Mini-CAT Final Name Arianne Diaz

Clinical Question: *Brief description of patient problem/setting (summarize the case very briefly)*
While on my LTC rotation, I encountered a handful of patients with vaginitis and recurrent UTIs. My preceptor informed me that post-menopausal women are more likely to develop these issues due to lack of estrogen. She said that application of vaginal estrogen would be beneficial in mitigating symptoms associated with vaginitis and UTI.

PICO Search Question: *Clearly state the question (including outcomes or criteria to be tracked)*
In post-menopausal women, how does use of vaginal estrogen versus no treatment affect rates of vaginitis and UTI?

PICO Search terms:

Population	Intervention	Comparison	Outcome
Post-menopausal women	Vaginal estrogen	No treatment	Decreased incidence of vaginitis
			Decreased incidence of UTI

Search tools and strategy used:
Please indicate what data bases/tools you used, provide a list of the terms you searched together in each tool, and how many articles were returned using those terms and filters.

Database	Terms	Filter	Articles
Wiley Online Library	Post-menopausal women AND vaginal estrogen AND no treatment AND vaginitis or UTI	Open access content published within the last ten years	4 results
Cochrane Library (Wiley)	Post-menopausal patients AND vaginal estrogen AND vaginitis/UTI	Randomized control trials published within the last ten years	14 results
PubMed	Post-menopausal women AND vaginal estrogen AND no treatment AND vaginitis OR UTI	Free full text systematic reviews published within the last ten years	211 results
UpToDate	Improvement of genitourinary syndrome in postmenopausal women using vaginal estrogen	Looked at the references section of *Genitourinary Syndrome of Menopause (Vulvovaginal Atrophy): Treatment* and selected "Systematic Review"	154 references
JAMA	Vaginal estrogen in postmenopausal women for vaginitis and UTI	Review articles including urinary tract infections and recurrent urinary tract infections	2 results
TRIP Database	PICO Format: P → post-menopausal women I → vaginal estrogen C → no treatment O → decrease in vaginitis AND UTI	Systematic reviews published within the last ten years	17 results
Google Scholar	Post-menopausal women AND vaginal estrogen AND no treatment AND vaginitis or UTI "systematic reviews"	Review articles published within the last ten years	179 results

Results found: 581 results

Explain how you narrow your choices to the few selected articles.

I narrowed down my searches to focus on articles of the highest level of evidence that were published within the last ten years. I aimed to find systematic reviews, meta-analysis, or randomized control trials conducted in the United States. Systematic reviews are of the highest level of evidence because they synthesize RCTs and other research that meets specific inclusion criteria. Meta-analyses provide the "numerical summary" of the results across a study and are often-times combined with systematic reviews. Randomized control trials implement blinding to mitigate bias and are used to evaluate the therapeutic and preventive aspects of medical practice. Since I am comparing the efficacy of vaginal estrogen in managing symptoms of vaginitis and UTI in postmenopausal women, RCTs are appropriate. The three databases that yielded the most results were PubMed, UpToDate, and Google Scholar. For PubMed, I skimmed through all the results because this is the database I have found to be most reliable when developing my previous PICOs. For UpToDate, I used the references section, but I realized that there were limited systematic reviews so after I scrolled through the first two pages, I decided I would use my other databases to select articles. Finally, for Google Scholar I skimmed through the first five pages and was able to find two articles.

Articles Chosen:

Article #1

CITATION	Rahn DD, Carberry C, Sanses TV, et al. Vaginal estrogen for genitourinary syndrome of menopause: a systematic review. *Obstet Gynecol*. 2014;124(6):1147-1156. doi:10.1097/AOG.0000000000000526
ABSTRACT	**Objective:** To comprehensively review and critically assess the literature on vaginal estrogen and its alternatives for women with genitourinary syndrome of menopause and to provide clinical practice guidelines. **Data sources:** MEDLINE and Cochrane databases were searched from inception to April 2013. We included randomized controlled trials and prospective comparative studies. Interventions and comparators included all commercially available vaginal estrogen products. Placebo, no treatment, systemic estrogen (all routes), and nonhormonal moisturizers and lubricants were included as comparators. **Methods of study selection:** We double-screened 1,805 abstracts, identifying 44 eligible studies. Discrepancies were adjudicated by a third reviewer. Studies were individually and collectively assessed for methodologic quality and strength of evidence. **Tabulation, integration, and results:** Studies were extracted for participant, intervention, comparator, and outcomes data, including patient-reported atrophy symptoms (eg, vaginal dryness, dyspareunia, dysuria, urgency, frequency, recurrent urinary tract infection (UTI), and urinary incontinence), objective signs of atrophy, urodynamic measures, endometrial effects, serum estradiol changes, and adverse events. Compared with placebo, vaginal estrogens improved dryness, dyspareunia, urinary urgency, frequency, and stress urinary incontinence (SUI) and urgency urinary incontinence (UUI). Urinary tract infection rates decreased. The various estrogen preparations had similar efficacy and safety; serum estradiol levels remained within postmenopausal norms for all except high-dose conjugated equine estrogen cream. Endometrial hyperplasia and adenocarcinoma were extremely rare among those receiving vaginal estrogen. Comparing vaginal estrogen with nonhormonal moisturizers, patients with two or more symptoms of vulvovaginal atrophy were substantially more improved using vaginal estrogens, but those with one or minor complaints had similar symptom resolution with either estrogen or nonhormonal moisturizer. **Conclusion:** All commercially available vaginal estrogens effectively relieve common vulvovaginal atrophy-related complaints and have additional utility in patients with urinary urgency, frequency or nocturia, SUI and UUI, and recurrent UTIs. Nonhormonal moisturizers are a beneficial alternative for those with few or minor atrophy-related symptoms and in patients at risk for estrogen-related neoplasia.

LINK/PDF	https://pmc.ncbi.nlm.nih.gov/articles/PMC4855283/ **PDF POSTED ON BLACKBOARD**

Article #2

CITATION AMA FORMAT	Weidlinger S, Schmutz C, Janka H, Gruetter C, Stute P. Sustainability of vaginal estrogens for genitourinary syndrome of menopause - a systematic review. *Climacteric*. 2021;24(6):551-559. doi:10.1080/13697137.2021.1891218
ABSTRACT	Genitourinary syndrome of menopause (GSM) is a highly prevalent, not self-limiting condition displaying a major negative impact on sexual function and emotional well-being. Various non-hormonal and hormonal treatment options are available. Many women consider GSM treatment to be a short-term interval cure rather than a long-term or lifelong treatment. The aim of this systematic literature search was to assess the sustainability of vaginal estrogens for GSM treatment after treatment cessation. We found that objective GSM signs mostly deteriorated within approximately 4 weeks after vaginal estro- gen treatment cessation, while vaginal estrogens had a more sustainable impact on subjective GSM symptoms up to 3–6months. However, overall, scientific evidence on sustainability of vaginal estro- gens was low. Thus, GSM treatment should not be considered a short-term interval cure but long- term therapy. Further studies in an internationally harmonized setting (Core Outcomes in Menopause [COMMA]) are needed.
LINK/PDF	https://pubmed.ncbi.nlm.nih.gov/33709861/#:~:text=We%20found%20that%20objective%20GSM,of%20vaginal%20estrogens%20was%20low **PDF POSTED ON BLACKBOARD**

Article #3

CITATION	Danan ER, Sowerby C, Ullman KE, et al. Hormonal Treatments and Vaginal Moisturizers for Genitourinary Syndrome of Menopause : A Systematic Review. *Ann Intern Med*. 2024;177(10):1400-1414. doi:10.7326/ANNALS-24-00610
ABSTRACT	**Background:** Postmenopausal women commonly experience vulvovaginal, urinary, and sexual symptoms associated with genitourinary syndrome of menopause (GSM). **Purpose:** To evaluate effectiveness and harms of vaginal estrogen, nonestrogen hormone therapies, and vaginal moisturizers for treatment of GSM symptoms. **Data Sources:** Medline, Embase, and CINAHL through 11 December 2023. **Study Selection:** Randomized controlled trials (RCTs) of at least 8 weeks' duration enrolling postmenopausal women with at least 1 GSM symptom and reporting effectiveness or harms of hormonal interventions or vaginal moisturizers. **Data Extraction:** Risk of bias and data extraction were performed by one reviewer and verified by a second reviewer. Certainty of evidence (COE) was assessed by one reviewer and verified by consensus. **Data Synthesis:** From 11 993 citations, 46 RCTs evaluating vaginal estrogen (k = 22), non-estrogen hormones (k = 16), vaginal moisturizers (k = 4), or multiple interventions (k = 4) were identified. Variation in populations, interventions, comparators, and outcomes precluded meta-analysis. Compared with placebo or no treatment, vaginal estrogen may improve vulvovaginal dryness, dyspareunia, most bothersome symptom, and treatment satisfaction. Compared with placebo, vaginal dehydroepiandrosterone (DHEA) may improve dryness, dyspareunia, and distress, bother, or interference from genitourinary symptoms; oral ospemifene may improve dryness, dyspareunia, and treatment satisfaction; and vaginal moisturizers may improve dryness (all low COE). Vaginal testosterone, systemic DHEA, vaginal oxytocin, and oral raloxifene or bazedoxifene may provide no benefit (low COE) or had uncertain effects (very low COE). Although studies did not report

	frequent serious harms, reporting was limited by short-duration studies that were insufficiently powered to evaluate infrequent serious harms. **Limitations:** Most studies were 12 weeks or less in duration and used heterogeneous GSM diagnostic criteria and outcome measures. Few studies enrolled women with a history of cancer. **Conclusion:** Vaginal estrogen, vaginal DHEA, oral ospemifene, and vaginal moisturizers may improve some GSM symptoms in the short term. Few long-term data exist on efficacy, comparative effectiveness, tolerability, and safety of GSM treatments.
LINK/PDF	https://www.acpjournals.org/doi/full/10.7326/ANNALS-24-00610?rfr_dat=cr_pub++0pubmed&url_ver=Z39.88-2003&rfr_id=ori%3Arid%3Acrossref.org **PDF POSTED ON BLACKBOARD**

Article #4

CITATION AMA FORMAT	Chen YY, Su TH, Lau HH. Estrogen for the prevention of recurrent urinary tract infections in postmenopausal women: a meta-analysis of randomized controlled trials. *Int Urogynecol J*. 2021;32(1):17-25. doi:10.1007/s00192-020-04397-z
ABSTRACT	**Introduction and Hypothesis**: Recurrent urinary tract infections (rUTIs) are commonly encountered in postmenopausal women. Optimal non-antimicrobial prophylaxis for rUTIs is an important health issue. The aim of this study was to evaluate the use of estrogen in the prevention of rUTIs versus placebo. **Methods**: Eligible studies published up to December 2019 were retrieved through searches of MEDLINE, Embase, and Cochrane Central Register of Controlled Trials and Database of Systematic Reviews. We included randomized controlled trials of estrogen therapies versus placebo regarding the outcomes of preventing rUTIs. Changes in vaginal pH and estrogen-associated adverse events were also analyzed. **Results**: Eight studies including 4702 patients (2367 who received estrogen and 2335 who received placebo) were identified. Five studies including 1936 patients evaluated the use of vaginal estrogen, which resulted in a significant reduction in rUTIs (relative risk, 0.42; 95% CI, 0.30–0.59). Three studies including 2766 patients evaluated the outcomes of oral estrogen in the prevention of UTIs and showed no significant difference in the number of rUTIs compared to treatment with placebo (relative risk, 1.11; 95% CI, 0.92–1.35). Two studies reviewed changes in vaginal pH and showed a lower pH (mean difference, −1.81; 95% CI, −3.10– −0.52) after vaginal estrogen therapy. Adverse events associated with vaginal estrogen were reported, including vaginal discom- fort, irritation, burning, and itching. There was no significance increase in the vaginal estrogen group (relative risk, 3.06; 95% CI, 0.79–11.90). **Conclusions**: Compared with placebo, vaginal estrogen treatment could reduce the number of rUTIs and lower the vaginal pH in postmenopausal women.
LINK/PDF	https://pubmed.ncbi.nlm.nih.gov/32564121/ **PDF POSTED ON BLACKBOARD**

Article #5

CITATION AMA FORMAT	Ali A, Iftikhar A, Tabassum M, et al. Efficacy and Safety of Intravaginal Estrogen in the Treatment of Atrophic Vaginitis: A Systematic Review and Meta-Analysis. *J Menopausal Med*. 2024;30(2):88-103. doi:10.6118/jmm.23037
ABSTRACT	**Objectives:** Postmenopausal females often experience genitourinary symptoms like vulvovaginal dryness due to estrogen decline. Hormone replacement therapy is effective in alleviating vaginal atrophy and genitourinary syndrome in this population. Evaluate local estrogen's safety and

	effectiveness for alleviating postmenopausal vaginal symptoms, including endometrial thickness, dyspareunia, vaginal pH, and dryness. **Methods:** We searched Google Scholar, Cochrane Library, ClinicalTrial.Gov, PubMed, and ScienceDirect databases until July 2023. All randomized controlled trials (RCTs) linking intravaginal estrogen supplementation to vaginal atrophy or vaginitis were included. The risk of bias was evaluated with RoB 2, and publication bias was assessed using Egger and Beggs analysis. **Results:** All evidence pertains to females. Eighteen studies (n = 4,723) compared estrogen with placebo. Patients using estrogen showed a significant increase in superficial cells (mean differences [MD]: 19.28; 95% confidence intervals [CI]: 13.40 to 25.16; I2 = 90%; P < 0.00001) and a decrease in parabasal cells (MD: –24.85; 95% CI: –32.96 to –16.73; I2 = 92%; P < 0.00001). Vaginal pH and dyspareunia significantly reduced in estrogen users (MD: –0.94; 95% CI: –1.05 to –0.84; I2 = 96%) and (MD: –0.52; 95% CI: –0.63 to –0.41; I2 = 99%), respectively. Estrogen did not significantly affect vaginal dryness (MD: –0.04; 95% CI: –0.18 to 0.11; I2 = 88%). Adverse events like vulvovaginal pruritis, mycotic infection, and urinary tract infection were reported, but the association was insignificant (risk ratio: 0.95; 95% CI: 0.88 to 1.02; I2 = 0%). **Conclusions:** Our meta-analysis of 18 RCTs suggests promising potential for intravaginal estrogen therapy in alleviating vaginal atrophy and vaginitis in postmenopausal females.
LINK/PDF	https://pmc.ncbi.nlm.nih.gov/articles/PMC11439571/ **PDF POSTED ON BLACKBOARD**

Article #6

CITATION AMA FORMAT	Archer DF, Kimble TD, Lin FDY, Battucci S, Sniukiene V, Liu JH. A Randomized, Multicenter, Double-Blind, Study to Evaluate the Safety and Efficacy of Estradiol Vaginal Cream 0.003% in Postmenopausal Women with Vaginal Dryness as the Most Bothersome Symptom. *J Womens Health (Larchmt)*. 2018;27(3):231-237. doi:10.1089/jwh.2017.6515
ABSTRACT	**Background**: Vulvovaginal atrophy (VVA) is characterized by vaginal/vulvar dryness, irritation, dyspareunia, or dysuria. The objective of this study was to examine the efficacy and safety of a very low-dose estradiol vaginal cream (0.003%) applied twice per week in postmenopausal women with VVA-related vaginal dryness. **Materials and Methods**: In this phase 3, randomized, double-blind, placebo-controlled, multicenter study, postmenopausal women with moderate–severe vaginal dryness as the most bothersome VVA symptom were randomized (1:1) to estradiol cream 0.003% (15 lg estradiol; 0.5 g cream) or placebo (0.5 g cream). Treatments were applied vaginally once daily for 2 weeks followed by two applications/week for 10 weeks. Coprimary outcomes were changes in severity of vaginal dryness, percentage of vaginal superficial and parabasal cells, and vaginal pH at final assessment. Additional outcomes comprised changes in severity of other VVA signs and symptoms. Adverse events (AEs) were assessed. **Results**: Of the 576 randomized participants, most were white and had an average age of 59 years. At final assessment, estradiol reduced vaginal dryness severity, decreased vaginal pH, increased superficial cell per- centage, and decreased parabasal cell percentage versus placebo (p £ 0.05, all). Estradiol also reduced vaginal dryness severity at Weeks 4–12 and dyspareunia at Week 8 versus placebo (p£0.05, all). Improvements in vaginal/vulvar irritation/itching severity and dysuria were similar between estradiol and placebo. Estradiol had comparable rates of treatment-emergent AEs to placebo. No deaths occurred. **Conclusions**: Very low-dose estradiol vaginal cream (0.003%) dosed twice weekly is an effective and well- tolerated treatment for VVA symptoms and dryness associated with menopause.
LINK/PDF	https://pubmed.ncbi.nlm.nih.gov/29193980/ **PDF POSTED ON BLACKBOARD**

Summary of the Evidence:

Authors	Level of Evidence	Sample/Setting (# of subjects/ studies, cohort definition etc.)	Outcome(s) studied	Key Findings	Limitations and Biases
David D. Rahn, Cassandra Carberry, Tatiana V. Sanses, Mamta M. Mamik, Renée M. Ward, Kate V. M., Cedric K. Olivera, Husam Abed, Ethan M. Balk, Miles Murphy	Systematic Review	44 studies were selected for this systematic review. These studies were randomized control trials and prospective comparative studies Authors selected fourteen studies comprised of 4,232 participants; eighteen studies comprised of 2,236; five studies comprised of 226 participants; five studies comprised of 264 participants, and two studies "which could not be characterized by the four groupings" Participants were defined as postmenopausal women identified as having genitourinary syndrome of menopause: vaginal/vulvar dryness, burning, dyspareunia, dysuria, urgency, and frequency	Primary outcomes: improvement in vaginal symptoms such as vaginal dryness, burning, and dyspareunia, changes in urinary symptoms such as dysuria, frequency, urgency, and nocturia	Fourteen trials compared a vaginal estrogen with placebo/no treatment. Studies primarily demonstrated improvement in vaginal dryness, itching, burning, dyspareunia, with estrogen use. Frequency of UTI was decreased in those who used vaginal estrogen Eighteen trials compared a vaginal estrogen to another vaginal estrogen. No differences found in efficacy between preparations. Patients reported relief in vaginal dryness, itching, burning, dyspareunia, dysuria, urgency, and nocturia. Five studies compared an estrogen (by various routes) designed to deliver a systemic dose. Administration of estrogen by various routes vs systemic dosing demonstrated comparable improvement in relieving vaginal dryness, dyspareunia, dysuria, urgency, frequency, and nocturia. Five studies compared a vaginal estrogen nonhormonal moisturizer or lubricant. Patients with two or more symptoms associated with genitourinary syndrome of menopause	Authors were unable to comment on the safety/efficacy of ospemifene, compound vaginal estrogen products, or herbal/natural alternatives Most studies in the review had 12 weeks of follow-up, long-term efficacy and safety cannot be determined Some studies were supported by "low-quality" evidence. No universal tool for assessing improvement in patient symptoms, results were patient-reported Limited data on the risk of thromboembolism or development of breast cancer

				reported more relief when using vaginal estrogen compared to a non-hormonal moisturizer/lubricant.	
S. Weidlinger, C. Schmutz, H. Janka, C. Gruetter, and P. Stute	Systematic Review	Nine studies were selected for this systematic review. These studies were randomized control trials, prospective cohort studies, and retrospective cohort studies. The sample size of the cohorts treated with the product of interest ranged from 19 to 222 subjects Participants were defined as postmenopausal women undergoing vaginal estrogen therapy for management of symptoms related to genitourinary syndrome (GSM)	Vaginal health index, vaginal maturation index, vaginal maturation value, estrogen index, vaginal pH Vaginal dryness, irritation, and itching, dyspareunia, leukorrhea, urinary frequency, and urinary urgency, quality of life	Types of vaginal estrogen used include estriol, estradiol, and conjugated equine estrogens. Formulations varied between gel, ovule, cream, ring, or pessary. Dosage was either ultralow dose, low dose, standard dorse, or high dose. Patients managed with vaginal estriol (low dose) reported significant VHI improvement during the three-month follow-up. VMI improved by 12 weeks of treatment. Vaginal pH significantly decreased. Dryness, irritation, dyspareunia, and chronic leukorrhea were markedly improved after 8 weeks of treatment Patients managed with vaginal estradiol (high dose) experienced significant improvement in symptoms associated with GSM after 8 weeks of treatment. Patients managed with vaginal estradiol (low dose) experienced significant improvement in these symptoms after 24 weeks. Patients managed with vaginal conjugated equine estrogens (varying doses) experienced improvement in Estrogen Index after 4 weeks of therapy, and improvement in urinary	Only three studies assess both the objective signs and subjective symptoms of GSM Study design, cohort characteristics, sample sizes, interventions, treatment duration, and follow-up of the different studies made direct comparison of vaginal estrogen products impossible. There is limited data to support whether different estrogen doses impact efficacy in managing symptoms Many studies had a short follow-up period and focused on the effects immediately after treatment cessation Lack of randomization control in some studies

				symptoms after 6 weeks of therapy In all studies, once treatment was discontinued, patients experienced a gradual return of symptoms, though not to the same severity as before starting therapy.	
Elisheva R. Danan, Catherine Sowerby, Kristen E. Ullman, Kristine Ensrud, Mary L. Forte, Nicholas Zerzan, Maylen Anthony, Caleb Kalinowski, Hamdi I. Abdi, Jessica K. Friedman, Adrienne Landsteiner, Nancy Greer, Rahel Nardos, Cynthia Fok, Philipp Dahm, Mary Butler, Timothy J. Wilt, and Susan Diem	Systematic Review	46 randomized control trials were selected for this systematic review. Ten studies comprised of 2,400 participants compared efficacy of vaginal estrogen to placebo or no treatment. The remaining studies compared efficacy of other products (vaginal/oral DHEA, oral ospemifene, oral raloxifene, vaginal oxytocin, vaginal testosterone, and vaginal estrogen) to placebo. Verification of vaginal atrophy was performed using vaginal cytology or by measurement of pH. For most trials, participants were defined as postmenopausal women (primarily in their 50s) with moderate to severe symptoms related to genitourinary syndrome of menopause.	Dyspareunia, vulvovaginal dryness, vulvovaginal discomfort or irritation, dysuria, change in the most bothersome symptom, distress, bother, or interference from genitourinary symptoms, satisfaction with treatment, adverse effects of treatment	Trials comparing vaginal estrogen to placebo reported their findings after 8-12 weeks of treatment. Seven trials that assessed vaginal dryness reported improvement in symptoms in those managed with estrogen. Only four trials, however, reported a clinically significant difference. Six trials that assessed dyspareunia reported improvement in symptoms in the estrogen group. Only three trials, however, reported a clinically significant difference. Six trials discontinued their studies due to adverse effects associated with estrogen use, including allergic vaginitis, breast pain, and pelvic pain Trials comparing vaginal estrogen to no treatment reported resolution of vulvovaginal dryness and dyspareunia in the vaginal estrogen group during the 36 week follow up. Five participants discontinued the study due to “local discomfort, hot flashes, or more frequent urinary tract infections”.	Increased heterogeneity of the studies made it difficult to synthesize findings through meta-analysis. Grading of recommendations, assessment, development, and evaluation as well as class of evidence ratings were based on statistical measures of significance as opposed to magnitude of effects or clinical significance. Lack information regarding management of genitourinary syndrome in women with a history of breast cancer or those receiving breast cancer or urogenital cancer treatment. Not all trials were considered “high-quality”

Ying-Yu Chen, Tsung-Hsien Su, Hui-Hsuan Lau	Meta-Analysis	Eight randomized control trials were selected for this meta-analysis. Five studies comprised of 1,936 patients evaluated the use of vaginal estrogen versus placebo in preventing UTI. Types of preparations include estradiol silicone rings, conjugated estrogen cream, and estriol vaginal inserts (creams, ovules). Three studies comprised of 2,766 patients evaluated the use of oral estrogen versus placebo in preventing UTI. These studies used estriol and a combination of conjugated estrogens with MPA. Participants were defined as postmenopausal women diagnosed with recurrent urinary tract infections, with recurrence being defined as at least two episodes of UTIs within 6 months or three episodes within one year.	Reduction in recurrent UTIs, efficacy of different estrogen preparations, pH, adverse effects	Use of vaginal estrogen versus placebo was associated with significant reduction in UTI recurrence in all five trials regardless of preparation type (relative risk, 0.42; 95% confidence interval, 0.30-0.59). Use of oral estrogen versus placebo did not demonstrate significant reduction in UTI recurrence in two trials (relative risk, 1.11; 95% confidence interval, 0.92-1.35). Use of oral estrogen versus placebo demonstrated significant improvement at 12 weeks Vaginal estrogen therapy was associated with significant decrease in vaginal pH (mean difference, -1.81; 95% confidence interval, -3.10-0.52) Adverse effects secondary to vaginal estrogen therapy included vaginal discomfort, irritation, burning, and pruritus Adverse effects secondary to oral estrogen included vaginal bleeding and breast pain.	Searches were limited to articles published in English Unclear long-term outcomes due to short duration of studies. The maximum duration of vaginal estrogen therapy reviewed was only 36 weeks. Bias from combination hormone therapy and insufficient data to assess the effects of progestins in patients with recurrent UTIs Individual characteristics, patient compliance, application skill, and delivery system may have influenced effectiveness (ie: an estrogen containing vaginal pessary providing continuous estrogen vs vaginal cream which requires daily application)
Abraish Ali, Aliha Iftikhar, Muzainah Tabassum, Rayaan Imran, Muhammad Usama Shaid, Mahnoor	Systematic Review and Meta-Analysis	Eighteen randomized control trials comprised of 4,723 post-menopausal women were selected for this systematic review and meta-analysis. Participants were defined as	Vaginal maturation index, vaginal pH, dyspareunia, vaginal dryness, common adverse events including vulvovaginal	When comparing vaginal estrogen to placebo, vaginal estrogen therapy demonstrated an increase in superficial cells (MD: 19.28; 95% CI: 13.40 to 25.16; I2 = 90%; P < 0.00001) and a decrease in parabasal cells (MD: –24.85; 95%	Baseline values for VMI and vaginal pH varied across studies Less than half of the RCTs reported on specific outcomes such as dysuria

Rehan Hashmi, Muhammad Saad, Mahnoor Humayun, Sidra Imtiaz, Eesha Baig		postmenopausal women who had not menstruated in >1 year or who had a serum FSH of >40 IU/L or women who underwent bilateral oophorectomy showing signs of vaginal atrophy or vaginitis. Vaginal estrogen was used in various formulations including creams, gels, pessaries, ovules, tablets, and estrogen releasing ring.	pruritus, vulvovaginal mycotic infection, and urinary tract infection	CI: –32.96 to –16.73; I2 = 92%; P < 0.00001) Vaginal estrogen therapy also demonstrated a significant reduction in vaginal pH (MD: –0.94; 95% CI: –1.05 to –0.84; I2 = 96%; P < 0.00001). Participants taking a 15 µg dosage of estrogen demonstrated a clinically significant reduction in vaginal pH (MD: –0.92; 95% CI: –1.08 to –0.75; I2 = 53%; P < 0.00001) when compared to those taking <2.5 µg and 50 µg. Significant reduction in dyspareunia was reported in patients using vaginal estrogen during the 12-week follow up (MD: –0.52; 95% CI: –0.63 to –0.41; I2 = 99%; P < 0.00001) There was no statistically significant improvement in vaginal dryness for patients using vaginal estrogen (MD: –0.04; 95% CI: –0.18 to 0.11; I2 = 88%; P = 0.60)	Comparing various formulations of vaginal estrogen made it difficult to determine which form was most efficacious Some studies did not report adverse events Lack of recently updated articles in the search databases including Cochrane, PubMed, and Google Scholar
David F. Archer, Thomas D. Kimble, F.D. Yuhua Lin, Simona Battucci, Vilma Sniukiene, James H. Liu	Randomized Control Trial	576 participants were randomized in the study: 573 were included in the safety population and 488 were included in the mITT population. Participants were randomized to estradiol cream 0.003% (15 lg estradiol; 0.5 g cream) or placebo (0.5 g cream). Majority of participants were white women and	Change in vaginal dryness, percentage of superficial and parabasal cells, vaginal pH, changes in severity of other symptoms associated with vulvovaginal atrophy such as vulvar itching, dysuria, and dyspareunia, adverse events	When comparing estradiol vaginal cream to placebo, estradiol reduced vaginal dryness, reduced dyspareunia, decreased vaginal pH, increased the number of superficial cells, and decreased the number of parabasal cells, indicating an overall improvement in vaginal tissue. Participants treated with estradiol vaginal cream reported similar adverse effects as those treated with placebo, demonstrating that the therapy is well-tolerated.	Majority of participants identified as white, limiting application of findings to other racial/ethnic groups No measurement of estradiol levels throughout study Limited information on the systemic effects of estradiol treatment for postmenopausal women with

		had a mean age of 59 years. Participants were selected for the study if they met at least one of the following criteria: women ≥ 35 years old who underwent bilateral oophorectomy with an FSH level > 40 mIU/mL, women ≥ 40 years old who underwent hysterectomy with an FSH level > 40 mIU/mL, women ≥ 40 years old with 12 months of amenorrhea, women ≥ 40 years old with 6 months of amenorrhea and an FSH level > 40 mIU/mL. Participants were required to identify vaginal dryness as the most bothersome symptom associated with vulvovaginal atrophy.		The most common adverse effect associated with this therapy was vulvovaginal mycotic infections. Serious treatment emergent adverse effects were reported in four participants, two in each treatment group. It was found that these adverse effects were not associated to the study drug, therefore no discontinuation of treatment was necessary. No deaths occurred during the study. Administration of Estradiol vaginal cream (0.003%) twice a week with is effective for management of vulvovaginal atrophy and dryness in postmenopausal women.	vulvovaginal atrophy and vaginal dryness

Conclusion(s):

Briefly summarize the conclusions of each article, then provide an overarching conclusion.

Article #1:

Post-menopausal women with genitourinary syndrome are initially managed with non-hormonal vaginal lubricants and moisturizers. While this may be effective for some, most postmenopausal women do not experience relief with these measures. Authors of this study determined that vaginal estrogen therapy is effective in managing genitourinary syndrome, particularly in addressing symptoms associated with vulvovaginal atrophy such as dryness, itching, burning, and dyspareunia. Vaginal estrogen was also effective in reducing urinary symptoms like urgency, frequency, and nocturia. To determine long-term efficacy and safety of this products, additional studies are required (most studies in this review had 12 weeks of follow-up). Furthermore, a standardized tool should be developed to assess therapeutic response and overall quality of life in patients using vaginal estrogen to manage genitourinary syndrome of menopause.

Article #2

Objective markers of vaginal health include the vaginal health index, vaginal maturation index, vaginal maturation value, estrogen index, and vaginal pH levels. For this systematic review, each marker played an important role in measuring improvement in signs associated with genitourinary syndrome. The vaginal health index uses 5 parameters to evaluate vaginal health: elasticity, pH, discharge, mucosal integrity, and mucosal moisture. The vaginal maturation value is used to determine the level of vaginal atrophy by comparing different cell types in a vaginal smear. Once a patient's VMI is determined, their response to estrogen is monitored using the vaginal maturation value. The estrogen index and vaginal pH are then used to monitor hormonal balance. It is important to include both objective outcomes as well as subjective symptoms when

determining the efficacy of vaginal estrogen in managing genitourinary syndrome for more accurate results. Studies showed that vaginal estrogen is effective in alleviating symptoms of vaginal dryness, dyspareunia, frequency, and urgency within four to twelve weeks. However, patients experienced a gradual return in symptoms upon cessation of treatment. Based on these results, it can be concluded that there is a need for randomized control trials with larger sample sizes and longer follow-up periods to better comprehend the efficacy and safety of vaginal estrogen for managing these symptoms.

Article #3

The authors of this systematic review compared the efficacy of various products (vaginal/oral DHEA, oral ospemifene, oral raloxifene, vaginal oxytocin, vaginal testosterone, and vaginal estrogen) to placebo in managing symptoms associated with genitourinary syndrome. Amongst high quality trials, four interventions were recognized as beneficial in treating symptoms associated with genitourinary syndrome: vaginal estrogen, vaginal DHEA, oral ospemifene, and vaginal moisturizers. It was concluded that when compared to placebo/no treatment, vaginal estrogen was superior in managing vaginal dryness and dyspareunia, vaginal dryness being a symptom of vaginitis in postmenopausal women. Vaginal DHEA and oral ospemifene trials showed superior "statistically significant benefit for vulvovaginal dryness and dyspareunia" when compared to vaginal estrogen vs placebo/no treatment trails. Of note, trials that compared vaginal DHEA and oral ospemifene to placebo were larger and more uniform compared to the smaller trials which compared vaginal estrogen to placebo/no treatment.

Article #4

Atrophic vaginitis is one of the physiologic changes which increases the risk of recurrent UTIs in postmenopausal women. This condition occurs when there are decreased levels of estrogen in the body, leading to thin, dry, and inflamed vaginal walls. As a result, patients are more likely to develop pelvic floor disorders such as urinary/fecal incontinence and pelvic organ prolapse. This creates an environment where UTI-causing bacteria are more likely to thrive. According to this study, vaginal estrogen is more effective than placebo in mitigating frequency of UTIs in post-menopausal women with a diagnosis of recurrent UTIs. Vaginal estrogen therapy is also associated with significant decrease in vaginal pH, contributing to a less favorable environment for UTI-causing bacteria. Although trials of vaginal estrogen versus placebo yielded these results, use of oral estrogen versus placebo did not demonstrate significant reduction in UTI recurrence in two trials. Although vaginal estrogen seems promising, more long-standing research is required before a definitive conclusion can be made.

Article #5

This study demonstrated that various formulations of vaginal estrogen were more effective than placebo in mitigating signs and symptoms associated with atrophic vaginitis. Participants who used vaginal estrogen experienced improvement in vaginal maturation index, vaginal pH, and dyspareunia. Improvement in vaginal maturation index was demonstrated by and increase in superficial cells and a decrease in parabasal cells, indicating presence of healthier vaginal epithelium compared to baseline. A meaningful reduction in pH was noted in patients administering 15 µg of vaginal estrogen specifically. Patients administering other dosages such as <2.5 µg or 50 µg also experienced a decrease in vaginal pH but not as significant as those who used 15 µg. Outcomes such as vaginal pH and dyspareunia, however, showed improvement during 12-week follow up. Vaginal estrogen therapy was tolerated well amongst participants, with the most common adverse effects being vulvovaginal mycotic infections and vulvovaginal pruritus.

Article #6

Vulvovaginal atrophy, atrophic vaginitis, and genitourinary syndrome of menopause are all terms that can be used to describe the process by which decreased estrogen levels leads to thinning, drying, and inflammation of the vaginal lining. Authors of this study recruited participants with vulvovaginal atrophy who complained of vaginal dryness as their most bothersome symptom. Participants managed with intravaginal estrogen reported improvement in dryness and reduced dyspareunia as well as decrease in vaginal pH, increase in number of superficial cells, and decrease in number of parabasal cells. There was minimal difference in irritation/pruritus, post-coital bleeding, and dysuria when comparing the intravaginal estradiol group to the placebo group.

Overarching Conclusion

The findings from these six studies show that vaginal estrogen therapy is effective in alleviating symptoms associated with genitourinary syndrome of menopause including vaginitis and urinary symptoms associated with UTI. Symptoms of GSM are initially managed with non-hormonal vaginal lubricants and moisturizers. These interventions are effective in mild symptoms but more aggressive treatment in the form of hormonal therapy is indicated once symptoms begin to affect quality of life. These results demonstrate that use of intravaginal estrogen can lead to an improvement in vaginal dryness, and reduce dyspareunia, dysuria, urinary frequency, urinary urgency, and nocturia. While authors were unable to compare the efficacy of

different formulations of vaginal estrogen, it seems that all modalities were able to provide symptom relief. Majority of these studies reported short follow-up periods, ranging from 2 weeks to 36 weeks, highlighting the need for more high-quality randomized control trials, preferably with larger sample sizes, and a longer-follow up period to determine the long-term safety and efficacy of intravaginal estrogen use. In addition, objective markers of vaginal health such as vaginal health index, vaginal maturation index, vaginal maturation value, estrogen index, and vaginal pH levels should be used in conjunction with subjective symptoms to determine the benefit of intravaginal estrogen in managing symptoms of genitourinary syndrome.

Weight of the Evidence

1 S. Weidlinger, C. Schmutz, H. Janka, C. Gruetter, and P. Stute →

This article is ranked #1 because it addresses both outcomes outlined in my PICO search question. This article is the only one which incorporates objective outcomes as well as subjective symptoms in assessing the efficacy of vaginal estrogen for managing genitourinary syndrome. As previously mentioned, objective markers of vaginal health include the vaginal health index, vaginal maturation index, vaginal maturation value, estrogen index, and vaginal pH levels. Subjective symptoms are the symptoms reported by the patient such as vaginal dryness, dyspareunia, urgency, frequency, etc. Measuring these two outcomes provides the most accurate results because it does not only rely on self-reported data. Additionally, authors included a table that provides an overview of studies included in the systematic review. These types of graphics help me comprehend and organize the information so that I can compare it to findings in my other systematic reviews. I also appreciate the use of plain language which helped me better understand the results and discussion.

2 Elisheva R. Danan, Catherine Sowerby, Kristen E. Ullman, Kristine Ensrud, Mary L. Forte, Nicholas Zerzan, Maylen Anthony, Caleb Kalinowski, Hamdi I. Abdi, Jessica K. Friedman, Adrienne Landsteiner, Nancy Greer, Rahel Nardos, Cynthia Fok, Philipp Dahm, Mary Butler, Timothy J. Wilt, and Susan Diem →

This article is ranked #2 because it directly addresses my intervention and comparison as well as both outcomes in my PICO search question. 46 RCTs were selected for this systematic review. Of these 46, ten studies comprised of 2,400 participants compared efficacy of vaginal estrogen to placebo or no treatment. Authors included a flowchart demonstrating how they selected their articles, as well as one table with the study characteristics, a second table detailing the outcomes for vaginal dryness and dyspareunia, and a third table with the GRADE statements for each intervention and outcome. The second table was a bit difficult to follow but the authors did an excellent job making the information more digestible.

3 David D. Rahn, Cassandra Carberry, Tatiana V. Sanses, Mamta M. Mamik, Renée M. Ward, Kate V. M., Cedric K. Olivera, Husam Abed, Ethan M. Balk, Miles Murphy →

This article is ranked #3 because, like my first two articles, it addresses both outcomes outlined in my PICO search question and the information is presented in plain language. I ranked it third because it did not incorporate objective markers of vaginal health as part of the studied outcomes. Additionally, the tables, graphs, and flowcharts are included at the end of the review which required me to scroll up and down between text and figures to fully appreciate the information that was being presented.

4 Ying-Yu Chen, Tsung-Hsien Su, Hui-Hsuan Lau →

This article is ranked #4 because it only addresses one outcome outlined in my PICO search question: rates of UTI. The article by Ali et al. also addresses only one outcome outlined in my PICO search question but, in comparison, this article uses simple language to convey the results which made it easier for me to understand. There was a table which included the characteristics of the included studies, as well multiple figures demonstrating statistical evidence. The table illustrating the characteristics of the included studies had the number of participants, study duration, characteristic of participants, interventions, tools for evaluations, and outcomes. The way this information was displayed made it easy to follow and I was able to compare the results of this study to the articles by Weidlinger et al., Danan et al., and Rahn, et al. since these articles also touched on the topic of urinary symptoms of genitourinary syndrome. Although this study was a meta-analysis, I did not feel overwhelmed by the statistical measurements because the authors did a great job explaining the results of their findings and consolidating the information in the discussion section.

5 Abraish Ali, Aliha Iftikhar, Muzainah Tabassum, Rayaan Imran, Muhammad Usama Shaid, Mahnoor Rehan Hashmi, Muhammad Saad, Mahnoor Humayun, Sidra Imtiaz, Eesha Baig →

This article is ranked #5 because it only addresses one outcome outlined in my PICO search question: rates of vaginitis. Ideally, I wanted to include six articles that addressed how vaginal estrogen therapy affected the rate of vaginitis and UTI. The authors acknowledge that urgency, dysuria, and recurrent UTIs are part of the constellation of symptoms which constitute genitourinary syndrome, but these symptoms are not included in the measured outcomes. Because this article is a systematic review and meta-analysis, it was a bit difficult to understand what the authors were trying to convey as a lot of the

information was presented using statistics. The tables in this study were written in plain language which made the information much easier to understand. Statistical measurements were still included in the table, but the integration of charts and texts helped enhance my understanding of the authors' points.

6 David F. Archer, Thomas D. Kimble, F.D. Yuhua Lin, Simona Battucci, Vilma Sniukiene, James H. Liu →

This article is ranked #6 because it only addresses one outcome outlined in my PICO search question: rates of vaginitis. Vaginitis can be caused by several things such as vaginal infections, allergic reactions, medications, or chronic conditions. In postmenopausal women, however, vaginitis is primarily due to estrogen deficiency which causes vaginal dryness. For this randomized control trial, authors solely focused on vaginal dryness, which contributes to symptoms associated with vaginitis. Additionally, the majority of participants were white women with a mean age of 59 years which limits the application of findings to other racial/ethnic groups.

Magnitude of Effects:

The magnitude of effect of these studies demonstrates the efficacy of vaginal estrogen therapy in managing symptoms associated with genitourinary syndrome. Across all studies, use of intravaginal estrogen was shown to reduce symptoms such as vaginal dryness and dyspareunia which contribute to vaginitis. This treatment modality was also effective at decreasing urinary symptoms such as dysuria, urgency, frequency, and nocturia which are symptoms associated with UTI. While some participants experienced adverse effects due to treatment, most participants tolerated therapy well. Additionally, authors of some articles pointed out the difficulty in comparing vaginal estrogen formulations due to the heterogeneity of the studies. Based on the results, however, it seems that all formulations of vaginal estrogens were effective for managing symptoms of GSM. One study suggested that dosing is what impacts parameters such as vaginal pH. Specifically, participants administering 15 µg of estrogen demonstrated a clinically significant reduction in vaginal pH when compared to <2.5 µg and 50 µg respectively. Another study demonstrated that cessation of treatment was associated with gradual return of symptoms, though not to the same severity as prior to receiving treatment.

Clinical Bottom Line/Clinical Significance:

Genitourinary syndrome of menopause is an umbrella term that encompasses a constellation of signs and symptoms that occur in the postmenopausal period. These changes take place due to decreased levels of estrogen in the body. In GSM, decreased estrogen levels increase the vaginal pH and disrupt the normal vaginal flora which makes it easier for women to develop vaginal infections/inflammation[1]. This same decrease in estrogen can cause urinary/fecal incontinence and pelvic organ prolapse which creates an environment where UTI-causing bacteria are more likely to thrive.

Based on the articles reviewed, the evidence indicates that vaginal estrogen is superior to no treatment/placebo for managing symptoms associated with GSM, specifically vaginitis and UTI. When compared to no treatment or placebo, use of vaginal estrogen demonstrated improvement in not only symptoms associated with GSM, but in signs as well. Of my six studies, only two used objective markers of vaginal health to determine if significant changes occurred to the vaginal tissue. It was determined that vaginal estrogen contributed to enhancements in vaginal health index, vaginal maturation index, vaginal maturation value, estrogen index, and vaginal pH levels. Majority of these studies reported a short follow-up period, small sample size, and short duration of therapy. To more accurately determine the safety and efficacy of vaginal estrogen for post-menopausal women, randomized control trials must be developed which address these deficits. Length of therapy plays a critical role in the outcomes. The range of study durations in the selected articles varied between 8 weeks to 12 months. This difference may help explain some variability in the outcomes such as gradual return of symptoms like those mentioned in the article by Weidlinger et al. Long-term/continuous therapy may be necessary to sustain the benefits associated with vaginal estrogen use. Additionally, a lack of follow-up periods restricts the ability to understand the long-term efficacy and safety of using vaginal estrogen. Further research needs to evaluate the outcomes over a longer period to determine whether the benefits outweigh the risks.

In clinical practice, I would recommend vaginal estrogen therapy for symptoms associated with GSM if my patient has no other health problems. I agree that more studies must be conducted to determine long-term efficacy and safety, but as the evidence stands, this intervention is effective at mitigating post-menopausal symptoms that can negatively impact quality of life. Across the studies, authors admitted that there is limited evidence on how this type of therapy may affect a patient with breast or endometrial cancer. If the patient has a low risk of recurrence, I would explain the risk and benefits before initiating treatment, and I would start them on the lowest dose while carefully monitoring them.

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[1] Carlson K, Nguyen H. Genitourinary syndrome of Menopause. StatPearls [Internet]. October 5, 2024. Accessed November 3, 2024. https://www.ncbi.nlm.nih.gov/books/NBK559297/.