SUBMITTED 6 JAN 24
REVISIONS REQ. 25 FEB & 2 MAY 24; REVISIONS RECD. 30 MAR & 15 MAY 24
ACCEPTED 4 JUN 24
ONLINE-FIRST: JUNE 2024
DOI: https://doi.org/10.18295/squmj.6.2024.040

Efficacy of Hormonal and Non-hormonal Vaginal Gel Preparations on Female Sexual Satisfaction Index in Postmenopausal Women with Sexual Dysfunction Syndrome

A PRISMA-compliant meta-analysis

Ahmed Soliman,[1,2] Hanaa Alrashidi,[3] Mohamed A. Mohamed,[4] Reem Ghorab,[5] Nihal Al Riyami,[6] *Ahmed S.A. Ashour,[7] Yasmine A. Mohammed,[8] Ahmed H. Saad[7]

[1]Faculty of Medicine and [2]Mansoura Research Team (MRT), Research Department, Mansoura University, Mansoura, Egypt; [3]Kuwait Institute for Medical Specializations, Kuwait City, Kuwait; [4]Faculty of Medicine, Zagazig University, Zagazig, Egypt; [5]Faculty of Medicine, Misr University for Science and Technology, 6th of October City, Egypt; [6]Department of Obstetrics & Gynecology, Sultan Qaboos University, Muscat, Oman; [7]Department of Obstetrics & Gynecology, Faculty of Medicine, Cairo University, Cairo, Egypt; [8]Faculty of Medicine, Assiut University, Assiut, Egypt.
**Corresponding Author's e-mail: a_negm8233@outlook.com*

Abstract

We aimed to compare efficacy of vaginal gel preparations versus placebo in postmenopausal women with sexual dysfunction syndrome. We searched electronic databases from inception to January 2023. We included trials reporting Female Sexual Function Index (FSFI) which compared hormonal (estrogen, oxytocin) and/or non-hormonal (chamomile, fennel) interventions versus placebo. We used Cochrane Risk of Bias assessment tool I to evaluate studies quality. Eight trials (N=672 participants) were included. Total FSFI endpoint score was higher in the vaginal gel preparations group (MD: 6.67; 95% CI: [3.79, 9.55]; p< 0.001) than placebo. Non-hormonal gel preparations had higher FSFI total score (MD: 6.73, 95% CI:

[4.7, 8.76], p< 0.001) than hormonal preparations (MD: 2.75, 95% CI: [1.87,3.64], p< 0.001). Non-hormonal interventions increased all FSFI domains. We conclude that Chamomile and fennel vaginal gel preparations could improve overall FSFI six domains score, which reflects on postmenopausal women's sexual activity and satisfaction.

Keywords: menopause, psychological sexual dysfunction, estrogen, Chamomile, Meta-analysis

Introduction

Menopause is defined as the permanent cessation of menstruation for at least one year.[1] Postmenopausal women experience different physiological and psychological changes that affect their daily life activities.[2] Lack of estrogen and hormonal changes are implicated in most of the postmenopausal changes, including vasomotor symptoms (hot flashes and night sweating), osteoporosis, vulvovaginal atrophy, and sexual dysfunction, in addition to other psychological symptoms.[3] Vaginal atrophy and dryness significantly contribute to sexual dysfunction and strongly impact sexual intimacy after menopause.[4]

Female sexual dysfunction (FSD) can result from the disruption of any component of the sexual response complex, including sexual physiology, emotions, experiences, beliefs, lifestyle, and/or relationships.[5] Women with FSD are vulnerable to frequent genital infections, bleeding, and chronic pain, which have a negative impact on their quality of life.[6] After menopause, FSD can result from estrogen deficiency and hormonal instability.[7,8] A global study of sexual attitudes and behaviours conducted among 13,882 women in the 40-69 age group showed that one-third of the study participants reported one or more problems with their sexual functions.[9] The prevalence of vaginal dryness and dyspareunia in postmenopausal women was estimated as 85% and 75%, respectively.[10]

Several treatment modalities are offered to manage FSD and improve sexual satisfaction among postmenopausal women. Therapeutic options are classified into two groups: (1) topical hormonal replacement therapy (e.g., estrogen, and oxytocin preparations) and (2) natural herbs and non-hormonal therapies (e.g., chamomile and fennel preparations).[11] Local vaginal preparations are favored over systemic treatments, with particular emphasis on their characteristics to ensure efficacy and tolerability. This becomes especially crucial post-menopause for alleviating vaginal dryness. Achieving optimally balanced osmolality and pH is essential for the effectiveness of these preparations.[12]

FSD affects one-third of women's lives with various troublesome symptoms, especially for younger women or those who have an active sexual life[13]. The treatment of FSD syndrome depends on the safety profile and effectiveness of such treatments, as well as patient preferences.[14] Genitourinary syndrome of menopause (GSM) is a descriptive term that refers to various complications associated with decreased levels of sex hormones that lead to changes to the labia minora/majora, clitoris, vestibule/introitus, vagina, urethra, and bladder.[15] GSM is primarily characterized by genital symptoms (dryness, irritation, and burning), sexual symptoms (dyspareunia, dysfunction, and lack of lubrication), and urinary symptoms (urgency, dysuria, recurrent urinary tract infections).[16] Treatment options for GSM include hormonal (systemic or topical) or non-hormonal (laser or complementary and alternative medicine)[17]. The North American Menopause Society (NAMS) recommends the use of non-hormonal lubricants during sexual intercourse. Furthermore, they recommend using long-acting vaginal moisturizers as needed[18]. The therapeutic standard for symptomatic women with moderate to severe vulvovaginal atrophy or those who do not sufficiently respond to lubricants or moisturizers is estrogen therapy, whether vaginal, in low doses, or systemic.[18,19]

Hormonal therapy is a commonly used treatment for the menopausal effects on the genitourinary tract.[4,20] Estrogen could be used orally or vaginally and is associated with reduced vaginal dryness, lower vaginal atrophy, and improved sexual function.[21] Additionally, oxytocin is another effective hormonal treatment that is associated with better sexual life and satisfaction.[22,23]

On the other hand, several natural treatments could be used for sexual dysfunction, including the use of the herb Maca (Lepidium meyenii), fennel (Foeniculum vulgare), chamomile, aloe vera, 18β-glycyrrhizic acid, hyaluronic acid, licorice, and flax seed.[24] Also, non-hormonal treatment options, including the use of inactive lubricants such as water-, silicone-, or oil-based lubricants, were useful in reducing friction during sexual activity.[25]

Despite the abundance of studies focusing on postmenopausal women and sexual dysfunction [26,27], a notable literature gap persists in terms of a comprehensive comparison between hormonal (estrogen and oxytocin) and non-hormonal (fennel and chamomile) treatments. Existing research tends to explore individual interventions, and there is a lack of direct head-

to-head comparisons assessing their efficacy using a standardized and widely accepted measure such as the FSFI. Additionally, most studies often focus on either hormonal [28–30] or non-hormonal treatments [31,32], making it challenging for clinicians and researchers to make informed decisions regarding the most effective approach for addressing sexual dysfunction in postmenopausal women. The synthesis of available evidence on these specific interventions and their direct comparison is essential for bridging this literature gap and providing valuable insights into the optimal management of postmenopausal sexual dysfunction.

This study aims to contribute significantly to the body of knowledge by conducting a systematic and comparative analysis of the most effective hormonal (estrogen and oxytocin) and non-hormonal (fennel and chamomile) preparations for addressing sexual dysfunction in postmenopausal women. The inclusion of a well-established and reliable measure such as the FSFI will provide a standardized framework for evaluating the efficacy of these interventions, allowing for a more nuanced understanding of their impact on sexual satisfaction [33].

By directly comparing these treatments, our study seeks to offer evidence-based recommendations for clinicians and healthcare providers, facilitating informed decision-making when tailoring treatment plans for postmenopausal women experiencing sexual dysfunction. This research is anticipated to fill the existing literature gap by providing a comprehensive overview of both hormonal and non-hormonal options, ultimately guiding future research endeavors and clinical practices in the realm of postmenopausal sexual health. As a result, our study has the potential to enhance the overall quality of care for postmenopausal women, addressing a critical aspect of their well-being and quality of life. Thus, we selected the most effective hormonal (estrogen & oxytocin) and non-hormonal preparations (fennel & chamomile) and compared them in terms of efficacy measured by the FSFI as a common, well-known, and reliable scale.

Materials & Methods

Review protocol:

We were guided by Cochrane Handbook for Systematic Reviews of Interventions, and Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement.[34,35] Ethical approval was not required due to the nature of the study, and the study

protocol was registered in the Open Science Framework (OSF);
https://doi.org/10.17605/OSF.IO/ZBWU3

Search strategy:

We systematically searched the following electronic databases; PubMed, Scopus, Web of Science (WOS), and Cochrane Central Register of Controlled Trials (CENTRAL) from inception until January 2023. Our search terms were "vaginal gel", "hormonal", "estrogen", "oxytocin", "chamomile", "fennel", "female sexual dysfunction", and "postmenopausal". A detailed search strategy is provided in **Supplementary File 1.** All the references for the included studies were screened to avoid missing any studies and to guarantee high-quality screening. Furthermore, Clinicaltrials.gov and the World Health Organization (WHO) Clinical Trials Registry were considered during our search for details of unpublished and ongoing trials.

Eligibility criteria:

We included studies that met all the following preselected criteria: (**i**) studies must enroll postmenopausal population with FSD; (**ii**) intervention must be a gel-based hormonal or non-hormonal preparation; (**iii**) only placebo-controlled trials are eligible and all other trials with active interventions were excluded; (**iv**) studies must report all domains and total score of FSFI to be included in the meta-analysis; (**v**) in order to generate stronger evidence, we included only randomized controlled trials (RCTs). On the other hand, we excluded non-human studies, conference abstracts, non-RCTs, cohorts, case-control, case series, and non-English studies.

Screening and study selection:

We collected the different records from the various databases using Endnote software and removed duplicates. The retrieved references were screened to assess their relevance. The screening was done in two steps: title and abstract screening, followed by full-text screening for final eligibility. Two independent authors (AS & RG) completed the task and resolved the conflicts with the assistance of a senior reviewer (HA).

Quality assessment:

Using the Cochrane Risk of Bias (ROB) assessment tool, two authors (MM & AS) evaluated each included study independently.[36] The following domains were assessed: randomization

process, deviation from the intended interventions, missing outcome data, measurement of the outcome, and selection of the reported result. Each domain and overall quality of the included studies were judged as having a "low", "some concerns", or "high" risk of bias. Low risk of bias indicating having adequate randomization, little or no evidence of systematic difference between groups, a small amount of missing data, objective, reliable, and valid measurement methods, and pre-specific outcomes reported. Some concerns indicated an unclear description of randomization process, having differences between groups in care but not lead to bias, some missing data, minor issues with measurement methods, and some discrepancies between pre-specific and reported outcomes. In addition, a high risk of bias indicated inadequate randomization, presence of systematic differences in care between groups, a high amount of missing data, measurement methods likely to introduce bias and post hoc changes in outcomes. In general, having one high risk in any domain gives a total high risk of bias of the study, while some concerns in any domain lead to make the overall quality as some concern[37]. Disagreements were solved later by group discussion. According to Egger et al., publication bias is unreliable for less than ten pooled studies[38]. So, in this review, we could not assess the existence of publication bias using Egger's test for funnel plot asymmetry.

Data extraction and outcomes:

The following data were extracted by two independent reviewers(DL & AS): (**i**) study-relevant data: location, year of publication, sample size, study design, and follow-up duration; (**ii**) data related to enrolled study participants; mean age, mean age of menopause, Body Mass Index (BMI), economic status, and coitus frequency, (**iii**) data about intervention: preparation base, category (hormonal/ non-hormonal), active ingredients, treatment period, and application schedule, (**iv**) FSFI reported data including all six domains (sexual desire, arousal, lubrication, orgasm, satisfaction, and pain) and overall total score collected at both baseline and endpoint.

Statistical analysis:

Meta-analysis was performed using Review Manager software (RevMan, version 5.3 for Windows), provided by the Cochrane Collaboration 2014, Nordic Cochrane Centre Copenhagen, Denmark[39]. All extracted data were continuous and pooled as mean difference (MD) with a 95% confidence interval (CI). The analyses were performed using the inverse variance method and the random-effects model. Heterogeneity was assessed by observation

of the graphs on forest plots and measured by chi-square and I-square (I^2) tests for the degree of heterogeneity. Significant heterogeneity was defined as a chi-square test with $p<0.1$ and I^2 test >50. We considered the endpoints statistically significant with a p-value <0.05[40]. We subgrouped the included studies according to the nature of their interventions into hormonal (estrogen & oxytocin) and non-hormonal (chamomile & fennel) preparations.

Results:

Literature search:

Our comprehensive search strategy retrieved 982 search results. After duplicate removal, 366 unique results were eligible for the first screening. Depending on the revision of the title and abstract, 349 articles were excluded. Only 17 full-text articles were retrieved to check their adherence to our predetermined article selection criteria. Finally, we agreed on eight RCTs, typically describing the inclusion criteria. After manually checking the included studies' reference lists, no missed publications were found. **Figure 1** shows the PRISMA flow diagram of the literature searching process.

Characteristics of the included trials:

In eight RCTs,[28,41–4723–30,] with a total of 672 postmenopausal women, 341 women were allocated to the interventional group (gel group), whereas 331 women were in the placebo group. Four trials used hormonal preparations, either estrogen or oxytocin gel interventions. The other four RCTs used non-hormonal preparations such as chamomile and fennel (**Table 1**). All interventions were applied for 12 weeks except for 3 trials[28,43,45] whose preparations were applied for 8 weeks. The average age of participating women was 52.6 years, while the average menopausal age was 49.9 years. 57% of enrolled participants described their economic status as "good", while 29% and 14% of them were "weak" and "high", respectively. The average frequency of coitus was two times per week (**Table 2**).

Quality assessment:

Four RCTs [43–45,47] were evaluated as having a "low" risk of bias. However, two RCTs [28,42] were evaluated as having an "unclear" risk of bias with some concerns because they provide no information about study personnel blinding details. Additionally, two funded RCTs[41,46] were evaluated as "high" risk of bias; one was due to missing data and providing no clear information related to blinding, and the other trial provided no information about the

randomization process and allocation concealment details. Supplementary **Figures 1 & 2** explain the risk of bias summary and graph, respectively.

Meta-analysis of the overall FSFI score:

Our results found a statistically significant difference between vaginal gel and placebo groups. Both the total FSFI endpoint score (MD: 6.67; 95% CI: [3.79, 9.55]; p< 0.001) and its change from the baseline (MD: 4.89; 95% CI: [3.19, 6.59]; p< 0.001) were found to be significantly increased in vaginal gel group. A subgroup analysis based on the preparation nature of interventions revealed that non-hormonal gel preparations more significantly increased FSFI to a higher score difference (MD: 6.73, 95% CI: [4.7, 8.76], p< 0.001) versus the hormonal gel preparations (MD: 2.75, 95% CI: [1.87,3.64], p< 0.001) (**Figure 2**). While both hormonal and non-hormonal preparations were effective in increasing the FSFI total score, studies using hormonal gel products showed no significant heterogeneity. In contrast, studies with non-hormonal interventions, incorporating various chemical and herbal active ingredients like fennel and chamomile, exhibited notable diversity.

Changes in the desire domain:

Results for the sexual desire domain showed a significant statistical difference between the vaginal gel and placebo groups. The total change from baseline was significantly higher in the vaginal gel group (MD: 0.92, 95% CI: [0.34, 1.51]; p= 0.002) (Supplementary **Figure 3**). The subgroup analysis displayed that non-hormonal gel preparations increased female sexual desire (MD: 1.32, 95% CI: [0.54, 2.11]; p= 0.001) more than estrogen & oxytocin gel preparations (MD: 0.53, 95% CI: [0.22, 0.84]; p< 0.001). Both hormonal and non-hormonal preparations were able to achieve a higher sexual desire score; however, there was homogeneity between studies using hormonal gel preparations, unlike the studies with different non-hormonal products.

Changes in the arousal domain:

The sexual arousal domain of the FSFI contained results that displayed a notable statistical difference between the vaginal gel and placebo groups. The difference from baseline was considerably higher in the vaginal gel group (MD: 1.41, 95% CI: [0.67, 2.15]; p< 0.001) (**Supplementary Figure 4**). The subgroup analysis indicated that hormonal gel products improved sexual arousal (MD: 1.45, 95% CI: [0.31, 2.48]; p= 0.02) more than their non-hormonal counterparts (MD: 1.40, 95% CI: [0.21, 2.68]; p= 0.01). Not only were the

hormonal and non-hormonal preparations effective in achieving higher sexual arousal, but they also had no notable heterogeneity between studies where I^2= 24%, p-value< 0.001.

Changes in the lubrication domain

Results in the sexual lubrication domain demonstrated a statistically significant difference between vaginal gel and placebo groups. The change from baseline was higher in the vaginal gel group (MD: 1.36, 95% CI: [0.45, 2.27]; p= 0.003) (**Supplementary Figure 5**). However, the subgroup analysis pointed out that the hormonal preparations did not have a statistically significant effect on lubrication (MD: 0.78, 95% CI: [-0.11, 1.67]; p= 0.08), unlike the non-hormonal products, which were highly effective (MD: 1.76, 95% CI: [0.23, 3.28]; p= 0.02). In addition, both groups of hormonal and non-hormonal studies had a considerable within-group heterogeneity between studies with I^2 = 97%, p-value< 0.001.

Changes in the orgasm domain

Results pointed to a significant statistical difference between vaginal gel and placebo groups. Change from baseline in the orgasm domain was more in the vaginal gel set than in the placebo group (MD: 0.87, 95% CI: [0.29, 1.46]; p= 0.003) (**Supplementary Figure 6**). Nevertheless, the subgroup analysis showed that non-hormonal products were more effective (MD: 1.16, 95% CI: [0.44, 1.89]; p= 0.002) than the hormonal gel interventions (MD: 0.45, 95% CI: [-0.53, 1.43]; p= 0.37). (I^2= 92%, p-value< 0.001). However, there was significant heterogeneity between studies in both hormonal and non-hormonal groups.

Changes in the satisfaction domain

Results in the sexual satisfaction domain showed a statistically significant variation between vaginal gel and placebo since the change from baseline was higher than the placebo group (MD: 1.10, 95% CI: [0.63, 1.57]; p< 0.001) (**Supplementary figure 7**). Further subgroup analysis indicated that women who used the non-hormonal preparations were more satisfied (MD: 1.34, 95% CI: [0.78, 1.90]; p< 0.001) than those who used the hormonal ones (MD: 0.68, 95% CI: [0.32, 1.05]; p< 0.001) (I^2=91%, p-value <0.001). Even though both preparations were effective in improving sexual satisfaction, there was no remarkable heterogeneity between studies that used the hormonal gel products, unlike studies that used non-hormonal interventions.

Changes in the pain domain

The results of the sexual pain domain indicated a substantial difference between vaginal gel and placebo. The change from baseline was higher in the vaginal gel group than in the placebo (MD: 1.60, 95% CI: [1.27, 1.94]; p< 0.001) (**Supplementary Figure 8**). Subgroup analysis showed that both hormonal (MD: 1.17, 95% CI: [0.19, 2.14]; p= 0.02) and non-hormonal (MD: 1.68, 95% CI: [1.28, 2.08]; p< 0.001) were effective to reduce pain in postmenopausal women with sexual satisfaction (I^2 =66%, p-value =0.004). Hormonal studies showed no notable heterogeneity, while non-hormonal studies had significant within-group heterogeneity.

Leave-one-out Sensitivity Analysis

By visualizing all the forest plots, we found that Nappi et al. (2016) [46] and Abedi et al. (2020) [42] seemed outliers in most forest plots. So, we did a leave-one-out sensitivity analysis of all the outcomes by excluding both studies. After removing both studies, the results were stable in all the outcomes except in the lubrication and pain domains.

In the total score of FSFI and the sexual desire domain, the overall results were still significant (MD: 5.06, 95% CI: [2.94, 7.18]; p< 0.00001) and (MD: 1.12, 95% CI: [0.47, 1.77]; p=0.0007) respectively. However, heterogeneity wasn't resolved (I^2 =95%, p-value <0.00001) and (I^2 =90%, p-value <0.00001) respectively. (**Supplementary Figure 9, Figure 10**).

The same thing happened with the overall results of sexual arousal, sexual orgasm, and sexual satisfaction domains, which were significant (MD: 1.74, 95% CI: [0.85, 2.64]; p= 0.0001), (MD: 1.01, 95% CI: [0.25, 1.77]; p=0.009), and (MD: 1.4, 95% CI: [0.95, 1.86]; p< 0.00001) respectively. However, the heterogeneity also wasn't resolved (I^2 =98%, p-value <0.00001), (I^2 =93%, p-value <0.00001), and (I^2 =88%, p-value <0.00001) respectively. (**Supplementary Figure 11 to Figure 13**).

In the domains of sexual lubrication and pain, the total results were significant (MD: 1.5, 95% CI: [0.2, 2.8]; p= 0.02), (MD: 1.7, 95% CI: [1.32, 2.08]; p-value <0.00001) and heterogenous (I^2 =98%, p-value <0.00001), (I^2 =69%, p-value=0.007), respectively. However,

the heterogeneity disappeared from the Hormonal gel subgroup of both outcomes (I^2 =0%, p-value=0.42), (I^2 =0%, p-value=0.45) (**Supplementary Figure 14 and Figure 15**).

Discussion

In our meta-analysis, we aimed to systematically review the published literature on the efficacy vaginal gel preparations versus placebo in the treatment of sexual dysfunction syndrome. We screened 982 articles and selected eight articles with data pertaining to the use of vaginal gel in postmenopausal women. Our meta-analysis shows a significant difference between vaginal gel and placebo groups, with the vaginal gel group showing an increased FSFI endpoint score and its change from baseline.

The observed statistically significant improvements in overall FSFI scores, sexual desire, arousal, lubrication, orgasm, satisfaction, and pain domains following vaginal gel interventions suggest a potential avenue for addressing sexual dysfunction in postmenopausal women. These findings align with the existing literature highlighting the physiological changes associated with menopause that can adversely affect sexual function [48,49]. The fact that both hormonal and non-hormonal gel preparations demonstrated positive effects indicates a promising range of options for addressing diverse needs and preferences among postmenopausal women.

Fernandes et al. assessed the effectiveness of topical estrogen as a vaginal lubricant in improving the sexual function of included females.[28] They noticed a positive trend of improved sexual function among women using estrogen-conjugated cream. Estrogen is well-absorbed in the vagina due to its highly vascularized nature. This also means that absorbed estrogen circumvents enterohepatic circulation, leading to fewer adverse effects. Similar results can be observed in the literature. Tanmahasamut et al. evaluated the efficacy and safety of estradiol gel on postmenopausal vaginal tissue.[47] They found that postmenopausal women treated with estradiol vaginal gel demonstrated an ability to reverse vaginal atrophy. Vaginally administered estradiol also demonstrated a high safety profile with low systemic absorption. Palacios et al. evaluated the effects of combined therapy of vaginal estriol with transdermal 17-beta-estradiol plus medroxyprogesterone acetate.[50] They found that adding vaginal estriol to the hormone replacement therapy may lead to shorter latency for urinary symptoms that occur due to vulvovaginal atrophy. Similarly, Nachtigall found that

menopausal women treated with vaginal estrogen cream exhibited significantly increased vaginal moisture, vaginal fluid volume, and vaginal elasticity, in addition to returning to the premenopausal pH state.[51]

Another hormone that has been recently studied to treat sexual dysfunction is oxytocin. Despite having some adverse effects, oxytocin has many benefits, including natural cell growth stimulation and accelerating healing processes, in addition to improving sexual satisfaction in women when administered intranasally.[52–55] On the other hand, Mesbahi et al. found no significant difference between oxytocin gel and placebo in terms of FSFI total score. [44] Despite that, an improvement in the sexual satisfaction domain was observed, in addition to improved symptoms of depression compared to the placebo. Abedi et al. reported an improved sexual function in postmenopausal women using vaginal oxytocin gel compared to a placebo.[41]

Another method that has been gaining popularity is using complementary and alternative medicine, particularly herbal medicine[56]. Multiple studies examine the use of medicinal plants to treat menopausal symptoms. These plants include soybean, red clover, chamomile, fennel, black cohosh, Pueraria Mirifica, flaxseed, and licorice, among others.[57–59] For instance, Bosak et al. investigated the effect of chamomile vaginal gel on the sexual function of postmenopausal women. Chamomile herb has been used in traditional and modern medicine due to its phytoestrogen/estrogen compound properties [43]. The chamomile flower has been widely used for its benefits in improving various pathological disorders such as inflammation, cardiovascular and gastrointestinal diseases, cancer, common cold, abdominal pain, diarrhea, hemorrhoids, mucositis, osteoporosis, insomnia, anxiety, seizures, diabetes, sore throat, vaginitis, and premenopausal syndrome among others. [58,60]

Phytoestrogens can bind to estrogen receptors in the body and exert their estrogenic effects more potently. In postmenopausal women, this can lead to a reduction in menopausal symptoms, including hot flashes and vaginal dryness.[61]

Abedi et al. investigated the effect of fennel vaginal cream on sexual function in postmenopausal women.[57] Foeniculum vulgare, also known as fennel, is a plant in the carrot family that is widely present on the shores of the Mediterranean Sea. The main chemical compounds in fennel are trans-anethole and dianethole, both having estrogenic effects.[62]

These compounds are known to possess estrogenic effects, which could potentially influence the hormonal milieu in postmenopausal women. The inclusion of fennel in vaginal cream formulations represents a novel approach, leveraging its natural properties to address sexual function concerns in this specific population[41]. The geographical prevalence of fennel in the Mediterranean region adds a contextual layer to the study, considering the potential influence of regional dietary and lifestyle factors on the outcomes[63]. This geographical connection may also have implications for generalizability, prompting future research to explore the cultural and environmental factors that could impact the efficacy of fennel-based interventions in diverse populations. Moreover, the choice of fennel as a therapeutic agent aligns with the growing interest in botanical remedies for menopausal symptoms[64]. Understanding the estrogenic effects of trans-anethole and dianethole in fennel sheds light on the potential mechanisms through which fennel vaginal cream may exert its impact on sexual function, providing a scientific basis for its application.

The subgroup analysis emphasizing the differential impact of hormonal and non-hormonal gel preparations on various domains of sexual function is a critical aspect of this discussion. Non-hormonal preparations, incorporating ingredients like chamomile and fennel, showed greater efficacy in enhancing sexual desire, lubrication, orgasm, and satisfaction. On the other hand, hormonal gel products appeared more effective in improving sexual arousal. This distinction is noteworthy, suggesting that tailoring interventions based on the specific aspects of sexual function may optimize treatment outcomes. Understanding the underlying mechanisms and interactions of these different compositions could guide future research and clinical practice.

Nearly all the outcomes had some heterogeneity that was not resolved by either a leave-one-out test or subgroup analysis. The heterogeneity may be related to different factors such as (1) baseline characteristics of included patients as all the studies included postmenopausal women except Nappi et al. (2016) [46], which included women over 18 years with potential for childbearing, and Mesbahi et al. (2022) [44] which included breastfeeding healthy women. (2) different active ingredients among the studies. (3) different formulations, all the studies used gel formulation except Abedi et al. (2018) [41] and Fernandes et al. (2014) [28], which used cream formulation, and Mitchell et al. (2018) [45], which used vaginal tablet. (4) application times: some studies asked the women to apply their interventions once daily, while others told them to apply them two to three times a week.

The findings of this meta-analysis have implications for healthcare providers involved in the care of postmenopausal women experiencing sexual dysfunction. The identification of effective interventions, particularly the observed benefits of non-hormonal gel preparations, opens avenues for personalized and patient-centered care. Recognizing the diversity in women's needs and preferences, clinicians can engage in informed discussions with patients to select interventions aligned with individual circumstances, potentially improving treatment adherence and satisfaction. In moving forward, researchers should consider conducting long-term follow-up studies to assess the sustained effects of vaginal gel interventions on postmenopausal women's sexual function. Additionally, investigating the safety profile of these interventions, especially hormonal preparations, is crucial for providing a comprehensive understanding of the risks and benefits associated with their use.

Strengths and limitations

To our knowledge, this is the first meta-analysis to describe pooled evidence about hormonal and non-hormonal vaginal gel products. The article stresses the real-life objective efficacy of these topical preparations to help postmenopausal women with FSD syndrome resulting from different types of pathology. However, due to the different nature of these interventions, nearly all the pooled analyses were heterogeneous. Four of the included studies were conducted in the same locality (Iran), which may influence the generalizability of our findings.

Conclusion

Chamomile and fennel vaginal gel preparations can significantly improve the overall score of FSFI and its six domains. Except for the lubrication and orgasm domains, estrogen and oxytocin hormonal gel preparations can also improve the FSFI total score and its domains. Based on our findings, we suggest offering both hormonal and non-hormonal gel products to improve sexual function and activity in postmenopausal women with FSD syndrome.

Authors' Contribution:

AS led the team, performed data collection, solved any conflict in the screening process and the quality assessment, performed the meta-analysis, and participated in writing and editing the final manuscript. HA participated in the screening process, quality assessment, and draft

writing. MAM took part in the quality assessment and draft writing. RG participated in the screening process, data extraction, and draft writing. ASAA edited the manuscript. NAR peer-reviewed the article. YAM critically revised and edited the manuscript and assessed the quality of evidence using the GRADE system. AHS supervised the authors in all steps and performed peer review.

References

1. Butler L, Santoro N. The reproductive endocrinology of the menopausal transition. *Steroids*. 2011;76(7):627-635. doi:10.1016/j.steroids.2011.02.026
2. McKinlay SM, Brambilla DJ, Posner JG. The normal menopause transition. *Am J Hum Biol*. 1992;4(1):37-46. doi:10.1002/ajhb.1310040107
3. Dalal P, Agarwal M. Postmenopausal syndrome. *Indian J Psychiatry*. 2015;57(6):222. doi:10.4103/0019-5545.161483
4. Sturdee DW, Panay N. Recommendations for the management of postmenopausal vaginal atrophy. *Climacteric*. 2010;13(6):509-522. doi:10.3109/13697137.2010.522875
5. Lee A, Kim TH, Lee HH, et al. Therapeutic Approaches to Atrophic Vaginitis in Postmenopausal Women: A Systematic Review with a Network Meta-analysis of Randomized Controlled Trials. *J Menopausal Med*. 2018;24(1):1. doi:10.6118/jmm.2018.24.1.1
6. Nazarpour S, Simbar M, Ramezani Tehrani F, Alavi Majd H. Quality of life and sexual function in postmenopausal women. *J Women Aging*. 2018;30(4):299-309. doi:10.1080/08952841.2017.1395539
7. Morali G, Polatti F, Metelitsa E, Mascarucci P, Magnani P, Brunenghi Marrè G. Open, Non-controlled Clinical Studies to Assess the Efficacy and Safety of a Medical Device in Form of Gel Topically and Intravaginally Used in Postmenopausal Women with Genital Atrophy. *Arzneimittelforschung*. 2011;56(03):230-238. doi:10.1055/s-0031-1296715
8. Cotreau MM, Chennathukuzhi VM, Harris HA, et al. A study of 17β-estradiol-regulated genes in the vagina of postmenopausal women with vaginal atrophy. *Maturitas*. 2007;58(4):366-376. doi:10.1016/j.maturitas.2007.09.009
9. Addis IB, Van Den Eeden SK, Wassel-Fyr CL, Vittinghoff E, Brown JS, Thom DH. Sexual Activity and Function in Middle-Aged and Older Women. *Obstet Gynecol*. 2006;107(4):755-764. doi:10.1097/01.AOG.0000202398.27428.e2

10. Cagnacci A, Carbone MM, Palma F. Prevalence and association between objective signs and subjective symptoms of vaginal atrophy: the AGATA study. *Menopause*. 2016;23(10):1139-1145. doi:10.1097/GME.0000000000000675
11. Warren MP, Shortle B, Dominguez JE. Use of alternative therapies in menopause. *Best Pract Res Clin Obstet Gynaecol*. 2002;16(3):411-448. doi:10.1053/beog.2002.0290
12. Naumova I, Castelo-Branco C. Current treatment options for postmenopausal vaginal atrophy. *Int J Womens Health*. 2018;Volume 10:387-395. doi:10.2147/IJWH.S158913
13. Nappi PRE, Cucinella L, Martella S, Rossi M, Tiranini L, Martini E. Female sexual dysfunction (FSD): Prevalence and impact on quality of life (QoL). *Maturitas*. 2016;94:87-91. doi:10.1016/j.maturitas.2016.09.013
14. Palma F, Volpe A, Villa P, Cagnacci A. Vaginal atrophy of women in postmenopause. Results from a multicentric observational study: The AGATA study. *Maturitas*. 2016;83:40-44. doi:10.1016/j.maturitas.2015.09.001
15. Portman DJ, Gass MLS. Genitourinary syndrome of menopause: New terminology for vulvovaginal atrophy from the International Society for the Study of Women's Sexual Health and The North American Menopause Society. *Maturitas*. 2014;79(3):349-354. doi:10.1016/j.maturitas.2014.07.013
16. Robinson D, Giarenis I, Cardozo L. New developments in the medical management of overactive bladder. *Maturitas*. 2013;76(3):225-229. doi:10.1016/j.maturitas.2013.07.003
17. Palacios S, Castelo-Branco C, Currie H, et al. Update on management of genitourinary syndrome of menopause: A practical guide. *Maturitas*. 2015;82(3):308-313. doi:10.1016/j.maturitas.2015.07.020
18. Society AM. Management of symptomatic vulvovaginal atrophy. *Menopause*. 2013;20(9):888-902. doi:10.1097/GME.0b013e3182a122c2
19. Biglia N, Bounous VE, Sgro LG, D'Alonzo M, Pecchio S, Nappi RE. Genitourinary Syndrome of Menopause in Breast Cancer Survivors: Are We Facing New and Safe Hopes? *Clin Breast Cancer*. 2015;15(6):413-420. doi:10.1016/j.clbc.2015.06.005
20. Leiblum S, Bachmann G, Kemmann E, Colburn D, Swartzman L. Vaginal atrophy in the postmenopausal woman. The importance of sexual activity and hormones. *JAMA*. 249(16):2195-2198. http://www.ncbi.nlm.nih.gov/pubmed/6834616
21. Lindahl S. Reviewing the options for local estrogen treatment of vaginal atrophy. *Int J Womens Health*. Published online March 2014:307. doi:10.2147/IJWH.S52555
22. Algoe SB, Kurtz LE, Grewen K. Oxytocin and Social Bonds: The Role of Oxytocin in

Perceptions of Romantic Partners' Bonding Behavior. *Psychol Sci*. 2017;28(12):1763-1772. doi:10.1177/0956797617716922

23. Al-Saqi SH, Uvnäs-Moberg K, Jonasson AF. Intravaginally applied oxytocin improves postmenopausal vaginal atrophy. *Post Reprod Heal*. 2015;21(3):88-97. doi:10.1177/2053369115577328

24. Shin B-C, Lee MS, Yang EJ, Lim H-S, Ernst E. Maca (L. meyenii) for improving sexual function: a systematic review. *BMC Complement Altern Med*. 2010;10(1):44. doi:10.1186/1472-6882-10-44

25. Pastore LM, Carter RA, Hulka BS, Wells E. Self-reported urogenital symptoms in postmenopausal women: Women's Health Initiative. *Maturitas*. 2004;49(4):292-303. doi:10.1016/j.maturitas.2004.06.019

26. Masliza W, Daud W, Yazid Bajuri M, et al. Sexual dysfunction among postmenopausal women. *Clin Ter*. 2014;165(2):83-89. doi:10.7471/CT.2014.1681

27. Harder H, Starkings RML, Fallowfield LJ, Menon U, Jacobs IJ, Jenkins VA. Sexual functioning in 4,418 postmenopausal women participating in UKCTOCS: a qualitative free-text analysis. *Menopause*. 2019;26(10):1100-1009. doi:10.1097/GME.0000000000001377

28. Fernandes T, Costa-Paiva LH, Pinto-Neto AM. Efficacy of Vaginally Applied Estrogen, Testosterone, or Polyacrylic Acid on Sexual Function in Postmenopausal Women: A Randomized Controlled Trial. *J Sex Med*. 2014;11(5):1262-1270. doi:10.1111/jsm.12473

29. Meziou N, Scholfield C, Taylor CA, Armstrong HL. Hormone therapy for sexual function in perimenopausal and postmenopausal women: a systematic review and meta-analysis update. *Menopause*. 2023;30(6):659-671. doi:10.1097/GME.0000000000002185

30. Simon JA. Identifying and Treating Sexual Dysfunction in Postmenopausal Women: The Role of Estrogen. *J Women's Heal*. 2011;20(10):1453-1465. doi:10.1089/jwh.2010.2151

31. Dehghan M, Isari Z, Abbaszadeh MH, et al. Postmenopausal women's usage of complementary and alternative medicine and its relationship to sexual function: A cross-sectional study in southeastern Iran. *Heal Sci Reports*. 2023;6(8). doi:10.1002/hsr2.1470

32. Modelska K, Milián ML. Treatment of female sexual dysfunction in postmenopausal women—What is the evidence? *Rev Gynaecol Pract*. 2004;4(2):121-132.

doi:10.1016/j.rigp.2004.01.001

33. Chongcharoen P, Choobun T, Khanuengkitkong S. Female sexual function index for screening of female sexual dysfunction using DSM-5-TR criteria in Thai women: A prospective cross-sectional diagnostic study. Di Donato V, ed. *PLoS One*. 2024;19(2):e0298935. doi:10.1371/journal.pone.0298935
34. Page MJ, McKenzie JE, Bossuyt PM, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *BMJ*. Published online March 29, 2021:n71. doi:10.1136/bmj.n71
35. Higgins JPT, Thomas J, Chandler J, et al., eds. *Cochrane Handbook for Systematic Reviews of Interventions*. Wiley; 2019. doi:10.1002/9781119536604
36. Higgins JPT, Altman DG, Gotzsche PC, et al. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. *BMJ*. 2011;343(oct18 2):d5928-d5928. doi:10.1136/bmj.d5928
37. Higgins ulian P, Savović J, Page MJ, Elbers RG, Sterne JA. *Chapter 8: Assessing Risk of Bias in a Randomized Trial*.; 2024. https://training.cochrane.org/handbook/current/chapter-08
38. Egger M, Smith GD, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. *BMJ*. 1997;315(7109):629-634. doi:10.1136/bmj.315.7109.629
39. Collaboration. C. Review Manager (RevMan) [Computer software]. Published online 2014. https://training.cochrane.org/online-learning/core-software/revman
40. Higgins JPT. Measuring inconsistency in meta-analyses. *BMJ*. 2003;327(7414):557-560. doi:10.1136/bmj.327.7414.557
41. Abedi P, Najafian M, Yaralizadeh M, Namjoyan F. Effect of fennel vaginal cream on sexual function in postmenopausal women: A double blind randomized controlled trial. *J Med Life*. 2018;11(1):24-28. http://www.ncbi.nlm.nih.gov/pubmed/29696061
42. Abedi P, Zohrabi I, Ansari S, Maraghi E, Maram NS, Houshmand G. The Impact of Oxytocin Vaginal Gel on Sexual Function in Postmenopausal Women: A Randomized Controlled Trial. *J Sex Marital Ther*. 2020;46(4):377-384. doi:10.1080/0092623X.2020.1738606
43. Bosak Z, Iravani M, Moghimipour E, Haghighizadeh M hosein, Jelodarian P. Effect of Chamomile Vaginal Gel on the Sexual Function in Postmenopausal Women: A Double-Blind Randomized Controlled Trial. *J Sex Med*. 2022;19(6):983-994. doi:10.1016/j.jsxm.2022.03.536
44. Mesbahi A, Mohammad-Alizadeh-Charandabi S, Ghorbani Z, Mirghafourvand M. The

effect of intra-vaginal oxytocin on sexual function in breastfeeding mothers: a randomized triple-blind placebo-controlled trial. *BMC Pregnancy Childbirth*. 2022;22(1):62. doi:10.1186/s12884-022-04384-w

45. Mitchell CM, Reed SD, Diem S, et al. Efficacy of Vaginal Estradiol or Vaginal Moisturizer vs Placebo for Treating Postmenopausal Vulvovaginal Symptoms. *JAMA Intern Med*. 2018;178(5):681. doi:10.1001/jamainternmed.2018.0116
46. Nappi RE, Benedetto C, Campolo F, et al. Efficacy, tolerability and safety of a new medical device, Monurelle Biogel ® vaginal gel, in the treatment of vaginal dryness: a randomized clinical trial in women of reproductive age. *Eur J Obstet Gynecol Reprod Biol*. 2016;203:82-88. doi:10.1016/j.ejogrb.2016.05.005
47. Tanmahasamut P, Jirasawas T, Laiwejpithaya S, Areeswate C, Dangrat C, Silprasit K. Effect of estradiol vaginal gel on vaginal atrophy in postmenopausal women: A randomized double-blind controlled trial. *J Obstet Gynaecol Res*. 2020;46(8):1425-1435. doi:10.1111/jog.14336
48. Heidari M, Ghodusi M, Rezaei P, Kabirian Abyaneh S, Sureshjani EH, Sheikhi RA. Sexual Function and Factors Affecting Menopause: A Systematic Review. *J Menopausal Med*. 2019;25(1):15. doi:10.6118/jmm.2019.25.1.15
49. Nazarpour S, Simbar M, Tehrani FR. Factors affecting sexual function in menopause: A review article. *Taiwan J Obstet Gynecol*. 2016;55(4):480-487. doi:10.1016/j.tjog.2016.06.001
50. Palacios S, Castelo-Branco C, Cancelo MJ, Vázquez F. Low-dose, vaginally administered estrogens may enhance local benefits of systemic therapy in the treatment of urogenital atrophy in postmenopausal women on hormone therapy. *Maturitas*. 2005;50(2):98-104. doi:10.1016/j.maturitas.2004.04.007
51. Nachtigall LE. Comparative study: Replens versus local estrogen in menopausal women. *Fertil Steril*. 1994;61(1):178-180. doi:10.1016/S0015-0282(16)56474-7
52. Kallak TK, Uvnäs-Moberg K. Oxytocin stimulates cell proliferation in vaginal cell line Vk2E6E7. *Post Reprod Heal*. 2017;23(1):6-12. doi:10.1177/2053369117693148
53. Behnia B, Heinrichs M, Bergmann W, et al. Differential effects of intranasal oxytocin on sexual experiences and partner interactions in couples. *Horm Behav*. 2014;65(3):308-318. doi:10.1016/j.yhbeh.2014.01.009
54. Uvnäs-Moberg K. OXYTOCIN MAY MEDIATE THE BENEFITS OF POSITIVE SOCIAL INTERACTION AND EMOTIONS1The purpose of this paper is to describe the neuroendocrine mechanisms of positive social interactions.1.

Psychoneuroendocrinology. 1998;23(8):819-835. doi:10.1016/S0306-4530(98)00056-0

55. Torky HA, Taha A, Marie H, et al. Role of topical oxytocin in improving vaginal atrophy in postmenopausal women: a randomized, controlled trial. *Climacteric*. 2018;21(2):174-178. doi:10.1080/13697137.2017.1421924

56. Kim M-S, Lim H-J, Yang HJ, Lee MS, Shin B-C, Ernst E. Ginseng for managing menopause symptoms: a systematic review of randomized clinical trials. *J Ginseng Res*. 2013;37(1):30-36. doi:10.5142/jgr.2013.37.30

57. Yaralizadeh M, Abedi P, Najar S, Namjoyan F, Saki A. Effect of Foeniculum vulgare (fennel) vaginal cream on vaginal atrophy in postmenopausal women: A double-blind randomized placebo-controlled trial. *Maturitas*. 2016;84:75-80. doi:10.1016/j.maturitas.2015.11.005

58. Miraj S, Alesaeidi S. A systematic review study of therapeutic effects of Matricaria recuitta chamomile (chamomile). *Electron physician*. 2016;8(9):3024-3031. doi:10.19082/3024

59. Asgharpoor M, hadizadeh talasaz fatemeh, Rahmany R. Medicinal Plants Used in Treatment of Vaginal Atrophy in Postmenopausal Women: A Systematic Review. *J Maz Univ Med Sci*. 2021;30(194):140-155. Accessed March 9, 2024. https://jmums.mazums.ac.ir/article-1-15861-en.html

60. Gupta. Chamomile: A herbal medicine of the past with a bright future (Review). *Mol Med Rep*. 2010;3(6). doi:10.3892/mmr.2010.377

61. Shoorei H, Khaki A, Ainehchi N, et al. Effects of Matricaria chamomilla Extract on Growth and Maturation of Isolated Mouse Ovarian Follicles in a Three-dimensional Culture System. *Chin Med J (Engl)*. 2018;131(2):218-225. doi:10.4103/0366-6999.222324

62. Khaleil MM, Alnoman MM, Elrazik ESA, Zagloul H, Khalil AMA. Essential Oil of Foeniculum vulgare Mill. as a Green Fungicide and Defense-Inducing Agent against Fusarium Root Rot Disease in Vicia faba L. *Biology (Basel)*. 2021;10(8):696. doi:10.3390/biology10080696

63. Mattavelli E, Olmastroni E, Bonofiglio D, Catapano AL, Baragetti A, Magni P. Adherence to the Mediterranean Diet: Impact of Geographical Location of the Observations. *Nutrients*. 2022;14(10):2040. doi:10.3390/nu14102040

64. Rahimikian F, Rahimi R, Golzareh P, Bekhradi R, Mehran A. Effect of Foeniculum vulgare Mill. (fennel) on menopausal symptoms in postmenopausal women: a

randomized, triple-blind, placebo-controlled trial. *Menopause*. 2017;24(9):1017-1021. doi:10.1097/GME.0000000000000881

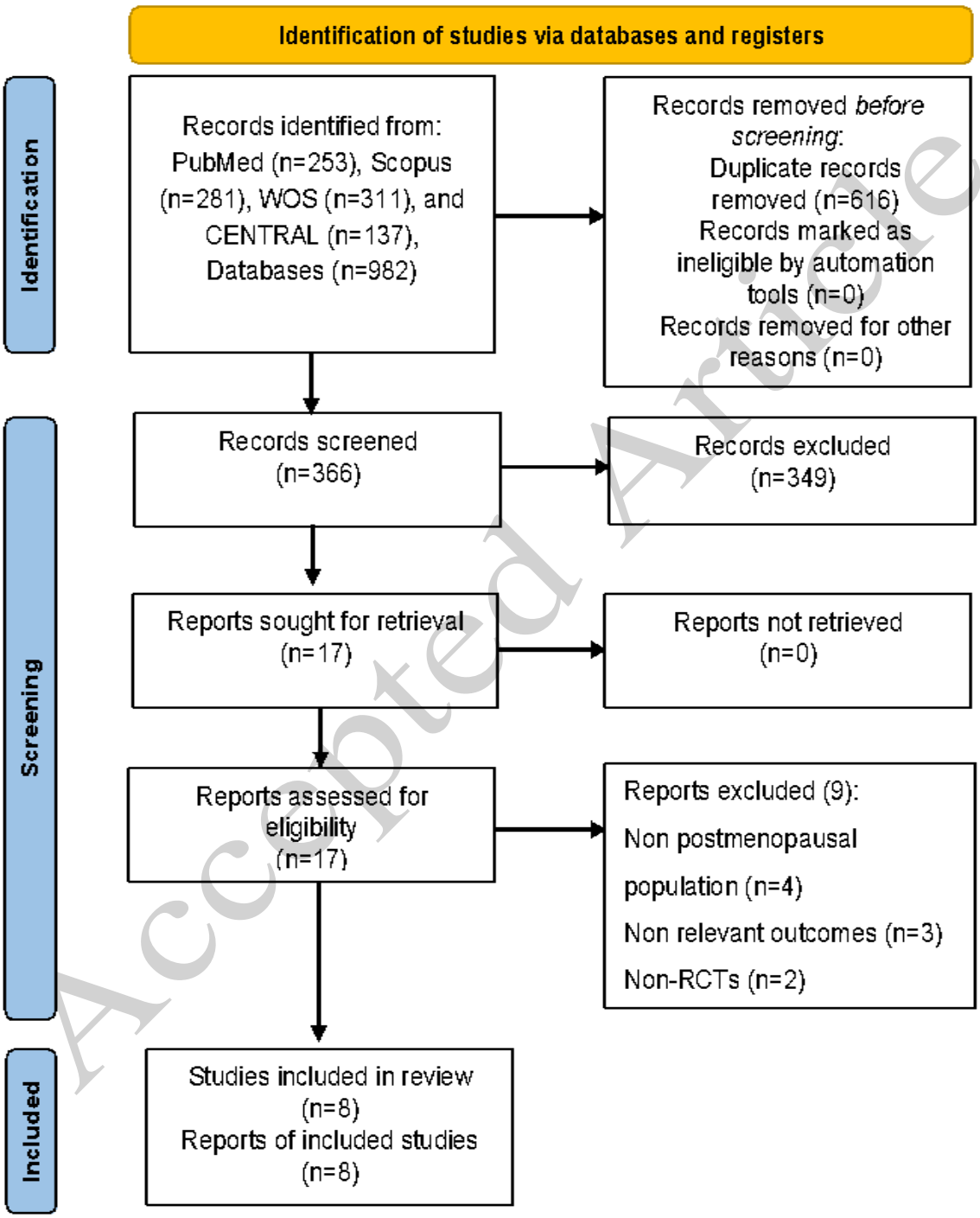

Figure 1: Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) flow diagram and chart.

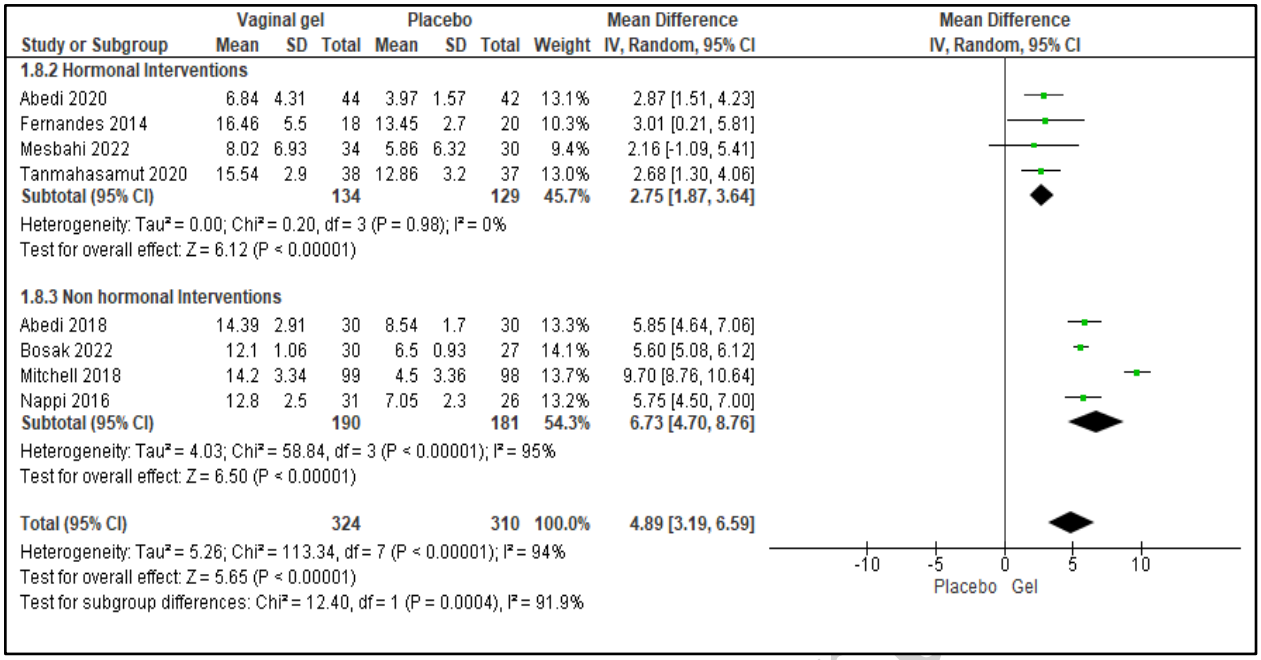

Figure 2: Meta-analysis of change (pre-/postinterventional) in total score of Female Sexual Function Index (FSFI).

682 **Table 1.** Summary of the included trials.

Study ID	Country	Trial duration (Weeks)	Total sample size, n	Study arms	
				Intervention	Control
Abedi 2018	Iran	8	n= 60	Fennel gel	Placebo gel
Abedi 2020	Iran	8	n= 86	Oxytocin gel	Placebo gel
Bosak 2022	Iran	12	n= 57	Chamomile gel	Placebo gel
Fernandes 2014	Brazil	12	n= 38	Estrogen gel	Oil lubricant
Mesbahi 2022	Iran	8	n= 64	Oxytocin gel	Placebo gel
Mitchell 2018	USA	12	n= 197	Moisturizer gel + placebo	Dual placebo
Nappi 2016	Italy	8	n= 95	Monurelle Biogel gel	Placebo gel
Tanmahasamut 2020	Thailand	8	n= 75	Estradiol gel	Placebo gel

683

Table 2. Baseline characteristics of the included trials.

Study ID	Group	Participants	Age (years)		Age of menopause (years)		Economic Status			Coitus frequency per week	
			Mean	SD	Mean	SD	Weak	Good	High	Mean	SD
Abedi 2018	Fennel gel	30	53.7	3.6	49.5	2.0	9	14	7	2.07	1.3
	Placebo gel	30	52.9	3.4	49.3	1.9	11	12	7	1.77	0.47
Abedi 2020	Oxytocin gel	44	54.2	3.3	50.0	2.2	17	21	6	2.75	1.34
	Placebo gel	42	54.1	3.7	50.4	2.6	16	19	7	2.38	0.88
Bosak 2022	Chamomile gel	30	53.5	5.7	49.0	2.3	5	21	4	1.5	0.94
	Placebo gel	27	54.3	5.5	50.0	1.8	5	20	2	1.69	1.32
Fernandes 2014	Estrogen gel	18	56.4	4.8	51.1	1.5	NR	NR	NR	NR	NR
	Oil lubricant	20	57.7	4.7	50.3	1.1	NR	NR	NR	NR	NR
Mesbahi 2022	Oxytocin gel	34	31.2	5.1	NR	NR	7	25	2	2.56	2.1
	Placebo gel	30	27.8	5.9	NR	NR	7	21	2	1.78	1.6
Mitchell 2018	Moisturizer gel + placebo	99	61.0	4.0	NR	NR	NR	NR	NR	NR	NR
	Dual placebo	98	61.0	4.0	NR	NR	NR	NR	NR	NR	NR
Nappi 2016	Monurelle Biogel gel	48	55.8	4.6	NR	NR	NR	NR	NR	NR	NR
	Placebo gel	47	56.5	5.9	NR	NR	NR	NR	NR	NR	NR
Tanmahasamut 2020	Estradiol gel	38	54.9	9.8	NR	NR	NR	NR	NR	NR	NR
	Placebo gel	37	56.4	4.5	NR	NR	NR	NR	NR	NR	NR

NR: Not Reported (in the study)