectiveness of nonhormonal products in the treatment of women with vaginal atrophy. A total of 98 women were included with a mean age of 54.6 years. Of the 98 women, 63.3% were treated with HA associated with Asian Centella cell lysate, whereas the remainder (36.7%) were treated with polycarbophil-associated glycerin. The rate of vaginal maturation improved significantly after 3 months of treatment with HA and *Centella asiatica*, with parabasal cell count decreasing (−8.4%; 95% CI, −10.6 to −6.2; $P = .001$), and the cell count of the intermediate region increased (3.6%; 95% CI 2.0−2.3; $P = .001$), as did the surface cell count (4.8%; 95% CI 3.8%−5.7; $P = .001$), this indicates increased cell maturation, which is expected when treating vaginal atrophy. In addition, all symptoms and signs of vaginal atrophy improved after 3 months with the use of HA and *C. asiatica*. For glycerin and polycarbophil treatment, there was no significant change in vaginal maturation index or symptoms and signs after 3 months of follow-up.

Regarding estrogen treatment, a systematic review conducted in 2016 by Lethaby et al[22] compared various local estrogen formulations for vaginal atrophy in postmenopausal women. Their results showed no significant differences in efficacy between the various intravaginal estrogen preparations when compared with each other. However, evidence of low quality as per the GRADE assessment has been reported owing to a high level of uncertainty associated with the estimated effect in the included studies that intravaginal estrogen preparations improve symptoms of vaginal atrophy compared with placebo (odds ratio = 12.47; 95% CI: 9.81−15.84; 2 randomized controlled trials included; n = 1,638; $I^2 = 83\%$). Evidences classified as low quality also demonstrated that cream estrogen may be associated with an increase in endometrial thickness compared with estrogen ring, this may have been because of higher cream doses (odds ratio = 0.36; 95% CI: 0.14−0.94, 2 included randomized controlled trials, n = 273; $I^2 = 0\%$). However, there was no difference in adverse events between the various estrogen preparations compared with each other or with placebo.

In a study by Karaosmanoglu et al (2011),[23] HA treatment was evaluated before and after in a group of 30 postmenopausal women aged 51−62 years. Intravaginal HA doses of 5 mg were used every other day for 2 weeks. After this period, the same dose was administered at the same time twice a week for 90 days. Women were asked about symptoms of atrophic vaginitis before and after 90 days of treatment. After treatment, the participants were subdivided into 4 groups as per their clinical outcome (worsening; unchanged; improved; asymptomatic or healing). Before treatment and after 90 days, biopsies were performed on the right side of the vaginal wall so that histopathologic changes could be observed. The study showed that the severity of all symptoms decreased after HA treatment, and symptoms of dyspareunia and dryness improved by 52.6% and 67.9%, respectively, showing benefits of treatment.

No treatment-related adverse events were observed, and the course of treatment was highly acceptable by the participants. This combination of substances in a single device can be considered a good alternative treatment and is effective and safe for treating GSM symptoms in postmenopausal women, especially when hormone treatment is not recommended. These results are in line with what is presented in all included studies, considering that although our results may be ineffective

Table 2. Description of the outcomes analyzed in the included studies

Author, y (country)	Type of intervention	Symptoms derived from vaginal atrophy		Vaginal pH		Dyspareunia		Cell maturation		Conclusions
		Before	After	Before	After	Before	After	Before	After	
Ekin et al, 2010[16] (Turkey)	HA	Mean ± SD: 9.24 ± 1.92	Mean ± SD: 3.86 ± 1.39 (**$P = .001$**)	pH < 5: 0 (0%); pH de 5.0 −5.49: 0 (0%)	pH < 5: 0 (0%); pH de 5.0 −5.49: 15 (71.4%) (**$P = .001$**)	Absent: 0 (0%); Mild: 1 (4.8%)	Absent: 3 (14.2%); Leve: 16 (76.1%)	Mean ± SD: 4.14 ± 0.85	Mean ± SD: 44.40 ± 9.32 (**$P = 0.01$**)	Both treatments provided relief from vaginal symptoms, improved epithelial atrophy, decreased vaginal pH and increased vaginal epithelial maturation. However, these improvements were greater in the group that received estriol.
	Estrogen	Mean ± SD: 3.71 ± 1.93	Mean ± SD: 2.67 ± 1.53 (**$P = .001$**)	pH < 5: 0 (0%); pH de 5.0 −5.49: 0 (0%)	pH < 5: 3 (14.3%); pH de 5.0 −5.49: 18 (85.7%) (**$P = .001$**)	Absent: 0 (0%); Mild: 0 (0%)	Absent: 9 (42.8%); Mild: 12 (57.3%)	Mean ± SD: 4.38 ± 0.80	Mean ± SD: 71.19 ± 12.96 (**$P = .001$**)	
Chen et al, 2013[17] (China)	HA	-	-	Mean ± SD: 5.63 ± 1.04	Mean: 5.30 (**$P < .05$**)	Mean ± SD: 24.33 ± 31.78	Mean ± SD: 56.96 ± 41.47 (**$P = .2551$**)	-	-	Both treatments were effective for vaginal dryness. However, estriol was more efficient when compared to HA.
	Estrogen	-	-	Mean ± SD: 5.61 ± 0.98	Mean: 4.87 (**$P < .05$**)	Mean ± SD: 26.64 ± 35.62	Mean ± SD: 62.33 ± 43.80 (**$P = .2551$**)	-	-	
Jokar et al, 2016[18] (Iran)	HA	Mean ± SD: 5.92 ± 2.15	Mean ± SD: 2.60 ± 1.39 (**$P < .001$**)	pH < 5: 11 (39.3%); pH 5.0–5.49: 4 (14.3%)	pH < 5: 17 (60.7%); pH 5.0–5.49: 7 (25.1%) (**$P = .463$**)	Mean ± SD: 5.8 ± 2.28	Mean ± SD: 4.10 ± 1.66 (**$P < .001$**)	Absent: 3 (10.7%); Mild: 25 (89.3%)	Absent: 0 (0%); Mild: 1 (3.6%) (**$P < .001$**)	Both treatments improve the symptoms of vaginal atrophy. However, HA was more effective.
	Estrogen	Mean ± SD: 5.80 ± 2.28	Mean ± SD: 4.10 ± 1.66 (**$P < .001$**)	pH < 5: 11 (39.3%); pH 5.0–5.49: 1 (3.6%)	pH < 5: 12 (42.9%); pH 5.0–5.49: 6 (21.4%) (**$P = .463$**)	Mean ± SD: 5.92 ± 2.15	Mean ± SD: 2.60 ± 1.39 (**$P < .001$**)	Absent: 10 (35.7%); Mild: 14 (50%);	Absent: 0 (0%); Mild: 0 (0%) (**$P < .001$**)	

(continued)

Table 2. Continued

Author, y (country)	Type of intervention	Symptoms derived from vaginal atrophy		Vaginal pH		Dyspareunia		Cell maturation		Conclusions
		Before	After	Before	After	Before	After	Before	After	
Duque-Estrada et al, 2017[19] (Brazil)	HA	A lot of dryness: 54.3%; Moderate dryness: 42.9%; Little dryness: 2.9%; No dryness: 0%	Sum of slight decrease, moderate decrease and much decrease: 97 ± 1 (**$P = .786$**)	-	-	-	-	-	-	Similar results between the groups using HA and estrogen for vaginal application, support the use of vaginal HA gel (Lubrinat) in the initial approach to symptoms of vaginal dryness.
	Estrogen	A lot of dryness: 57.6%; Moderate dryness: 42.4%; Little dryness: 0%; No dryness: 0%	Sum of slight decrease, moderate decrease and much decrease: 100 (**$P = .786$**)	-	-	-	-	-	-	
Grimaldi et al, 2012[14] (Italy)	HA	Mean ± SD: 7.46 ± 0.23	Mean ± SD: 3.73 ± 0.57 ($P < .001$)	-	-	-	-	-	-	High molecular weight HA can be effective in subjective and objective improvement of postmenopausal vaginal atrophy, providing good adherence. No adverse events occurred during the entire study period.
	Placebo	Mean ± SD: 7.14 ± 0.29	Mean ± SD: 4.88 ± 0.36 ($P < .001$)	-	-	-	-	-	-	

HA = hyaluronic acid.

compared with vaginal estrogen treatment, the studies provided individual evidence of the efficacy of HA use. Although effective, hormone treatment still requires close vigilance regarding the high risk for women with endometrial cancer and breast cancer. This risk is further increased when prolonged use is made. The North American Menopause Society (2007)[24] considers treatments with non-hormonal vaginal lubricants and moisturizers first-rate. For this reason, the available non-hormonal options are considered of utmost importance for relieving discomfort, especially during sexual intercourse. Because the vagina loses the ability to retain collagen and water at menopause, HA is used as an adjunct to the repair processes of atrophic and dystrophic vaginal mucosal states, dryness, and estrogen deficiency.[25,26] Thus, HA is suitable for the treatment of symptoms of vaginal dryness, regardless of the cause. Compared with estrogenic derivatives such as estriol, HA has better applicability characteristics, no side effects that are similar to those of hormonal treatment, and greater safety.[27]

In general, the results presented in this review suggest that the treatment with HA compared with the use of vaginal estrogens does not present a significant difference from the results obtained for all outcomes, thus it can be stated that both treatments have similar efficacy. Although some studies have shown that HA is inferior to the use of vaginal estrogens, the results presented in this article show their HA as a good substitute for women suffering from menopausal symptoms because when comparing treatment — hormonal to placebo — realized that there is a significant increase in positive effects, showing the effectiveness of treatment with HA. Thus, the various comparisons presented suggest that HA has an efficacy, safety, and tolerability profile comparable with estrogens for the treatment of GSM symptoms, being a possible alternative to women who cannot use hormone treatment.

It is important to highlight that this systematic review has limitations, as the included studies measured the data in different ways, causing the performance of meta-analyzes to be impaired, owing to both the lack of standardization of the analyzes and the high heterogeneity found, being greater than 95%. Besides, few studies have been found in the literature, also the included studies that assessed the use of AH, are older, the most recent being in the year 2017. Another important point to be mentioned is the lack of sufficient information in primary studies, for this reason, no conclusive findings can be reported, but the information provided is useful for women who want alternatives to hormonal treatment for GSM. The lack of standardization of the formulations and concentrations used to assess the effectiveness of HA is also a limitation to be presented because the differences in the method of application and each formulation used make it difficult to carry out analyses. For a better evaluation of the product, a randomized and advanced study is needed, which recruits women who have not been successful in water-based lubricant therapy in their GSM management. This would be the best way to suggest more definitive recommendations on estrogen and HA. The most recent studies, carried out between the years 2018 and 2020, that address the use of HA make other types of comparison, different from estrogen, because as there is no statistical difference in existing studies, HA has been tested as adjuvant therapy in several studies, as well as in comparison to other types of non-hormonal treatments.

In accordance with the GRADE approach, a descriptive quality of evidence and strength of the systematic review was carried out, the outcomes vaginal atrophy, dyspareunia, vaginal pH, and cell maturation were overall judged as very low quality evidence. We downgraded the body of evidence −1 for inconsistency, −1 inaccuracy, and −1 for risk of bias. This low evidence is mainly because of the lack of sufficient information present in primary studies. The studies, in general, did not present information on the blinding of participants and professionals, which is a key point in randomized controlled trials because it is one of the factors that most reduce potential bias. This was also observed in the blinding of the evaluators and in the concealment of allocation, which results in selection and detection bias.

CONCLUSION

Despite the lack of sufficient information in the primary articles to carry out the meta-analysis, the results suggested that treatment with HA, when compared with the use of estrogens or placebo, does not present a significant difference in the results obtained for the outcomes epithelial atrophy, vaginal pH, dyspareunia, and cell maturation evaluated in this systematic review. Thus, it can be said that both treatments appear to similar efficacy for dyspareunia. Therefore, the comparisons presented suggest that HA has a profile of efficacy, safety, and tolerability comparable with vaginal estrogens for the treatment of the outcomes assessed in this review. It is a possible alternative for women who cannot use hormonal treatment.

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