**Hormone Therapy for Sexual Function in Perimenopausal and Postmenopausal Women: A Systematic Review and Meta-Analysis Update**

Running Title: Hormone Therapy for Sexual Function

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# Key points

## Question

What is the effect of Hormone Therapy (HT) on sexual function in perimenopausal and postmenopausal women?

## Findings

Forty-seven RCTs (35,912 participants) evaluating the effect of HT were included. Estrogen therapy, estrogen plus progestogen therapy, tibolone, and selective estrogen receptor modulators, compared to control, may result in no effect to small benefit on sexual function in perimenopausal and postmenopausal women. Heterogeneity of effects across studies was low to high.

## Meaning

HT may slightly improve sexual function. The effect of HT on sexual function should be considered when discussing treatment options for other menopausal symptoms.

# abstract

## Importance

Distressing sexual problems are a common complaint of menopausal women. In 2013, a Cochrane review assessed the effect of hormone therapy on sexual function in menopausal women; however, new evidence has since been published which should be considered.

## Objective

This systematic review and meta-analysis aims to update the evidence synthesis on the effect of hormone therapy, compared to control, on sexual function in perimenopausal and postmenopausal women.

## Evidence Review

Thirteen databases and clinical trial registries (Cochrane Central Register of Controlled Trials, EMBASE, Medical Literature Analysis and Retrieval System Online, PsycINFO, Web of Science, Cumulative Index to Nursing and Allied Health Literature, Literatura Latino-Americana e do Caribe em Ciéncias da Saúde, Database of Abstracts of Reviews of Effects, ClinicalTrials.gov, International Clinical Trials Registry Platform, Iranian Registry of Clinical Trials, Chinese Clinical Trial Registry, ISRCTN) were searched from December, 2012 until March 30, 2022. Backward reference searching on all retrieved full texts was also performed. Study quality was assessed using the Cochrane ROB.2 tool. Data was pooled in random effect model meta-analyses which included all studies identified in the present search as well as all studies previously included in the 2013 Cochrane review.

## Findings

Forty-seven randomized controlled trials (35,912 participants) were included in the systematic review, and 34 randomized controlled trials (15,079 participants) were included in the meta-analysis. The meta-analysis revealed that in comparison to control estrogen therapy (SMD=0.16, 95%CI, 0.02 to 0.29, I2=59%, 2925 participants, 16 studies), estrogen plus progestogen therapy (SMD= 0.11, 95%CI, -0.07 to 0.29, I2=65%, 2432 participants, 7 studies), tibolone (SMD=0.15, 95%CI, 0.02 to 0.28, I2=0%, 916 participants, 2 studies), and selective estrogen receptor modulators (SMD=0.18, 95%CI, 0.06 to 0.30, I2=0%, 1058 participants, 4 studies) may result in no effect to small benefit on sexual function composite score.

## Conclusion and Relevance

Hormone therapy may slightly improve sexual functioning. This potential small benefit should be considered when discussing treatment options for other menopausal symptoms.

## Key words

Menopause, Hormone Therapy, Sexual Function, Meta-analysis

# INTRODUCTION

With 71-76% of middle-aged women stating that sexual activity is an important aspect of their lives,1,2 sexual well-being during menopause is a necessary concern. Sexual function is often described in opposition to Female Sexual Dysfunction (FSD) which is a clinically significant disturbance in a person’s ability to respond sexually, or to experience sexual pleasure, that causes distress.3 Distressing sexual problems peak among middle-aged women while sexual problems without accompanying distress tend to increase with age.4 The International Menopause Society recommends a biopsychosocial approach of sexual function accounting for fluctuations in health status, neurochemical balance, psychological issues, interpersonal concerns, and sociocultural beliefs and values.5

Hormone therapy (HT) is the first line treatment for moderate to severe genitourinary symptoms of menopause.6-8 The genitourinary syndrome of menopause (GSM), affecting half of postmenopausal women, results in lack of lubrication, discomfort, and pain during sexual activity.9 Postmenopausal sexually-active women with FSD are nearly four times more likely to have GSM than those without FSD.10 Therefore, HT might improve sexual function in menopause by decreasing genitourinary symptoms.5 Additionally, HT may also improve sexual function by decreasing sleep disturbance in women with vasomotor symptoms.11-13

In 2013, a Cochrane systematic review found that HT, compared to placebo or no intervention, slightly improved sexual function in perimenopausal and recently postmenopausal women.14 Since the publication of this review, new clinical trials have been conducted. This systematic review aims to update the evidence synthesis on the effect of estrogen therapy, estrogen plus progestogen therapy, tibolone, and selective estrogen receptor modulators (SERMs) on sexual function in perimenopausal and postmenopausal women.

# METHODS

## Protocol and registration

The review protocol was registered on PROSPERO on March 30, 2022 (CRD42022320302).

## Criteria for study inclusion

### Types of studies

Published and unpublished randomized controlled trials (RCTs) were included. Crossover trials were considered but only data from the first phase was included because urogenital symptoms often reoccur after HT is stopped.15 Studies including only a subset of eligible participants were considered for inclusion when data was reported for the subset of interest.

### Types of participants

Perimenopausal or postmenopausal women were included. Perimenopausal women were defined as women who had their last menstrual period (LMP) within the last 12 months before inclusion.16 Postmenopausal women were defined as women with menopause induced by a medical intervention or with natural menopause defined as 12 consecutive months of spontaneous amenorrhea.16 Recently postmenopausal women had their LMP within the last 5 years.16 Symptomatic menopausal women are women with any menopausal symptom described in Monteleone et al.,17 including vulvovaginal atrophy, vasomotor symptoms, and sexual dysfunction.

### Types of interventions

The intervention of interest is HT compared with control. All HT therapies included in Nastri et al.14 were considered: estrogen therapy, estrogen plus progestogen therapy, tibolone, and SERMs. This review did not include dehydroepiandrosterone (DHEA) and testosterone as their effect on sexual function has already been investigated elsewhere.18,19 Only trials in which the interval between the onset of the intervention and the assessment of outcomes was ≥1 month were included. For studies with multiple assessments, only the assessment closest to 6 months after starting the intervention was considered. Indeed, tolerability should be assessed 3 months after beginning treatment,15 therefore a 6-month time point is conservative.

### Types of outcome measures

All outcomes reported in Nastri et al.14 were considered for inclusion, as were any other relevant aspect of sexual function. The primary outcome of this review is sexual function composite score. Secondary outcomes are desire, arousal, lubrication, orgasm, pain, and sexual satisfaction. Only outcomes measured and scored by validated questionnaires were included. As this is an update of Nastri et al.14 adverse events related to HT were not an outcome of this review.

## Search methods for identification of studies

In Nastri et al.14 the last search was performed on 12 December 2012. When the searching interface allowed date limitation by month, the search was restricted from December 2012 to present. Otherwise, the search was restricted from 2013 to 2022 with good faith that any missed article between 13 December and 31 December 2012 would be found by citation tracking. The search strategy was inspired from previous reviews.14,20-22 Most electronic databases used in Nastri et al.14 were searched including: Cochrane Central Register of Controlled Trials (CENTRAL) through the Cochrane Library, EMBASE, Medical Literature Analysis and Retrieval System Online (MEDLINE), PsycINFO, Web of Science (WOS), Cumulative Index to Nursing and Allied Health Literature (CINAHL), Literatura Latino-Americana e do Caribe em Ciéncias da Saúde (LILACS), and Database of Abstracts of Reviews of Effects (DARE). In order to increase specificity, validated RCT filters were added to the MEDLINE,23 Embase,24 and CINAHL25 search strategies. Protocols of ongoing trials on all registers used in Nastri et al.14 were searched via: ClinicalTrials.gov and the World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP). Additionally, the Iranian Registry of Clinical Trials (IRCT), the Chinese Clinical Trial Registry (ChiCTR), and the ISRCTN registry were also searched (Appendix A1-10). Some sources used in Nastri et al.14 were unable to be used: The Menstrual Disorders and Subfertility database (MDSG) Specialised Register and Current Controlled-Trials could not be found, and OpenGrey was shut down in 2021. Additionally, DARE updates stopped in 2015. Finally, backward reference searching on all retrieved full texts was also performed.

## Data collection and analysis

### Study selection

Titles and abstracts of all retrieved studies were screened using Rayyan® and full texts of all potentially eligible studies were searched. The first author applied the selection criteria to determine included articles in consultation with the final author if eligibility was unclear. When a full text could not be retrieved, authors were contacted if possible. The entire selection process is documented using the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram26 (Figure 1).

### Data extraction and management

Data extraction and checking was performed by the first author in consultation with the final author. For studies with multiple publications, the main trial report was used as the reference and secondary papers were used for additional details. Data were extracted as Mean ±Standard Deviation (SD). Standard errors and 95% confidence intervals (95%CI) were converted to SDs.27 Data reported as Median [Interquartile Range] was converted with formulas assuming a normal distribution of the data.28

### Assessment of risk of bias in included studies

Risk of bias assessment was performed by the first author, in consultation with the final author, using the ROB.2 tool developed by the Cochrane Collaboration.29 Bias arising from randomization process (Domain 1) was assessed at study level, whereas all other domains were assessed at outcome level. Every domain was rated as “low”, “some concerns”, or “high” risk of bias. If all five domains were rated “low”, the overall risk of bias was “low”. If one to three domains were rated “some concerns”, with all other domains rated “low”, the overall risk of bias was “some concerns”. If four or more domains were rated “some concerns”, or one or more domain was rated “high”, the overall risk of bias was “high”. Regarding bias due to missing outcome data (Domain 3), data was considered available for all or nearly all participants when ≥95% of randomized participants had outcome data. Proportions of missing data were considered to differ between groups when the difference was ≥5%. For bias in measurement of the outcome (Domain 4), all outcomes were considered subjective.

### Measures of treatment effect

All outcomes were reported as continuous. Standardized mean differences (SMDs) are reported as different scales were used. When a meta-analysis was possible, effect sizes were pooled along with those previously published in Nastri et al.14 An inverse variance random-effect model was used because studies were not expected to measure the same true value as trial contexts varied (Table 1).30 Revman® was used to pool the data.

For consistency of results interpretation with Nastri et al.14 a SMD between -0.49 and -0.20 was considered small harm, between -0.19 and 0.19 was considered no effect, between 0.20 and 0.49 was considered small benefit, between 0.50 and 0.79 was considered moderate benefit, and ≥0.80 was considered large benefit.31

### Unit of analysis issues

When reported, the Intention to Treat (ITT) or modified-Intention-To-Treat (mITT) data was used. ITT data was prioritized over mITT data.

### Missing data

In case of missing trial information, authors of included papers were contacted and sent a personalized data request form.

### Assessment of heterogeneity

To explore clinical heterogeneity, the overall population was divided in two subgroups as defined in Nastri et al.14 1. Perimenopausal, recently postmenopausal, and symptomatic women, and 2. Asymptomatic postmenopausal women with more than five years since their LMP. Indeed, Nastri et al.14 showed different results were to be expected in these populations. Likewise, as different routes of administration have different indications and different safety profiles,32 a subgroup analysis comparing Systemic Hormone Therapy to Vaginal Hormone Therapy was run. Statistical heterogeneity was assessed using the I2 statistic. Statistical heterogeneity was considered high when I2≥70%, moderate when 50%≤I2<70%, and low when I2≤50%*.*15However, as thresholds for the interpretation of the I2 statistic can be misleading,27 a sensitivity analysis excluding studies at high risk of bias was performed.

### Assessment of non-reporting bias

To minimise language bias, English, French, or Spanish language studies were considered. To avoid selective non-reporting bias, authors were contacted when outcomes relevant to the review and presented in the protocol or the Method section were absent from the final report. When more than 10 studies were included in an analysis, a funnel-plot was examined. Symmetry was assessed visually and if asymmetric, all potential causes of small study effect, including publication bias, were considered. Likewise, in such situation, a fixed effect meta-analysis giving less weight to small studies was performed to investigate a potential shift of the random-effect meta-analysis estimate toward the result of small studies.27

# Results

## Description of studies

### Search results and study design

From the original search performed on December 2012 in Nastri et al.,14 27 studies were included in the systematic review, of which 19 were included in the current meta-analysis (Figure 1). In this systematic review update, database and clinical trial registry searches were performed on March 30, 2022. 5062 records were retrieved (Figure 1) and 20 studies from 33 records were identified for inclusion (Table 1). From these, 15 were included in the meta-analysis. All were parallel-arms RCTs. Six studies reported funding by the pharmaceutical industry.33-38 One study is an unpublished master’s thesis.39 Further definition of “studies”, “records” and “reports” is provided in Page et al.26

### Participants

The 20 studies included 4358 participants: 2489 in the HT arms and 1869 in the placebo or no intervention arms. Two studies included perimenopausal and recently postmenopausal women, one included recently postmenopausal women only, all other studies included postmenopausal women (Table 1). Ten studies included sexually active women.33,37,38,40-50 Of these, three studies defined sexual activity as penetrative sex,33,38,41 four studies included penetrative sex, non-penetrative sex, and masturbation,37,42-48 and the remaining studies did not report any information on the definition of sexual activity. Two studies included participants who reported sexual activity with a female partner.43-48

### Interventions

Among the 20 studies published since December 2012, fourteen studies evaluated estrogen therapy.36,38-54 Four studies evaluated estrogen plus progestogen therapy.35,37,55,56. One study evaluated tibolone.56 Two studies evaluated the SERM Ospemifene.33,34 The intervention was delivered vaginally in fourteen studies. Other studies reported oral33-35,37,47,48 or transdermal administration.37 The route of administration was unclear in one study.55 When studies had several groups using the same drug with different route of administration, dosage or treatment duration, these groups were merged in the meta-analysis.37-39 In three studies, the control was no intervention.42,49,54 All other studies used matching placebos.

### Outcomes

Sexual functioning was assessed using different measures including: Female Sexual Function Index (FSFI),57 Larson Sexual Satisfaction Questionnaire (LSSQ),58,59 Menopause Quality Of Life questionnaire (MENQOL),60 Menopause Rating Scale (MRS),61 Day-to-Day Impact of Vaginal Aging questionnaire (DIVA),62 and Pelvic Organ Prolapse/Urinary Incontinence Sexual Questionnaire-12 (PISQ-12)63 (Table 1). When sexual function was measured on different scales, data from the FSFI was used if reported. Sexual function composite score was measured in all studies except one that only measured sexual satisfaction.40 One study measured sexual function composite score in the overall population and in sexually active participants only.47,48 Only data from the sexually active participants was included in the evidence synthesis because the FSFI is only validated in sexually active women.64 Four studies reported adjusted effect estimates.33,37,43-48

## Risk of bias in included studies

Overall risk of bias was assessed to be low for one study, of some concern for four studies, and high for fifteen studies (Table 2). The main source of high risk of bias was missing outcome data. Regarding bias due to deviation from intended intervention (Domain 2), one study measured sexual function using the FSFI without excluding sexually inactive participants from the analysis.37 Therefore, the method of analyzing the data was judged inappropriate to estimate the effect of assignment to the intervention as it could lead to an underestimation of the FSFI score.64 For bias in measurement of the outcome (Domain 4), in two studies,50,52 the overall FSFI mean score in one of the groups fell outside of the possible range of 2-36 indicating that sexual function was incorrectly scored.57,64 Thus, the method of measurement of the outcome was judged inappropriate and both studies were excluded from the meta-analysis.

## Meta-Analyses

The studies described above were pooled as appropriate with the effect sizes previously published in Nastri et al.14 As such, 47 RCTs (35,912 participants) were included in the systematic review, and 34 RCTs (15,079 participants) were included in the meta-analysis.

## Estrogen therapy vs Control

In symptomatic or recently postmenopausal women, estrogen therapy had no effect to small benefit on sexual function composite score with moderate heterogeneity (SMD=0.17, 95%CI, 0.01 to 0.32, I2=63%, 2447 participants, 13 studies36,38,39,41,43-49,51,53,54,65-67) (Figure 2). In unselected postmenopausal women, HT had no effect to small benefit on sexual function composite score with low heterogeneity (SMD=0.11, 95%CI, -0.18 to 0.41, I2=47%, 478 participants, 3 studies68-70). Any difference between the two groups is likely due to chance (p=0.76). Among all participants of included studies, estrogen therapy had no effect to small benefit on sexual function composite score with moderate heterogeneity (SMD=0.16, 95%CI, 0.02 to 0.29, I2=59%, 2925 participants, 16 studies). The sensitivity analysis led to the same conclusion (SMD= 0.25, 95%CI, 0.07 to 0.43, I2=48%, 1006 participants, 5 studies). No concerning asymmetry was observed on the funnel plot (Appendix B).

## Estrogen plus progestogen therapy vs Control

In symptomatic or recently postmenopausal women, estrogen plus progestogen therapy had small harm to small benefit on sexual function composite score with high heterogeneity (SMD=0.04, 95%CI, -0.31 to 0.39, I2=76%, 1118 participants, 4 studies35,37,56,71) (Figure 2). In unselected postmenopausal women, estrogen plus progestogen therapy had no effect to small benefit on sexual function composite score with moderate heterogeneity (SMD=0.09, 95%CI, -0.19 to 0.37, I2=54%, 1314 participants, 3 studies72-74). Any difference between the two groups is likely due to chance (p=0.82). Among all participants of included studies, estrogen plus progestogen therapy had no effect to small benefit on sexual function composite score with moderate heterogeneity (SMD= 0.11, 95%CI, -0.07 to 0.29, I2=65%, 2432 participants, 7 studies). The sensitivity analysis found large harm to small benefit of estrogen plus progestogen therapy on sexual function composite score (SMD= -0.57, 95%CI, -1.40 to 0.27, 23 participants, 1 study). However, this result is limited because of the small number of participants included in the analysis (Appendix B).

## Tibolone vs Control

In symptomatic or recently postmenopausal women, tibolone had no effect to small benefit on sexual function composite score with low heterogeneity (SMD=0.15, 95%CI, 0.02 to 0.28, I2=0%, 916 participants, 2 studies56,75) (Figure 2). In unselected postmenopausal women, tibolone had no effect to moderate benefit on sexual function composite score with low heterogeneity (SMD=0.38, 95%CI, 0.04 to 0.71, I2=0%, 142 participants, 2 studies73,76). Any difference between the two groups is likely due to chance (p=0.21). Among all participants of included studies, tibolone had no effect to small benefit on sexual function composite score with low heterogeneity (SMD=0.18, 95%CI, 0.06 to 0.30, I2=0%, 1058 participants, 4 studies). No sensitivity analysis could be run as all studies were assessed at high risk of bias.

## SERMs vs Control

In symptomatic or recently postmenopausal women, SERMs had no effect to small benefit on sexual function composite score with low heterogeneity (SMD=0.18, 95%CI, 0.05 to 0.32, I2=0%, 842 participants, 2 studies33,77) (Figure 2). In unselected postmenopausal women, SERMs had small harm to small benefit on sexual function composite score with low heterogeneity (SMD=0, 95%CI, -0.24 to 0.24, I2=0%, 283 participants, 1 study70). Any difference between the two groups is likely due to chance (p=0.20). Among all participants of included studies, SERMs had no effect to small benefit on sexual function composite score with low heterogeneity (SMD=0.14, 95%CI, 0.02 to 0.26, I2=0%, 1125 participants, 3 studies). The sensitivity analysis lead to the same conclusion (SMD= 0.11, 95%CI, -0.12 to 0.34, I2=36%, 498 participants, 2 studies) (Appendix B).

## Systemic Hormone Therapy VS Vaginal Hormone Therapy

For all outcomes of all comparisons, there was no significant difference between the subgroups Systemic Hormone Therapy and Vaginal Hormone Therapy (Appendix B).

# Discussion

## Summary of main results

This systematic review includes 47 RCTs (35,912 participants). The meta-analysis revealed that, compared to control, estrogen therapy, estrogen plus progestogen therapy, tibolone, and SERMs may result in no effect to small benefit on sexual function composite score in perimenopausal and postmenopausal women. No significant difference in effect was noted between perimenopausal, recently postmenopausal, or symptomatic women VS unselected postmenopausal women. While adverse events related to HT were not included in this review, other systematic reviews have investigated the safety profile of HT.78-84

## Overall completeness and applicability of evidence

### Population

Among the 20 studies published since December 2012, 10 included sexually active women and one included both sexually inactive and sexually active women. As most trials measured sexual function using the FSFI,57 it is likely that studies that did not specify included sexually active women, even though missuses of the scale are common.64 As low sexual function may lead to sexual inactivity, future researchers could use a scale validated for non-sexually active women,60 although these also have limitations. Moreover, only two newer studies reported the inclusion of women who have sex with women and mixed evidence exists regarding the prevalence and intensity of genito-pelvic pain in women who have sex with women compared with women who have sex with men.85 Nevertheless, previous research has suggested that better communication between lesbian women, compared to heterosexual and bisexual women, is likely to diminish the impact of genito-pelvic pain by allowing for variations in sexual activities.86 Indeed, women who have sex with women tend to rely more on relationship dynamics and partner support as they have described healthcare providers’ advice unhelpful for their sexual problems.87 Future research should actively recruit and focus on better understanding sexual function among women who have sex with women.

### Intervention

In Nastri et al.14, most interventions were administered orally, while vaginal administration was more common in newer studies. The meta-analysis did not reveal any difference in the effect of HT on sexual function when comparing routes of administration. However, results from this analysis are limited as it was not pre-specified in the protocol.

### Outcomes

The scales included in this review were designed to measure sexual functioning. However, none can be used to diagnosis FSD as they do not include measures of distress.3 Only two newer studies measured sexual distress using a single item from the revised Female Sexual Distress Scale (FSDS-R).43,44,46-48 Future clinical trials investigating sexual function should also measure sexual distress which may help reduce stigma around low sexual functioning during the menopausal transition.88,89 However, as the FSDS-R needs further validation in this population, these results were not included in the current review.90 Traditionally an FSFI score <26.55 has been used to indicated clinical levels of sexual dysfunction;91 however, new evidence suggests a cutoff score <21 is associated with greater sexual distress.92 Additionally, different scales can lead to different prevalence estimates within the same population93 which can influence the estimated clinical effect of the intervention and may also explain some of the observed heterogeneity. Further, using the FSFI with sexually inactive women could lead to an underestimation of the overall effect of HT on sexual function composite score.64

## Study quality

Seventeen of the 20 studies published since December 2012 might suffer from attrition bias given the high amount of missing data. Nevertheless, the effect of HT on sexual function did not change when excluding studies at high risk of bias. Among these trials, missingness for sexual function was usually higher than other outcomes. As discussed, proper use of the FSFI could reduce the amount of missing data.64 Additionally, measuring sexual function over a six-month period rather than four-weeks could reduce the number of participants excluded post-randomization; this has been previously suggested94 and is validated in women who have sex with women.95 Similarly, missing data could also be reduced by rephrasing the FSFI to include all forms of vaginal penetration95,96 or using a measure such as the DIVA62 which considers non-penetrative sexual activity. Further, nearly all studies that investigated sexual satisfaction used the FSFI satisfaction domain; however, one question cannot be answered by unpartnered women and high rates of missing data for this question were reported in the MsFLASH trials.97 Therefore, restricting inclusion to women who have a partner, or using a scale which does not require the responder to have a partner, could reduce the amount of missing data. Finally, clinical trial participants may be uncomfortable discussing sexuality as compared with other health-related topics so future RCTs could add willingness to answer sexuality questionnaires as an inclusion criterion. Practitioners should also start open conversations about sex with their patients to normalize discussing sexual health in medical settings. Indeed, in the Real Women's Views of Treatment Options for Menopausal Vaginal Changes (REVIVE) survey, only 19% of women reported their healthcare provider asked about their sexual health while 40% expected their healthcare provider would start the conversation about vulvovaginal symptoms.98

## Potential biases in the review process

This review has limitations. Screening, data extraction, and risk of bias assessment were performed primarily by the first author, in consultation with the final author in case of doubt. Ideally, these would have been performed by two reviewers blinded from each other with a third investigator resolving potential conflicts.27 When a full-text publication could not be found, authors were contacted, but none responded. Finally, this review might suffer from language bias as only reports in English, French, or Spanish were considered for inclusion. However, only one record in another language was found and records in English reporting the same study were also retrieved.

## Genitourinary Syndrome of the Menopause

Results of this review do not invalidate the use of topical HT for the treatment of GSM, nor the need to diagnose GSM. Evidence shows only 14% of women who discuss their genitourinary symptoms with a healthcare provider receive a GSM diagnosis, resulting in underdiagnosis of the condition.98 With almost half of postmenopausal women judging their symptoms as a natural part of aging or not bothersome enough to mention,98 it is essential that healthcare providers investigate genitourinary symptoms among their patients as effective treatments exist. The International Menopause Society strongly recommends that practitioners initiate a conversation on female sexual well-being at the beginning of menopause.5 Furthermore, cross-cultural studies reveal that more distressing symptoms are noted in cultures where menopause is taboo99 and more negative attitudes towards menopause are associated with increased symptom reporting.100 Healthcare providers should open the dialogue on menopausal transition before the onset of perimenopause to set realistic expectations about symptoms and offer knowledge on available treatment options, empowering women to encourage positive reappraisal and reduce the stigma around the menopause.

## Implications for research

Summary effects of this review are accompanied by wide confidence intervals and 33 of 47 studies were assessed at high risk of bias, lowering the level of confidence in the results. However, any potential benefit of HT on sexual function is expected to be small and HT is already recommended in the treatment of GSM-related dyspareunia. Therefore, it can be concluded that the effect of HT on sexual function in perimenopausal and postmenopausal women is well understood and unlikely to change in the future. Expert consensus statements tend toward a biopsychosocial understanding of FSD with treatment strategies including both pharmacological and psychological interventions.101,102 Future clinical trials may wish to evaluate their synergic effect in menopausal women with distressing sexual problems. A more holistic appraisal of sexuality would lead to more pragmatic patient-relevant research embracing the WHO’s definition of sexual health as “a state of physical, emotional, mental and social well-being in relation to sexuality [that] is not merely the absence of disease, dysfunction or infirmity”.103

# CONCLUSION

This systematic review and meta-analysis found that HT may slightly improve sexual functioning. This potential small benefit should be considered when discussing treatment options for other menopausal symptoms. Future research should consider the role of HT as one component of a more holistic approach to managing low sexual functioning in perimenopausal and postmenopausal women.

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Figures and Tables

Figure 1: PRISMA flow diagram

Table 1: Characteristics of included studies

Table 2: Risk of bias of included studies

Figure 2: Forest plots showing the comparison of Hormone Therapy and control for sexual function composite score for: (A) Estrogen Therapy, (B) Estrogen plus Progestogen Therapy, (C) Tibolone, (D) SERMs.

Supplemental Digital Content (SDC)

SDC1, Appendix A1-10: Search Strategies, Word Document

SDC2, Appendix B: Additional Forest Plots, Word Document

**Identification of new studies via other methods**

**Previous studies**

**Identification of new studies via databases and registers**

Studies included in Nastri et al.14 (n = 27)

Reports of studies included in Nastri et al.14

(n = 36)

Records identified from:

Backward citation searching

(n = 4)

Records removed *before screening*:

Duplicate records removed (n = 1426)

Records identified (n = 5062) from:

CENTRAL (n = 826)

EMBASE (n = 1429)

Medline (n = 417)

PsychINFO (n = 110)

WOS (n = 1057)

CINHAL (n = 527)

LILACS (n = 21)

DARE (n = 5)

Clinicaltrials.gov (n = 460)

ICTRP (n = 47)

IRCT (n = 121)

ChiCTR (n = 25)

ISRCTN (n = 17)

**Identification**

Reports sought for retrieval

(n = 4)

Reports excluded

(n = 4)

No HT arm (n = 3)

Did not evaluate sexual function

(n = 1)

Reports not retrieved

(n = 0)

Records excluded (n = 3466)

Records screened (n = 3636)

Reports not retrieved (n = 24)

Ongoing trial (n = 20)

Terminated trial (n = 4)

Reports sought for retrieval

(n = 170)

Reports assessed for eligibility

(n = 4)

Reports excluded (n = 113)

Did not evaluate sexual function (n = 29)

Did not use a validated scale (n = 26)

Not a RCT (n = 10)

No placebo or no intervention arm (n=9)

Crude sexual function scores reported elsewhere (n = 6)

Review of several RCTs (n = 5)

Sexual function data published before December 2012 (n = 4)

A questionnaire including a sexual domain is applied but crude sexual function scores are not reported (n = 3)

No HT arm (n = 2)

Language exclusion (n = 1)

Full text not available (n = 18, 12 studies)

Reports assessed for eligibility

(n = 146)

**Screening**

New studies included in review (n = 20)

Reports of new included studies (n = 33)

**Included**

Total studies included in review (n = 47)

Reports of total included studies (n = 69)

CENTRAL, Cochrane Central Register of Controlled Trials; ChiCTR, Chinese Clinical Trial Registry; CINAHL, Cumulative Index to Nursing and Allied Health Literature; DARE, Database of Abstracts of Reviews of Effects; HT, Hormone Therapy; ICTRP, International Clinical Trials Registry Platform; IRCT, Iranian Registry of Clinical Trials; ISRCTN, International Standard Randomized Controlled Trial Number; LILACS, Literatura Latino-Americana e do Caribe em Ciéncias da Saúde; MEDLINE, Medical Literature Analysis and Retrieval System Online; n, number; RCT, Randomized Controlled Trial; WOS, Web of Science

# Figure 2[[1]](#footnote-1)a: Forest plots showing the comparison of Hormone Therapy and control for sexual function composite score for: (A) Estrogen Therapy, (B) Estrogen plus Progestogen Therapy, (C) Tibolone, (D) SERMs. Table Description automatically generated with low confidence

# Figure 2, A: Forest plots showing the comparison of Estrogen Therapy and control for sexual function composite score.

## Figure 2, B: Forest plots showing the comparison of Estrogen plus Progestogen Therapy and control for sexual function composite score.

## Table Description automatically generated with medium confidence

## Figure 2, C: Forest plots showing the comparison of Tibolone and control for sexual function composite score.

## Table Description automatically generated

## Figure 2, D: Forest plots showing the comparison of SERMs and control for sexual function composite score.

**Table 1. Characteristics of included studies**

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| Study | Country | Center(s) | Population | Menopause status | Follow-up | Scale |
| Archer 2019 | United States | Multicenter | GSMa with vaginal dryness as MBS at baseline | Postmenopausal | 12 weeks | FSFI |
| Bosak 2020 | Iran | Single center | GSM with dyspareunia at baseline | Postmenopausal | 12 weeks | LSSQ |
| Bumphenkiatikul 2020 | Thailand | Single center | GSM and female sexual dysfunction at baseline | Postmenopausal | 12 weeks | FSFI |
| Carmigani 2015 | Brazil | Multicenter | Urogenital symptoms at baseline. | Postmenopausal | 16 weeks | MRS |
| Caruso 2017 | Italy | Single center | Significant vaginal bulging caused by pelvic organ prolapse and GSM at baseline. | Postmenopausal | 25 weeks | PISQ-12 |
| Constantine 2015 | United States | Multicenter | GSM at baseline: with dyspareunia (n=605) or vaginal dryness (n=314) as MBS | Postmenopausal | 12 weeks | FSFI |
| Cruz 2015 | Brazil | Single center | GSM at baseline | Postmenopausal | 20 weeks | FSFI |
| Davison 2013 | Australia | Single center | Healthy postmenopausal women | Recently postmenopausal | 6 months | MENQOL |
| Ferrante 2021 | United States | Multicenter | 3 or more/2 documented urinary tract infections in the past year/6 months before enrollment | Postmenopausal | 6 months | FSFI |
| Hirschberg 2017 | Spain Sweden | Multicenter | Hormone receptor positive early breast cancer treated with aromatase inhibitors for at least 6 months and severe to moderate vaginal dryness at baseline | Perimenopausal and postmenopausal | 12 weeks | FSFI |
| KEEPS-sexual 2017 | United States | Multicenter | Symptomatic or asymptomatic menopausal women | Peri- or recently postmenopausal | 48 months | FSFI |
| Lillemon 2022 | United States | Single center | Postmenopausal women | Postmenopausal | 12 weeks | FSFI |
| Mac Bride 2014 | United States | Single center | GSM at baseline | Postmenopausal | 12 weeks | MENQOLFSFI |
| MsFLASH VMS 2014, 2015 | United States | Multicenter | Vasomotor symptoms at baseline | Peri- or recently postmenopausal | 8 weeks | FSFI |
| MsFLASH VHT 2018, 2018, 2019, 2020 | United States | Multicenter | GSM at baseline | Postmenopausal | 12 weeks | FSFI |
| Olmez 2017 | Turkey | Single center | Cervical cancer survivors with radiotherapy treatment at least 6 months before enrollment in the trial | Postmenopausal | 6 months | FSFI |
| REJOICE 2016 | United States Canada | Multicenter | GSM with dyspareunia as MBS at baseline | Postmenopausal | 12 weeks | FSFI |
| Sun 2016 | China | Single center | Women with severe uterine and anterior vaginal wall prolapse at baseline referred for transvaginal pelvic reconstructive surgery with mesh. | Postmenopausal | 12 months | PISQ-12 |
| Tanmahasamut 2020 | Thailand | Single center | GSM at baseline | Perimenopausal and postmenopausal | 8 weeks | FSFI |
| Verghese 2020 | United-Kingdom | Multicenter | Women with pelvic organ prolapse at baseline having pelvic organ prolapse surgery without use of vaginal mesh | Postmenopausal | 12 months | PISQ-12 |

**Table 1**. *Continued*

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| Study | Arm | N | Intervention/Control | Posology | Authors’ conclusion |
| Archer 2019 | I | 313 | Oral ospemifene | 60mg once daily for 12 weeks | Women in the ospemifene group reported significantly higher FSFI total scores than women in the placebo group at week 12. |
| C | 314 | Placebo |
| Bosak 2020 | I | 32 | CE vaginal cream | 1g once daily for 2 weeks, then twice weekly for 10 weeks | There is a significant difference in sexual satisfaction between estrogen and placebo groups. |
| C | 32 | Placebo |
| Bumphenkiatikul 2020 | I | 34 | CE vaginal tablet | 0.625 mg once daily for 3 weeks, then twice weekly for 9 weeks | The 12-week study with vaginal administration of CE tablet had no demonstrable effects on the changes in the FSFI |
| C | 33 | Placebo |
| Carmignani 2015 | I | 20 | E2 and norethisterone acetate tablet | 1 mg of E2 and 0.5 mg of norethisterone acetate once daily for 16 weeks | Sexual symptoms did not change with treatment. |
| C | 20 | Placebo |
| Caruso 2017 | I | [1]19  [2]19 | 0.005% E2 vaginal cream | [1] 1g once daily for 3 weeks, then twice weekly for 9 weeks, then 1 week with no treatment, then once daily for 3 weeks, then twice weekly for 9 weeks  [2] 1g once daily for 3 weeks, then twice weekly for 9 weeks | The improvement in the no intervention group was lower than that in E2 vaginal gel before and after surgery (25 weeks) group, and similar to that in E2 vaginal gel before surgery only group (12 weeks). |
| C | 37 | No intervention |
| Constantine 2015 | I | 463 | Oral ospemifene | 60mg once daily for 12 weeks | Treatment with ospemifene significantly improved the total FSFI score and FSFI domain scores. |
| C | 456 | Placebo |
| Cruz 2015 | I | 15 | E2 vaginal cream | 1mg three times a week for 20 weeks | CO2 laser+E2 vaginal cream and CO2 laser+placebo arms were not compared in this trial. |
| C | 15 | Placebo |
| Davison 2013 | I | 12 | E2 and drospirenone oral tablet | 1 mg of E2 and 2 mg of drospirenone once daily for 26 weeks | At 26 weeks, there was a significant difference between treatment groups in the MENQOL sexual function score adjusted for age and baseline, indicating E2 and drospirenone treatment benefit. |
| C | 11 | Placebo |
| Ferrante 2021 | I | 17 | Vaginal CE cream or E2 ring | 0.5 g (=0.312mg of CE) twice weekly for 6 months or 2mg ring every 3 months | CE vaginal cream and placebo were not compared in this trial. |
| C | 17 | Placebo |
| Hirschberg 2017 | I | 50 | E3 vaginal gel | 1g (=50mg of E3) once daily for 3 weeks, then 1g (=50mg of E3) twice weekly for 9 weeks | The pairwise comparison did not reveal significant differences between active and placebo groups regarding the total FSFI score and the scores of each domain. |
| C | 11 | Placebo |
| KEEPS-sexual 2017 | I | [1]230  [2]222 | [1] CEE oral pill and progesterone oral capsule  [2] 17ß-E2 transdermal patch and progesterone oral capsule | [1] 0.45mg of CEE daily and 200mg of progesterone for 12 days a month  [2] 50µg E2 daily and 200mg of progesterone for 12 days a month | Compared with placebo, the E2 group showed significant improvements in desire, arousal, orgasm, and satisfaction scores at 18 months. Treatment with CEE demonstrated fewer significant improvements relative to placebo. |
| C | 275 | Placebo |
| Lillemon 2022 | I | 20 | E2 vaginal ring | 2mg E2 ring for 12 weeks | There were no significant changes in FSFI scores |
| C | 19 | Placebo |
| Mac Bride 2014 | I | [1]19  [2]18 | [1] E2 vaginal cream  [2] E3 vaginal cream | [1] 0.5g (=10µg of E2) once daily for 2 weeks, then twice weekly for 10 weeks | There was not a statistically significant difference in sexual function composite score either between the 3 groups or between the 2 active treatment groups and the placebo group |
|  | C | 19 | Placebo | [2] 0.5g (=10µg of E3) once daily for 2 weeks, then twice weekly for 10 weeks |
| MsFLASH VMS 2014, 2015 | I | 97 | Oral 17ß-E2 | 0.5mg daily for 8 weeks | In an adjusted linear regression model, 8-week treatment with E2 compared with placebo did not affect composite FSFI among the women who were sexually active at baseline. |
| C | 146 | Placebo |
| MsFLASH VHT 2018, 2018, 2019, 2020 | I | 102 | E2 vaginal tablet | 10µg once daily for 2 weeks, then twice weekly for 10 weeks | Change in FSFI did not significantly vary between treatment groups, either total score or any of the 6 domains |
| C | 100 | Placebo |
| Olmez 2017 | I | [1]16  [2]16 | [1] Tibolone  [2] E2 and MPA | [1] 2.5mg daily  [2] 0.625mg of E2 and 5mg of MPA daily | HT and placebo arms FSFI scores were not compared. Only before and after treatment FSFI scores in each arm were compared. |
| C | 17 | Placebo |
| REJOICE 2016 | I | [1]191  [2]191  [3]190 | 17ß-E2 vaginal soft-gel capsule | [1] 4µg once daily for 2 weeks, then twice a week for 10 weeks  [2] 10µg once daily for 2 weeks, then twice a week for 10 weeks  [3] 25µg once daily for 2 weeks, then twice a week for 10 weeks | 17ß-E2 vaginal soft-gel capsule improved FSFI scores in a dose-dependent manner. |
| C | 192 | Placebo |
| Sun 2016 | I | 93 | Promestriene vaginal cream | 0.5g twice weekly for 6 weeks | There was no significant difference in PISQ-12 decrease from baseline to month 12 among women receiving and not receiving vaginal estrogen therapy. |
| C | 93 | No intervention |
| Tanmahasamut 2020 | I | 40 | 17ß-E2 vaginal gel | 2mL (=25µg of E2) once daily for 2 weeks, then twice weekly for 6 weeks | The mean FSFI summary score was significantly increased at week 8 in the E2 group, but they were not significantly different in the control group. At week 8, the E2 group had statistically significant improvement in lubrication, orgasm and pain. |
| C | 40 | Placebo |
| Verghese 2020 | I | 50 | E2 vaginal pessaries | 10µg once daily for 2weeks, then twice weekly for 4weeks, then 6 weeks with no treatment after surgery, then twice weekly for 20 weeks | The majority of women in both trial groups reported improvement in their sexual function. |
| C | 50 | No intervention |

a C, Control; CE, Conjugated Estrogen; CEE, Conjugated Equine Estrogen; DIVA, Day-to-Day Impact of Vaginal Aging questionnaire; E2, Estradiol; E3, Estriol; FSFI, Female Sexual Function Index; GSM, Genitourinary Syndrome of the Menopause; HT, Hormone Therapy; I, Intervention; LSSQ, Larson sexual satisfaction questionnaire; MBS, Most Bothersome Symptom; MENQOL, Menopause Quality Of Life questionnaire; MPA, medroxyprogesterone acetate; MRS, Menopause Rating Scale; N, Number of participants randomized; PISQ12, Pelvic Organ Prolapse/Urinary Incontinence Sexual Questionnaire-12

**Table 2. Risk of bias of included studies**[[2]](#footnote-2)

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Study** | Bias arising from the randomization process  (Domain 1) | Bias due to deviation from intended intervention (Domain 2) | Bias due to missing outcome data  (Domain 3) | Bias in measurement of the outcome (Domain 4) | Bias in selection of reported results (Domain 5) | **Overall risk of bias** |
| **Estrogen Therapy vs Control** | | | | | | |
| **Bosak 2020** | Some concerns | Low | High | Low | Some concerns | **High** |
| **Bumphenkiatikul 2020** | Low | Low | Some concerns | Low | Some concerns | **Some concerns** |
| **Caruso 2017** | Some concerns | Some concerns | High | Some concerns | Some concerns | **High** |
| **Cruz 2015** | Low | Low | High | Low | Some concerns | **High** |
| **Ferrante 2021** | Low | Low | High | High | Some concerns | **High** |
| **Hirschberg 2020** | Low | Low | High | Low | Some concerns | **High** |
| **Lillemon 2022** | Some concerns | Some concerns | Some concerns | Low | Some concerns | **High** |
| **Mac Bride 2014** | Some concerns | Low | Some concerns | Low | High | **High** |
| **MsFLASH VHT** | Low | Low | Low | Low | Low | **Low** |
| **MsFLASH VMS** | Low | Low | High | Low | Some concerns | **High** |
| **REJOICE** | Some concerns | Some concerns | Some concerns | Low | Some concerns | **High** |
| **Sun 2016** | Low | Some concerns | High | Some concerns | Some concerns | **High** |
| **Tanmahasamut 2020** | Low | Low | High | High | Some concerns | **High** |
| **Verghese 2020** | Low | Some concerns | High | Some concerns | Low | **High** |
| **Estrogen plus Progestogen Therapy vs Control** | | | | | | |
| **Carmigani 2015** | Low | Low | Low | Low | Some concerns | **Some concerns** |
| **Davison 2013** | Low | Low | Some concerns | Low | Some concerns | **Some concerns** |
| **KEEPS-sexual** | Some concerns | High | High | Low | Low | **High** |
| **Olmez 2017** | Some concerns | Low | High | Low | Some concerns | **High** |
| **Tibolone vs Control** | | | | | | |
| **Olmez 2017** | Some concerns | Low | High | Low | Some concerns | **High** |
| **SERMs vs Control** | | | | | | |
| **Archer 2019** | Low | Low | High | Low | Low | **High** |
| **Constantine 2015** | Some concerns | Low | Some concerns | Low | Some concerns | Some concerns |

1. a CI, Confidence Interval; HT, Hormone Therapy; IV, Inverse Variance; SD, Standard Deviation; Std., Standardized [↑](#footnote-ref-1)
2. For the outcome sexual function composite score for all studies except Bosak 2020 (outcome sexual satisfaction) [↑](#footnote-ref-2)