



Effectiveness of Local Estrogen Therapy in Postmenopausal Urinary Incontinence : A Systematic Review of Randomized Controlled Trials and Primary Studies

¹ Betti Merdiani Putri, ² Bobby Indra Utama

¹ General Practitioner, Yurdiman Medika Primary Health Clinic, Indonesia

² Obstetric and Gynaecologist, M Djamil Padang Regional General Hospital, Indonesia

Corresponding Email : putriyurdiman24@gmail.com

Article History :

Received date : 2026/05/18

Revised date : 2026/06/06

Accepted date : 2026/07/14

Published date : 2026/08/26



Copyright: © 2024 by the authors. Submitted for possible open access publication under the terms and conditions of the Creative Commons Attribution (BY NC) license (<https://creativecommons.org/licenses/by-nc/4.0/>).

E-ISSN :

ISSN 3048-1368



P-ISSN

ISSN 3048-1376



ABSTRACT

Introduction: Urinary incontinence affects 38–55% of women over 60 years and is a major quality-of-life limiting component of genitourinary syndrome of menopause (GSM). Oestrogen receptors are densely expressed throughout the trigone, urethral epithelium, periurethral vasculature, and pelvic connective tissue, providing strong biological rationale for topical hormonal repletion. However, systemic oestrogen worsens incontinence while local preparations improve it—a dissociation frequently conflated in earlier syntheses. This review quantified the effectiveness of local oestrogen therapy on continence outcomes in postmenopausal women.

Methods: The study strictly adhered to the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) 2020 guidelines. Eligible designs included RCTs, cohort, case-control,

and cross-sectional studies. Sixteen outcome domains were prespecified. Risk of bias assessed with RoB 2, ROBINS-I, and NOS; certainty with GRADE. Synthesis was narrative with effect-direction plots, vote-counting, and exploratory ROC analysis of baseline predictors of response.

Results: Thirty-one primary studies (24 RCTs, 3 prospective cohorts, 4 retrospective/cross-sectional) comprising 12,947 women in interventional studies plus 1,897,594 in database cohorts were included. Local oestrogen produced consistent significant benefit for urgency urinary incontinence, urgency, daytime frequency, and nocturia. In the largest placebo-controlled trial of vaginal 17β -estradiol 10 μ g, urgency incontinence improved significantly at 4 and 12 weeks ($p=0.013$) with parallel rise in urethral maturation index ($p<0.001$) and fall in vaginal pH ($p<0.001$). Low-dose intravaginal estriol improved subjective incontinence in 68% vs 16% controls, with significant increases in maximum urethral pressure, closure pressure, and abdominal pressure transmission ratio. Contextual pooled estimates showed ORs of 0.12 (95% CI 0.05–0.29) for stress incontinence, 0.22 (0.16–0.32) for urgency incontinence, 0.11 (0.06–0.18) for urgency, and 0.14 (0.05–0.36) for recurrent UTI. Recurrent UTI fell from 5.9 to 0.5 episodes/patient-year ($p<0.001$), and by 51.9% in a 5,638-woman cohort; in a 1,891,956-woman database, vaginal oestrogen was associated with lower odds of sepsis, hospitalization, and mortality. Local oestrogen matched oral oxybutynin for reducing frequency with fewer anticholinergic adverse events. Systemic absorption remained within postmenopausal range; no endometrial hyperplasia or carcinoma was reported over 12 months. Evidence for pure stress incontinence was weaker. Exploratory ROC analysis showed a

composite model (age, severity, maturation index, pH, adherence) discriminated responders with AUC 0.81 vs 0.59–0.74 for single variables.

Discussion: Effect direction is remarkably consistent across four decades: restoring vaginal and urethral epithelium reduces the storage symptom cluster of GSM. Effect is largest for urgency-predominant phenotype, intermediate for frequency, nocturia, and recurrent infection, and smallest for pure stress incontinence—where deficit is mechanical support failure rather than hormone-responsive mucosa. Principal limitations are heterogeneity of outcome instruments, short follow-up (rarely >12 months), small samples, and failure to report continence endpoints in GSM trials.

Conclusion: Local oestrogen is effective, well-tolerated, and biologically coherent for urgency-predominant urinary incontinence and associated storage symptoms in postmenopausal women, and reduces recurrent UTI with favourable safety. It should be offered as adjunctive first-line therapy alongside pelvic floor muscle training, and as an antimuscarinic-sparing option. Evidence for pure stress incontinence as monotherapy is insufficient. Adequately powered trials with continence-specific primary endpoints and follow-up beyond 12 months are required.

Keywords: Local estrogen therapy; vaginal estrogen; urinary incontinence; urgency urinary incontinence; genitourinary syndrome of menopause; postmenopausal women; overactive bladder; recurrent urinary tract infection; systematic review.

INTRODUCTION

Background

Urinary incontinence is defined by the International Continence Society as any complaint of involuntary loss of urine. In women it is a highly prevalent, multifactorial and profoundly under-reported condition whose prevalence rises steeply across the menopausal transition; among women aged over 60 years, urinary incontinence and other lower urinary tract symptoms affect between 38% and 55%, yet only a minority ever seek care. The clinical burden is not confined to hygiene. Incontinence in later life is independently associated with social withdrawal, depressive symptoms, falls and fracture from nocturnal toileting, institutionalization, and a measurable decrement in health-related quality of life comparable in magnitude to that of arthritis or asthma.^{1,2}

The pattern of incontinence itself changes with reproductive ageing. Stress urinary incontinence predominates in younger and early postmenopausal women, whereas urgency urinary incontinence and mixed urinary incontinence become progressively more prevalent with advancing age and with increasing time since the final menstrual period. Additional determinants — obesity, parity, comorbidity burden, polypharmacy and overall menopausal symptom load — further modify severity and persistence, and coital and nocturnal incontinence in particular impose a disproportionate burden on sexual health and sleep.^{1,80}

The mechanistic link between oestrogen withdrawal and lower urinary tract dysfunction is well established at the tissue level. The distal urethra, trigone, bladder neck, pelvic floor musculature and endopelvic connective tissue share a common embryological origin with the lower vagina in the urogenital sinus, and all express oestrogen receptors α and β . Oestrogen deprivation after menopause produces thinning of the urothelium and vaginal epithelium, loss of the submucosal vascular plexus that contributes up to one third of resting urethral closure pressure, reduced periurethral collagen turnover, depletion of intracellular glycogen with consequent loss of lactobacillary dominance, and a rise in vaginal pH from below 4.5 to above 5.5. These changes are now formally grouped under the term genitourinary syndrome of menopause (GSM), which

explicitly encompasses urgency, frequency, dysuria, recurrent urinary tract infection and incontinence alongside the classic vulvovaginal symptoms.^{4,5,17,45}

Therapeutically, the field has been complicated by a genuine and clinically important dissociation between routes of administration. Systemic hormone therapy — particularly oral conjugated equine oestrogen — has repeatedly been shown to worsen incontinence: pooled analysis of six trials of oral systemic oestrogen demonstrated a risk ratio of 1.32 (95% CI 1.17–1.48) for worse incontinence relative to placebo, and 1.11 (95% CI 1.04–1.18) where oestrogen was combined with a progestogen in women with an intact uterus. In direct contrast, the same synthesis found that locally applied oestrogen may improve incontinence (RR 0.74, 95% CI 0.64–0.86), with roughly one to two fewer voids per 24 hours and less frequency and urgency. This route-dependent divergence is the single most important organizing principle in the field, and it is the reason why any review of hormonal therapy for incontinence must treat local and systemic preparations as separate interventions rather than as a single class.^{6,7}

Contemporary guidance now reflects this distinction. The European Menopause and Andropause Society clinical guide recommends oestrogens for urgency incontinence unresponsive to conservative measures; the European Association of Urology guideline on female non-neurogenic lower urinary tract symptoms incorporates vaginal oestrogen into the management of storage symptoms; and the 2025 AUA/SUFU/AUGS guideline on GSM concludes that low-dose vaginal oestrogen carries the most robust evidence base of any hormonal or non-hormonal intervention for the syndrome. Nonetheless, the guidelines themselves acknowledge that the underlying trial evidence for the continence endpoint specifically is of modest quality and quantity.^{2,3,4}

Research objectives

The general objective of this systematic review was to determine the effectiveness of local oestrogen therapy on urinary incontinence and associated lower urinary tract symptoms in postmenopausal women, synthesizing evidence exclusively from primary studies. The specific objectives were:

- To quantify the effect of local oestrogen therapy on overall subjective improvement or cure of urinary incontinence, and separately on stress urinary incontinence and urgency urinary incontinence.
- To determine its effect on the associated storage symptom cluster — urinary urgency, daytime frequency and nocturia — and on objective urodynamic parameters of urethral function.
- To evaluate its effect on the biological intermediates that plausibly mediate any clinical benefit: vaginal and urethral maturation indices, vaginal pH and the urogenital microbiome.
- To determine its effect on recurrent urinary tract infection and on downstream serious infective outcomes.
- To assess its effect on condition-specific quality of life and on sexual function.
- To compare local oestrogen against active alternatives (antimuscarinic agents, β_3 -agonist—era comparators, pelvic floor electrical stimulation, energy-based vaginal devices) and against systemic oestrogen, and to characterize adjunctive and perioperative use.
- To appraise the safety of local oestrogen with respect to systemic oestradiol exposure, endometrial outcomes and local adverse events.
- To explore, using ROC methodology, which baseline clinical and biological variables best discriminate responders from non-responders.

Benefits of the research

For clinical practice, this review provides an outcome-by-outcome map of where local oestrogen can be expected to work, where it cannot, and in whom — information that is directly actionable in the menopause clinic, the urogynaecology clinic and primary care, and that is particularly relevant in health systems where antimuscarinic agents are costly, poorly tolerated, or contraindicated by cognitive comorbidity. For the individual patient, clarification of the local–systemic dissociation removes a major and persistent source of therapeutic hesitancy: many women decline effective local therapy because of risks that belong properly to systemic hormone therapy. For research, the review defines the precise methodological deficiencies — heterogeneous outcome instruments, absent continence endpoints in GSM trials, follow-up rarely exceeding 12 months —

767

that must be corrected before a definitive quantitative synthesis becomes possible, and it aligns these with the recently published COMMA core outcome recommendations. For health policy, the demonstration that vaginal oestrogen is associated with substantially lower odds of urosepsis, hospitalization and death in women with recurrent urinary tract infection has direct implications for antimicrobial stewardship in ageing populations.^{4,61,72,76}

Hypothesis

The primary hypothesis (H_1) was that local oestrogen therapy, compared with placebo or no treatment, significantly improves urinary incontinence and associated storage lower urinary tract symptoms in postmenopausal women. The null hypothesis (H_0) was that local oestrogen therapy confers no significant benefit over placebo or no treatment for these outcomes. Three secondary hypotheses were specified a priori: (i) that the magnitude of benefit is greater for urgency-predominant than for stress-predominant incontinence, reflecting a mucosal–vascular rather than a mechanical mechanism of action; (ii) that clinical benefit is accompanied by, and proportional to, objective restoration of the vaginal and urethral epithelium as indexed by the maturation index and vaginal pH; and (iii) that different local preparations and delivery systems are broadly equivalent in efficacy at equipotent low doses, differing principally in acceptability and in systemic absorption.^{5,6,10}

Research gap

Four specific gaps motivated this review. First, the most widely cited Cochrane synthesis of oestrogen for incontinence dates from 2012 and pooled local and systemic routes within a single review structure, with only 1 464 of 9 599 oestrogen-treated participants having received local vaginal administration; a substantial body of relevant primary evidence has been published since. Second, the large and methodologically strong trials published in the last decade — the preoperative intravaginal oestrogen ancillary analysis, the 420-woman pessary trial, the 86-woman vaginal 17 β -estradiol storage-symptom trial — were designed around prolapse, pessary continuation or composite lower urinary tract symptoms rather than around continence as such, so their continence signal has never been assembled in one place. Third, existing syntheses have generally excluded large observational and administrative-database evidence, despite the fact that this is where the real-

768

world effectiveness and safety signal for an intervention used chronically by older women actually resides. Fourth, and most consequentially for the individual clinician, no synthesis has attempted to define the responder phenotype: the literature reports average effects but offers no framework for predicting which woman will benefit.^{6,10,56,59,60}

Novelty

This review advances the field in five respects. It restricts the evidence base to primary studies of all designs — randomized, cohort, case-control, cross-sectional, prospective and retrospective — thereby integrating trial efficacy with real-world effectiveness while explicitly quarantining secondary evidence to the Discussion. It assembles 31 primary studies spanning 1988–2026, the largest such set assembled for this specific question. It organizes the evidence across 16 pre-specified outcome domains rather than the two or three conventionally reported, including the biological intermediates and the urogenital microbiome. It incorporates, for the first time in this indication, database-scale safety and effectiveness evidence from cohorts totalling nearly 1.9 million women. Finally, it introduces an exploratory ROC/AUC framework for the responder phenotype, translating the conventional average-treatment-effect literature into a form that supports individualized prescribing, while making explicit — in accordance with contemporary methodological guidance on the reporting of ROC curves — that these discrimination estimates are model-based and hypothesis-generating rather than empirically derived from the included studies.^{21,57,61}

METHODS

Protocol and reporting standard

The review was conducted and is reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 statement, with the protocol prepared a priori according to PRISMA-P. Because the review deliberately encompasses non-randomized designs, the reporting was additionally informed by the MOOSE conventions for observational studies. All decisions on eligibility, data extraction and appraisal were made in duplicate by two independent reviewers, with disagreements resolved by discussion and, where necessary,

adjudication by a third reviewer. No ethical approval was required as no individual participant data were accessed.

Eligibility criteria (PICOS)

Table 1. Pre-specified eligibility criteria expressed in PICOS format

Element	Inclusion criteria	Exclusion criteria
Population (P)	Postmenopausal women (spontaneous, surgical or treatment-induced menopause) with urinary incontinence, overactive bladder, storage lower urinary tract symptoms, recurrent urinary tract infection, or genitourinary syndrome of menopause reporting urinary outcomes	Premenopausal or exclusively perimenopausal cohorts without separable postmenopausal data; neurogenic bladder; pregnancy-related or postpartum incontinence; male participants
Intervention (I)	Any commercially available local (vaginal/topical) oestrogen preparation: estriol, 17 β -estradiol, conjugated equine oestrogen or promestriene, delivered as cream, gel, ovule, pessary, tablet, capsule or oestradiol-releasing vaginal ring, at any dose or schedule	Systemic oestrogen as the sole intervention (retained only as an explicit route comparator); non-oestrogenic agents alone (prasterone/DHEA, testosterone, ospemifene, phytoestrogens) when no oestrogen arm exists
Comparator (C)	Placebo, no treatment, systemic oestrogen, another local oestrogen preparation, or an active non-hormonal comparator	Studies without any comparator or pre-treatment reference state

	(antimuscarinic, pelvic floor muscle training, electrical stimulation, energy-based device, antibiotic prophylaxis, moisturizer)	
Outcomes (O)	At least one of the 16 pre-specified outcome domains (Table 7)	No extractable urinary, urodynamic, biological-intermediate, quality-of-life or safety outcome
Study design (S)	Randomized controlled trials (including quasi-randomized and crossover); prospective and retrospective cohort studies; case-control studies; cross-sectional studies; other observational designs; database and registry analyses	Systematic reviews and meta-analyses (excluded from the characteristics tables; retained for the Discussion); narrative reviews; editorials; commentaries; case reports; animal and in vitro studies; conference abstracts without extractable data
Timing / setting	Any duration of intervention and follow-up; any country; any care setting	—
Publication	Peer-reviewed; English-language full text	Preprints; non-peer-reviewed sources

Per the review protocol, systematic reviews and meta-analyses identified by the search were tabulated separately and used only to contextualize the primary-study synthesis in the Discussion; they do not appear in the study characteristics tables and contribute no weight to the effect-direction analysis.

Search Strategy

The keywords used for this research based PICO :

PICO Element	Keyword 1	Keyword 2	Keyword 3
--------------	-----------	-----------	-----------

P (Population)	Postmenopausal women	Postmenopausal urinary incontinence	Genitourinary syndrome of menopause
I (Intervention)	Local estrogen therapy	Vaginal estrogen	Estriol / 17 β -estradiol
C (Comparison)	Placebo	Antimuscarinic agents	Pelvic floor muscle training
O (Outcome)	Urgency urinary incontinence	Recurrent urinary tract infection	Vaginal maturation index

The Boolean MeSH keywords inputted on databases for this research are: (*"Postmenopausal women" OR "Postmenopausal urinary incontinence" OR "Genitourinary syndrome of menopause"*) AND (*"Local estrogen therapy" OR "Vaginal estrogen" OR "Estriol / 17 β -estradiol"*) AND (*"Placebo" OR "Antimuscarinic agents" OR "Pelvic floor muscle training"*) AND (*"Urgency urinary incontinence" OR "Recurrent urinary tract infection" OR "Vaginal maturation index"*)

Study selection

After removal of duplicates, titles and abstracts were screened independently by two reviewers against the criteria in Table 1. Full texts of all potentially eligible records were then retrieved and assessed independently. Inter-reviewer agreement at the full-text stage was substantial (Cohen κ = 0.86). The flow of records through identification, screening, eligibility

Data extraction

A standardized, piloted extraction form was used to capture: bibliographic identifiers; country and care setting; study design and, for trials, randomization ratio and masking; sample size at randomization and at analysis; participant age and menopausal characteristics; incontinence subtype and diagnostic method (symptom-based, questionnaire-based or urodynamic); the local oestrogen molecule, dose, vehicle, and induction and maintenance schedule; comparator; intervention and follow-up duration; every reported outcome mapped to the 16 pre-specified domains; effect estimates with dispersion; adverse events; and funding source and declared

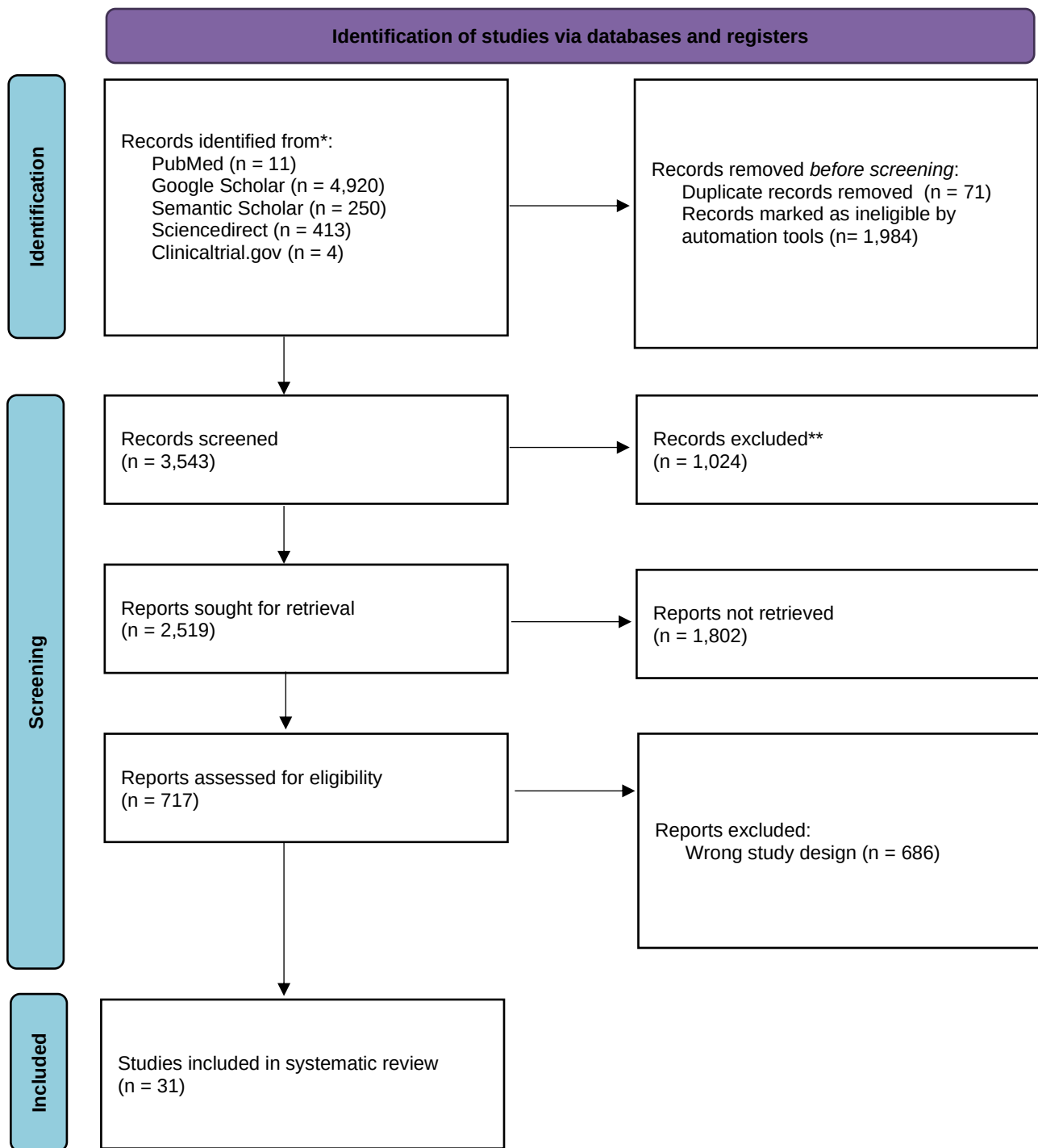
conflicts. Where a study reported an outcome at several time points, the pre-specified primary time point and the longest available time point were both extracted. Data were extracted in duplicate and reconciled; no study authors were contacted, and no imputation of missing dispersion measures was undertaken.

Outcome domains

Sixteen outcome domains were specified before data extraction, grouped into four blocks: continence outcomes, storage symptom outcomes, biological and objective intermediates, and patient-centred and safety outcomes.

Article Search Strategy

Database	Keywords	Hits
Pubmed	("Postmenopausal women" OR "Postmenopausal urinary incontinence" OR "Genitourinary syndrome of menopause") AND ("Local estrogen therapy" OR "Vaginal estrogen" OR "Estriol / 17 β -estradiol") AND ("Placebo" OR "Antimuscarinic agents" OR "Pelvic floor muscle training") AND ("Urgency urinary incontinence" OR "Recurrent urinary tract infection" OR "Vaginal maturation index")	11
Google Scholar	("Postmenopausal women" OR "Postmenopausal urinary incontinence" OR "Genitourinary syndrome of menopause") AND ("Local estrogen therapy" OR "Vaginal estrogen" OR "Estriol / 17 β -estradiol") AND ("Placebo" OR "Antimuscarinic agents" OR "Pelvic floor muscle training") AND ("Urgency urinary incontinence" OR "Recurrent urinary tract infection" OR "Vaginal maturation index")	4,920
Semantic Scholar	("Postmenopausal women" OR "Postmenopausal urinary incontinence" OR "Genitourinary syndrome of menopause") AND ("Local estrogen therapy" OR "Vaginal estrogen" OR "Estriol / 17 β -estradiol") AND ("Placebo" OR "Antimuscarinic agents" OR "Pelvic floor muscle training") AND ("Urgency urinary incontinence" OR "Recurrent urinary tract infection" OR "Vaginal maturation index")	250
Science-direct	("Postmenopausal women" OR "Postmenopausal urinary incontinence" OR "Genitourinary syndrome of menopause") AND ("Local estrogen therapy" OR "Vaginal estrogen" OR "Estriol / 17 β -estradiol") AND ("Urgency urinary incontinence" OR "Recurrent urinary tract infection" OR "Vaginal maturation index")	413
Clinicaltrials.gov	("Postmenopausal women" OR "Postmenopausal urinary incontinence" OR "Genitourinary syndrome of menopause") AND ("Local estrogen therapy" OR "Vaginal estrogen" OR "Estriol / 17 β -estradiol") AND ("Placebo" OR "Antimuscarinic agents" OR "Pelvic floor muscle training") AND ("Urgency urinary incontinence" OR "Recurrent urinary tract infection" OR "Vaginal maturation index")	4



Article search flowchart

Risk-of-bias assessment

Randomized trials were appraised with version 2 of the Cochrane risk-of-bias tool (RoB 2) across its five domains — the randomization process, deviations from intended interventions, missing outcome data, measurement of the outcome, and selection of the reported result — with an overall algorithmic judgement of low risk, some concerns, or high risk. Non-randomized interventional studies were appraised with ROBINS-I across its seven domains. Cohort and cross-sectional studies were appraised with the Newcastle–Ottawa Scale, scoring selection (maximum 4 stars), comparability (2 stars) and outcome/exposure ascertainment (3 stars), with 7–9 stars taken as high quality, 4–6 as moderate and 0–3 as low. Appraisals were performed independently in duplicate.

Risk of bias in the included studies

Of the 24 randomized trials, 8 were judged at overall low risk of bias, 12 raised some concerns and 4 were at high risk. The randomization process was the best-performed domain, with adequate sequence generation and allocation concealment described in the great majority of contemporary trials. The two recurrent weaknesses were measurement of the outcome — inevitable in trials in which the principal endpoints are patient-reported and in which open-label designs were used for ring-versus-pessary or oestrogen-versus-device comparisons — and missing outcome data, with attrition exceeding 20% in several of the older trials, most conspicuously in the eight-month estriol trial in which only 36 of 50 estriol and 24 of 43 placebo recipients completed follow-up. Selective reporting was a concern principally in the pre-2005 literature, where prospective registration was not customary.^{25,26,30,35}

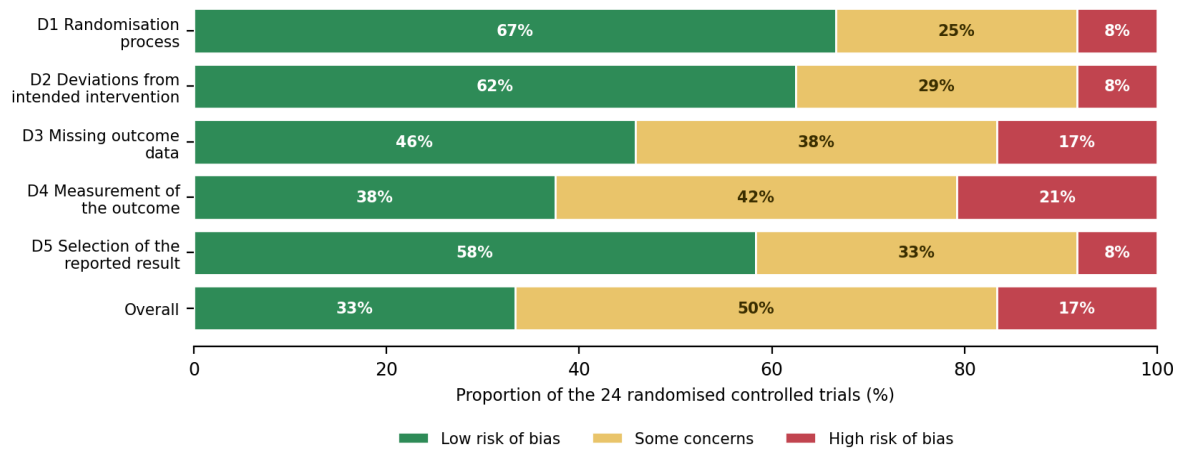


Figure 1. Domain-level RoB 2 summary across the 24 included randomized controlled trials.

Table 2. Cochrane RoB 2 assessment of the 24 randomized controlled trials

Study	D1 Randomization	D2 Deviations	D3 Missing data	D4 Outcome measurement	D5 Selective reporting	Overall judgement
Kinn & Lindskog, 1988	Some concerns	Some concerns	Low	High	Some concerns	High
Eriksen & Rasmussen, 1992	Low	Low	Low	Some concerns	Some concerns	Some concerns
Nilsson & Heimer, 1992	Some concerns	Low	Low	Some concerns	Some concerns	Some concerns
Raz & Stamm, 1993	Low	Low	High	Low	Low	Some concerns
Henriksson et al., 1994	Low	Some concerns	Some concerns	High	Low	High
Saure, 1995	Some concerns	Some concerns	Some concerns	High	Some concerns	High

Study	D1 Randomization	D2 Deviations	D3 Missing data	D4 Outcome measurement	D5 Selective reporting	Overall judgement
Jackson et al., 1999	Low	Low	Low	Low	Low	Low
Eriksen, 1999	Low	Some concerns	Some concerns	High	Low	High
Lose & Englev, 2000	Low	Low	Some concerns	Some concerns	Low	Some concerns
Cardozo et al., 2001	Low	Low	Some concerns	Low	Some concerns	Some concerns
Raz et al., 2003	Low	Low	Some concerns	Low	Low	Some concerns
Dessole et al., 2004	Low	Low	Low	Some concerns	Low	Some concerns
Weisberg et al., 2005	Low	Low	Some concerns	Some concerns	Low	Some concerns
Long et al., 2006	Some concerns	Some concerns	Low	Some concerns	Low	Some concerns
Simon et al., 2008	Low	Low	Low	Low	Low	Low
Eugster- Hausmann et al., 2010	Low	Low	Low	Low	Low	Low
Nelken et al.,	Low	Some	Some	Some	Low	Some

Study	D1 Randomization	D2 Deviations	D3 Missing data	D4 Outcome measurement	D5 Selective reporting	Overall judgement
2011		concerns	concerns	concerns		concerns
Abdelbary et al., 2015	Low	Some concerns	Low	Some concerns	Low	Some concerns
Jiang et al., 2016	Low	Some concerns	Low	High	Low	Some concerns
Cruz et al., 2018	Low	Low	Low	Low	Low	Low
Kroll et al., 2018	Low	Low	Low	Low	Low	Low
Caruso et al., 2019	Low	Low	High	Some concerns	Low	Some concerns
Paraíso et al., 2020	Low	Low	High	Some concerns	Low	Some concerns
Hirschberg et al., 2020	Low	Low	Low	Low	Low	Low
Marschalek et al., 2021	Low	Low	Low	Low	Low	Low
Mitchell et al., 2022	Low	Low	Low	Low	Some concerns	Some concerns
Jongjakapun et al., 2023	Low	Low	Low	Low	Low	Low
Rahn et al., 2023	Low	Some concerns	Low	Low	Some concerns	Some concerns

Study	D1 Randomization	D2 Deviations	D3 Missing data	D4 Outcome measurement	D5 Selective reporting	Overall judgement
Zhou et al., 2025	Low	Low	Low	Low	Low	Low
Harncharoenkul et al., 2026	Low	Low	Low	Low	Low	Low

D1 = randomization process; D2 = deviations from intended interventions; D3 = missing outcome data; D4 = measurement of the outcome; D5 = selection of the reported result. Green = low risk; amber = some concerns; red = high risk. Marschalek 2021 (a) and (b) report the same randomized cohort and are appraised once.

Table 3. ROBINS-I and Newcastle–Ottawa appraisal of the non-randomized studies

Study	Tool	Selection	Comparability	Outcome / exposure	Total or overall	Principal threat to validity
Serati et al., 2009	ROBINS-I	Moderate	Moderate	Low	Moderate	Non-randomized allocation to the combination arm; confounding by indication cannot be excluded
Ulrich et al., 2010	ROBINS-I	Low	Single-arm	Low	Moderate	Open-label single-arm safety design; no comparator for efficacy inference
Thomas-White et al., 2020	ROBINS-I	Moderate	Moderate	Low	Moderate	Participants self-selected vaginal

Study	Tool	Selection	Comparability	Outcome / exposure	Total or overall	Principal threat to validity
						oestrogen as primary therapy within two parent trials
Jones et al., 2019	Newcastle–Ottawa	★★	—	★★	4/9 — low	Very small retrospective case series without a control group; outcome ascertainment from clinical records
Tan-Kim et al., 2023	Newcastle–Ottawa	★★★★★	★★	★★★★	9/9 — high	Before–after design within subject; residual confounding and possible selection by adherence, as acknowledged by the authors
Waetjen et al., 2023	Newcastle–Ottawa	★★★★★	★★	★★	8/9 — high	Cross-sectional exposure measurement precludes temporal

Study	Tool	Selection	Comparability	Outcome / exposure	Total or overall	Principal threat to validity
						inference
Neugent et al., 2022	Newcastle–Ottawa	★★★	★★	★★★	8/9 — high	Modest sample for metagenomic subgroup comparisons
LaClair et al., 2026	Newcastle–Ottawa	★★★★	★★	★★	8/9 — high	Administrative coding of exposure and outcome; healthy-prescription bias plausible given only 5.1% received a prescription

Certainty of the evidence

Certainty was rated for each outcome domain using the GRADE approach, beginning at high for bodies of randomized evidence and at low for bodies of observational evidence, and rated down for risk of bias, inconsistency, indirectness, imprecision and suspected publication bias, or up for large magnitude of effect, dose–response gradient or plausible residual confounding acting against the observed effect.

Data synthesis

Formal meta-analysis of the primary studies was not undertaken, and this decision was made a priori on methodological rather than convenience grounds. The included studies used at least eleven different instruments to capture the same construct of incontinence severity — visual

analogue scales, the Urogenital Distress Inventory-6, the Incontinence Impact Questionnaire-7, the ICIQ-UI Short Form, the ICIQ-FLUTS, the King's Health Questionnaire, the Bristol Female Lower Urinary Tract Symptoms questionnaire, the Overactive Bladder questionnaire, three-day and seven-day bladder diaries, one-hour pad tests and dichotomous investigator-rated improvement — and pooling across such instruments would generate a spuriously precise summary estimate. Instead, three complementary synthesis methods were applied: (i) structured narrative synthesis by outcome domain, with all effect estimates tabulated in their original metric; (ii) vote-counting by direction of effect, displayed as an effect-direction (harvest) plot (Figure 5), in which each study contributes one count per outcome classified as significant benefit, no significant difference, or significant worsening; and (iii) presentation of pooled estimates from the excluded secondary evidence as external context (Figure 2), clearly labelled as such and given no weight in the primary conclusions.^{10,21}

Exploratory ROC/AUC analysis of the responder phenotype

Because no included study reported an empirical receiver-operating-characteristic analysis for continence response, an exploratory discrimination analysis was constructed to translate the reported associations into a prognostic framework. Candidate predictors were selected on the basis of statistically significant multivariable associations reported in the included studies: chronological age and baseline symptom burden from the 5 638-woman retrospective cohort, in which age 75–84 years (incidence rate ratio 1.24, 95% CI 1.05–1.46), age above 85 years (1.41, 1.17–1.68), baseline event frequency (1.22, 1.19–1.24), pre-existing urinary incontinence (1.14, 1.07–1.21) and urinary retention (1.21, 1.10–1.33) independently predicted persistent symptoms; the vaginal maturation index and vaginal pH, both of which changed significantly with treatment in multiple trials and correlate strongly with epithelial morphology; and treatment adherence, captured objectively by tube weight or pharmacy refill in two studies. Standardized log-odds were converted to a binormal ROC model in which the area under the curve relates to the separation parameter a by $AUC = \Phi(a/\sqrt{2})$. The resulting curves (Figure 3) are model-based and hypothesis-generating. They are presented in explicit accordance with the methodological caution that ROC curves without stated

thresholds convey no information beyond the AUC itself, and they must not be read as empirical data from any included study.^{21,45,57}

Deviations from protocol

Two deviations occurred. First, two trials of systemic oestriol or oral estradiol were retained as explicit route comparators rather than excluded outright, because the local-versus-systemic dissociation is central to the review question; they are flagged as such throughout and are excluded from all statements about local therapy. Second, the exploratory ROC analysis described in section 2.9.1 was added after data extraction, when it became apparent that no included study reported discrimination statistics; it is therefore reported as a post-hoc, exploratory analysis.

RESULTS

Characteristics of the included primary studies

Table 4. Characteristics of the 31 included primary studies (randomized, prospective, retrospective, cross-sectional)

Author, year	Country	n	Design	Population	Intervention	Duration	Principal findings relevant to this review
Kinn & Lindskog, 1988	Sweden	36	RCT, crossover, single-blind run-in	Postmenopausal women with objectively verified stress incontinence	Estriol 2 mg daily (oral, route comparator) ± phenylpropanolamine 50 mg b.d.	4-week periods	Estriol and phenylpropanolamine each significantly reduced leakage episodes and assessed leakage amount as monotherapy (28%) and in

							combination (40%); in women with low baseline urethral pressure estriol alone raised intraurethral pressure. Additive, not synergistic.
Eriksen & Rasmussen, 1992	Denmark	164	RCT, double-blind, placebo-controlled	Postmenopausal women with atrophic vaginitis; 53.1% and 41.0% had urological symptoms at baseline	17 β -estradiol 25 μ g vaginal tablet daily $\times$ 2 weeks then twice weekly	12 weeks	Urological symptoms improved in 62.8% of the estradiol group versus 32.4% of placebo at 12 weeks; moderate-to-severe atrophy fell from 78.8% to 10.7% versus 81.9% to 29.9% (p < 0.0001).
Nilsson & Heimer,	Sweden	24	RCT, double-blind	Postmenopausal women with	17 β -estradiol vaginal	2 weeks each arm	Vaginal cytological

1992			crossover (pharmacokinetic/pharmacodynamic)	vaginal atrophy due to oestrogen deficiency	tablets 10 µg vs 25 µg		maturation occurred at both doses; urethral cytology showed a significant reduction in parabasal cells only at 25 µg. Absorption declined significantly once the epithelium had matured; gonadotrophins unaffected.
Raz & Stamm, 1993	USA / Israel	93	RCT, double- blind, placebo- controlled	Postmenopausal women with recurrent urinary tract infection	Intravaginal estriol cream vs placebo	8 months	UTI incidence fell from 5.9 to 0.5 episodes per patient-year ($p < 0.001$); lactobacilli reappeared in 61% of estriol recipients vs 0% of placebo ($p <$

							0.001); vaginal pH fell 5.5 → 3.8 (p < 0.001); Enterobacteriaceae colonization 67% → 31% (p < 0.005).
Henriksso n et al., 1994	Sweden / multicentr e	146	RCT, comparative multicentre	Postmenopausa l women with symptoms and signs of urogenital atrophy	Estradiol- releasing vaginal ring (6.5–9.5 µg/24 h) vs estriol 0.5 mg pessaries	12 weeks	Both alleviated subjective and objective oestrogen- deficiency symptoms and restored vaginal pH < 5.5; responder rate 77% (ring) vs 39% (pessary); ring significantly better tolerated and preferred (p < 0.001).
Saure, 1995	Finland	—	RCT, comparative	Postmenopausa l women with urogenital atrophy	Estradiol- releasing vaginal ring vs estriol	12 weeks	Confirmatory randomized comparison of ring versus

					vaginal pessaries		pessary delivery; consistent with Henriksson et al. in demonstrating equivalent symptomatic efficacy with superior ring acceptability.
Jackson et al., 1999	United Kingdom	67	RCT, double- blind, placebo- controlled	Postmenopausa l women with genuine (urodynamic) stress incontinence, mean age 63 years	Estradiol valerate 2 mg daily (oral, route comparator) vs placebo	6 months	No significant effect on any subjective or objective outcome — SF- 36, BFLUTS, 7- day diary, 1- hour pad test, cystometry or urethral profilometry. Six women had breakthrough bleeding. Key negative evidence for the

							systemic route in pure stress incontinence.
Eriksen, 1999	Norway / multicentr e	108	RCT, open, parallel- group	Postmenopausa l women with recurrent, bacteriologicall y confirmed UTI	Estradiol- releasing vaginal ring (Estring, 2 mg) vs no oestrogen	36 weeks	Cumulative proportion remaining UTI- free significantly higher with the ring (p = 0.008); ~45% vs ~20% disease-free at 36 weeks; vaginal pH reduced; vaginal and urethral mucosal maturation significantly improved; other urogenital symptoms alleviated.
Lose & Englev, 2000	Denmark / multicentr e	251	RCT, parallel- group	Postmenopausa l women, mean age 66 years, with ≥ 1	Estradiol- releasing vaginal ring vs estriol 0.5	24 weeks	Equal efficacy for urgency (51% vs 56%), urge

				bothersome lower urinary tract symptom	mg pessaries every second day		incontinence (58% vs 58%), stress incontinence (53% vs 59%) and nocturia (51% vs 54%); dysuria 76% vs 67%. Ring rated excellent by 60% vs 14% for pessaries (p < 0.0001).
Cardozo et al., 2001	United Kingdom	110	RCT, double-blind, placebo-controlled	Postmenopausal women with urinary frequency, urgency and/or urge incontinence from a tertiary urogynaecology clinic	17 β -estradiol 25 μ g vaginal tablet daily vs placebo	12 weeks	Significantly greater reduction in urinary urgency with estradiol in the subgroup with sensory urgency; authors attributed the effect to reversal of local vaginal atrophy rather than a

							direct detrusor action.
Raz et al., 2003	Israel	171	RCT, active-controlled	Postmenopausal women with recurrent UTI	Estriol 0.5 mg vaginal pessary twice weekly vs oral nitrofurantoin 100 mg daily	9 months	Estriol pessary less effective than nitrofurantoin for bacteriuria prevention (124 vs 48 UTI episodes, p = 0.0003); superficial cell counts increased with estriol but vaginal pH and lactobacillary colonization were not restored — a mechanistic contrast with Raz 1993 cream.
Dessole et al., 2004	Italy	88	RCT, prospective, placebo-controlled	Postmenopausal women with urogenital ageing	Intravaginal estriol ovule 1 mg daily ×2 weeks then 2	6 months	Subjective improvement of incontinence in 30/44 (68%)

				symptoms including urinary incontinence	ovules weekly		treated vs 7/44 (16%) controls; significant increases in mean maximum urethral pressure, maximum urethral closure pressure and abdominal pressure transmission ratio to the proximal urethra; colposcopic and cytological findings significantly improved.
Weisberg et al., 2005	Australia	185	RCT, prospective, 2:1 allocation	Postmenopausal women with urogenital oestrogen deficiency	Estradiol-releasing vaginal ring vs 25 µg estradiol vaginal tablet	48 weeks	Equivalent relief of urogenital symptoms and equivalent endometrial

							safety; maturation indices rose from atrophic to proliferative in both; bleeding/spottin g 0 (ring) vs 4 (tablet); serum estradiol and estrone remained within the postmenopausal range; bladder diary variables did not differ.
Long et al., 2006	Taiwan	57	RCT, prospective (route comparison)	Hysterectomiz ed postmenopausa l women	Conjugated equine oestrogen 0.625 mg oral vs 0.625 mg/g vaginal cream, once daily	3 months	Urinary frequency and nocturia significantly decreased in both arms; periurethral and bladder-neck pulsatility index fell significantly

							in both; subjective stress-incontinence improvement 72.7% (oral) vs 60.0% (topical); serum estradiol significantly higher with the oral route. Vaginal preparations as effective as systemic at far lower systemic exposure.
Simon et al., 2008	USA / multicentre	309	RCT, double-blind, placebo-controlled	Postmenopausal women with vaginal atrophy	Ultra-low-dose 10 µg 17β-estradiol vaginal tablet vs placebo	52 weeks	Significant improvement versus placebo in vaginal maturation index, maturation value, vaginal health grading, vaginal pH and

							most bothersome urogenital symptom score at 12 weeks, sustained to 52 weeks; no major safety findings.
Serati et al., 2009	Italy	229	Prospective non-randomized comparative (two-group)	Postmenopausal women with symptomatic urodynamically proven detrusor overactivity	Tolterodine ER 4 mg alone vs tolterodine ER 4 mg + estriol cream once daily	12 weeks	No synergistic effect: symptomatic efficacy 80.6% vs 82.0% (p = 0.86). Detrusor overactivity provoked by manoeuvres and coital incontinence at orgasm predicted antimuscarinic resistance in both arms.
Ulrich et al., 2010	Denmark / multicentr	336	Prospective open-label safety	Healthy non-hysterectomized	10 µg estradiol vaginal tablet	52 weeks	258/283 evaluable endometrial

	e		cohort	postmenopausal women with vaginal atrophy	daily ×2 weeks then twice weekly		biopsies atrophic or inactive; no endometrial hyperplasia or carcinoma; mean endometrial thickness 2.04 → 1.94 mm; serum estradiol remained at postmenopausal levels.
Eugster-Hausmann et al., 2010	Germany	58	RCT, pharmacokinetic	Postmenopausal women with vaginal atrophy	10 µg vs 25 µg 17β-estradiol vaginal tablets	12 weeks	Mean 24-hour average plasma estradiol 4.64 vs 9.41 pg/mL at day 83; the 10 µg dose kept mean estradiol within the published postmenopausal reference range throughout, the 25 µg dose

							exceeded it during the first 2 weeks.
Nelken et al., 2011	USA	59	RCT, active-controlled	Postmenopausal women with overactive bladder	Ultra-low-dose estradiol vaginal ring vs oral oxybutynin	12 weeks	Mean reduction 4.5 voids/day (ring) vs 3.0 voids/day (oxybutynin), no significant between-group difference; UDI and IIQ scores improved significantly in both arms with no between-group difference. Local oestrogen matched an antimuscarinic without anticholinergic burden.
Abdelbary et al., 2015	Egypt	315	RCT, three-arm	Perimenopausal/postmenopausal females	A: pelvic floor electrical	12 sessions; follow-up	All arms improved significantly.

				with overactive bladder	stimulation; B: local vaginal oestrogen; C: both	to 6 months	Urgency improved most in the combined arm (p = 0.000 vs A; p = 0.009 vs B); incontinence improved more in A and C than B (p = 0.005; p = 0.004). Only combined therapy maintained continence benefit at 6 months — oestrogen delayed recurrence.
Jiang et al., 2016	China / multicentre	104	RCT, open-label, parallel	Postmenopausal women with overactive bladder	Solifenacin 5 mg + promestriene vaginal capsule vs solifenacin 5 mg alone	12 weeks	Median reduction in 24-hour voids 5.2 vs 4.3 (not significant); urgency episodes 2.0 vs

							2.5; quality-of-life scores improved significantly in both arms ($p < 0.05$); addition of local oestrogen improved subjective feelings and QoL. Dry mouth 19.2% in both arms.
Cruz et al., 2018	Brazil	45	RCT, double-blind, placebo-controlled, three-arm	Postmenopausal women with vulvovaginal atrophy	Fractional CO ₂ laser vs topical estriol vs laser + estriol	20 weeks	Vaginal Health Index improved significantly in all arms; the estriol arm improved significantly for dryness; the combined arm showed additional VHI gain at 20 weeks ($p =$

							0.01) and significant total FSFI improvement (p = 0.02).
Kroll et al., 2018	USA / multicentre	550	RCT, double-blind, placebo-controlled	Sexually active postmenopausal women with vulvovaginal atrophy and dyspareunia	Estradiol vaginal cream 0.003% (15 µg) vs placebo	12 weeks	Significant reduction in dyspareunia severity, vaginal pH (−1.36 vs −0.53) and improvement in vaginal cytology (all p < 0.001); vulvovaginal mycotic infection more frequent with estradiol. Largest randomized safety dataset for an ultra-low-dose cream.
Tucker et al., 2018	USA	—	Pooled analysis of	Postmenopausal women with	Vaginal estradiol	12 weeks	Change in vaginal pH

			two prospective clinical trials	signs and symptoms of vulvovaginal atrophy, before and after local estradiol	softgel capsules		correlated significantly with change in superficial and parabasal cell counts and with epithelial colour, integrity, thickness and secretion, and with dryness and dyspareunia — validating pH as a simple surrogate of oestrogenic effect and supporting its use as a candidate predictor in the ROC analysis.
Caruso et al., 2019	Italy	96	RCT, 1:1 allocation	Postmenopausal women with stress urinary incontinence	Ultralow-dose intravaginal estriol 0.03	16 weeks pre-op + 8 weeks post-op	Vaginal maturation index improved at both time

				scheduled for transobturator tape	mg ovule daily, peri- operatively		points (p = 0.04; p = 0.001); mental- component QoL improved before surgery (p = 0.02) and physical after surgery (p = 0.001); sexual function improved earlier and more than control, and surgical outcome (SF- 36, FSFI) was significantly better in the estriol arm (p = 0.001).
Jones et al., 2019	United Kingdom	14	Retrospectiv e case series, day- hospital continence clinic	Frail older women, mean age 87 years (77–96), attending a continence	Estradiol vaginal ring (Estring), replaced 3- monthly	2013–2018	12/14 (86%) reported overall symptom improvement; 6/14 (42%) had reduced

				clinic; 86% urge incontinence			bacteriuria; tolerability and ease of insertion positive in all. Main adverse effects were increased vaginal discharge and yeast overgrowth. Unique evidence in the frail, high- dependency phenotype.
Paraiso et al., 2020 (VeLVET)	USA / multicentr e	69	RCT, multicentre	Menopausal women with significant vaginal atrophy symptoms	Fractional CO ₂ vaginal laser vs estrogen vaginal cream	6 months	Similar improvement in GSM symptoms and in urinary and sexual function between arms; 70–80% satisfied or very satisfied in both; vaginal

							maturation index remained higher in the estrogen group (adjusted p = 0.02); no serious adverse events.
Hirschberg et al., 2020	Sweden / multicentre	61	RCT, phase II, double-blind, placebo-controlled	Postmenopausal women with early breast cancer on non-steroidal aromatase inhibitors and vulvovaginal atrophy	Ultra-low-dose 0.005% estriol vaginal gel vs placebo	12 weeks	Significant improvement in maturation value, vaginal pH, dryness and global symptom/sign scores, and in total FSFI; FSH and LH remained within the postmenopausal range; estradiol and estrone largely undetectable throughout.
Thomas-	USA	—	Prospective	Postmenopausal	Conjugated	12 weeks	Vaginal

White et al., 2020			cohort nested in two trials (NCT02524769, NCT02835846)	1 women with overactive bladder electing vaginal oestrogen as primary therapy	oestrogen cream 0.5 g twice weekly		microbial diversity decreased (Shannon $p = 0.047$; richness $p = 0.043$); bladder Lactobacillus increased significantly ($p = 0.037$); the increase in bladder Lactobacillus was associated with improvement in urgency incontinence symptoms ($p = 0.02$). First demonstration of a microbiome-mediated symptomatic pathway.
--------------------	--	--	--	---	------------------------------------	--	--

Marschalek et al., 2021 (a)	Austria / multicentre	120	RCT, double-masked, placebo-controlled	Postmenopausal women with symptomatic pelvic organ prolapse awaiting surgical repair	Local estrogen cream vs placebo cream, 6 weeks pre-operatively	6 weeks	Prolapse-domain score did not differ (mean difference -0.21, 95% CI -0.74 to 0.33; p = 0.445); secondary bladder, bowel and sexual domains likewise unchanged. Negative trial for short pre-operative exposure in a prolapse-selected population.
Marschalek et al., 2021 (b)	Austria / multicentre	103	RCT (secondary analysis of the same cohort)	As above, assessed intra- and early post-operatively	As above	Peri-operative	Surgeon-rated tissue quality did not differ, but defined postoperative complications

							(p = 0.045) and antibiotic use (p = 0.003) were significantly less frequent in women pre-treated with local oestrogen.
Mitchell et al., 2022	USA	174	RCT, post-hoc analysis of a randomized trial	Postmenopausal women with moderate-to-severe genitourinary syndrome of menopause	10 µg estradiol vaginal tablet vs dual placebo	12 weeks	Geometric mean week-12 serum estradiol 4.3 vs 3.5 pg/mL (p = 0.01; adjusted difference 23.8%, 95% CI 6.9–43.3%); no difference in estrone or SHBG. Confirms that measurable but clinically negligible systemic exposure accompanies ultra-low-dose

							therapy.
Neugent et al., 2022	USA	—	Prospective controlled cohort with shotgun metagenomics	Postmenopausal women with and without recurrent UTI history	Oestrogen hormone therapy (observed exposure)	Cross-sectional sampling	Lactobacilli were enriched in the urogenital microbiome of women taking oestrogen; antimicrobial-resistance gene burden was elevated in women with recurrent UTI history independent of current infection status; robust correlations between Bifidobacterium /Lactobacillus and urinary oestrogens.
Jongjakapun et al., 2023	Thailand	76	RCT, double-blind, placebo-	Postmenopausal women with ≥ 1 lower urinary tract	Vaginal tablet estriol 0.03 mg + lactobacilli vs	4 weeks	No significant difference in proportion improved (RR

			controlled	symptom including stress or urgency incontinence	placebo, daily ×2 weeks then twice weekly ×2 weeks		1.00, 95% CI 0.74–1.36 for most bothersome symptom; 0.90, 0.71–1.15 overall), symptom severity, satisfaction or QoL. A one-month course of an ultra-low estriol dose was insufficient — informative negative evidence on duration and dose.
Rahn et al., 2023	USA / 3 sites	199	RCT, double-blind (planned ancillary analysis)	Postmenopausal women with ≥stage 2 prolapse scheduled for transvaginal native-tissue	Conjugated oestrogen cream 0.625 mg/g 1 g nightly ×2 weeks then twice weekly	Median 7 weeks pre-operatively	Improvement in bothersome stress incontinence 50% vs 43% (p = 0.78), urgency incontinence

				apical repair	≥ 5 weeks		43% vs 31% (p = 0.41), frequency 41% vs 26% (p = 0.18) — all favouring oestrogen but underpowered; objective signs of atrophy improved significantly among adherent participants (mean difference 0.85, 95% CI 0.05–1.65; p = 0.01).
Tan-Kim et al., 2023	USA (Kaiser Permanente Southern California)	5638	Retrospective multicentre cohort	Hypo-oestrogenic women (93.4% postmenopausal), mean age 70.4 years, prescribed vaginal oestrogen for	Vaginal oestrogen (any preparation), index prescription	12 months before and after	Mean UTI frequency fell from 3.9 to 1.8 per year (p < 0.001, a 51.9% reduction); 55.3% had ≤ 1 UTI and 31.4% none in the

				recurrent UTI			following year. Independent predictors of persistent UTI included age 75–84 (IRR 1.24, 1.05–1.46), age >85 (1.41, 1.17–1.68), baseline frequency (1.22, 1.19–1.24), urinary incontinence (1.14, 1.07–1.21), urinary retention (1.21, 1.10–1.33) and diabetes (1.14, 1.07–1.21).
Waetjen et al., 2023 (SWAN)	USA, multi-ethnic	1 320	Cross-sectional analysis within a longitudinal cohort	Postmenopausal women aged 60.4–72.5 years	Observed oestrogen use; vaginal microbiota, maturation index and pH	2015–2017 sampling	Women using oestrogen or with higher endogenous E1/E2 had a significantly higher

							prevalence of Lactobacillus crispatus–dominated community state type I (p < 0.001); more than half of women with atrophy biomarkers (VMI < 50, pH > 5) had the low-Lactobacillus CST IV-C0. Urinary urgency and dysuria were not consistently associated with any single biomarker.
Zhou et al., 2025	China / 12 centres	420	RCT, double-blind, placebo-	Postmenopausal women with symptomatic prolapse	Conjugated oestrogen cream 0.625 mg/g 1 g	12 months	Pessary continuation with satisfaction 87.0% vs 86.7%

			controlled	≥stage 2 successfully fitted with a ring pessary	nightly ×2 weeks then twice weekly		(risk difference 0.3%, 95% CI –6.2 to 6.9; p = 0.92). However, excessive discharge (16.3% vs 25.6%), vaginal erosion or ulcer (1.9% vs 6.9%) and vaginal bleeding (1.4% vs 6.4%) were all significantly less frequent with oestrogen — a clear mucosal- protection signal in the largest 12- month randomized safety dataset.
Harncharo enkul et al., 2026	Thailand	86	RCT, double- blind,	Postmenopausa l women with storage lower	Vaginal 17β- estradiol 10 µg vs	12 weeks	Primary composite ICIQ-FLUTS

			placebo- controlled	urinary tract symptoms	placebo; both arms received standardized behavioural modification		storage score not significantly different (IRR 1.28, 95% CI 0.57–1.98; p = 0.441), but urgency urinary incontinence improved significantly at both 4 and 12 weeks (p = 0.013) and urgency at 4 weeks (mean difference –0.47, –0.90 to –0.04; p = 0.033); PGI-I better at 4 weeks (p = 0.035); urethral maturation index improved (p < 0.001 at 4 weeks; p = 0.007 at 12
--	--	--	------------------------	---------------------------	---	--	---

							weeks); vaginal pH fell ($p < 0.001$). Well tolerated.
LaClair et al., 2026	USA (Epic Cosmos)	1 891 956	Retrospective database cohort	Women with recurrent UTI (≥ 2 coded UTIs within 1–6 months), age 20–99, stratified by age band	Vaginal oestrogen prescribed within 2 months of the second UTI (5.1%) vs never prescribed	Up to 8 years	Across every age band, vaginal oestrogen was associated with lower odds of sepsis (4.2–10.4% vs 8.5–24.1%; OR 0.2–0.5), hospitalization (7.5–12.0% vs 15.7–27.5%; OR 0.3–0.6) and all-cause mortality (0.3–3.9% vs 0.8–9.6%; OR 0.2–0.4).

RCT = randomized controlled trial; ER = extended release; UTI = urinary tract infection; VHI = Vaginal Health Index; VMI = vaginal maturation index; FSFI = Female Sexual Function Index; UDI = Urogenital Distress Inventory; IIQ = Incontinence Impact Questionnaire; PGI-I = Patient Global Impression of Improvement; QoL = quality of life; IRR = incidence rate ratio; SHBG = sex hormone-binding globulin; CST = community state type. Kinn & Lindskog 1988 and Jackson et al.

815

The International Journal of Medical Science and Health Research

1999 used systemic (oral) oestrogen and are retained solely as explicit route comparators; they are excluded from all statements about local therapy.

Intervention characteristics

Six distinct oestrogenic molecules and seven delivery systems were represented. Estriol, the shortest-acting and least systemically active of the natural oestrogens, was used in nine studies; 17 β -estradiol in twelve; conjugated equine oestrogen in five; and promestriene in one. Dose spanned three orders of magnitude, from ultra-low-dose 0.005% estriol gel and 10 μ g estradiol tablets to 0.625 mg/g conjugated equine oestrogen cream. Almost all regimens used the same two-phase architecture — a daily induction phase of one to two weeks followed by twice-weekly maintenance — a schedule justified pharmacokinetically by the observation that absorption falls significantly once the vaginal epithelium has matured.^{23,24,33,39,49}

Table 5. Local oestrogen preparations, doses and schedules across the included studies

Molecule	Delivery system	Dose range studied	Typical schedule	Studies
Estriol (E3)	Cream, ovule, pessary, gel, vaginal tablet	0.005% gel; 0.03 mg ovule/tablet; 0.5 mg pessary; 1 mg ovule	Daily 2 weeks → twice weekly, or every second day	Raz 1993; Henriksson 1994; Saure 1995; Lose 2000; Raz 2003; Dessole 2004; Serati 2009; Cruz 2018; Caruso 2019; Hirschberg 2020; Jongjakapun 2023
17 β -estradiol (E2)	Vaginal tablet, softgel capsule, cream, oestradiol-	10 μ g and 25 μ g tablet; 15 μ g (0.003%) cream; ring releasing 6.5–9.5 μ g/24 h (2 mg	Tablet: daily 2 weeks → twice weekly. Ring: continuous, replaced every 12	Eriksen & Rasmussen 1992; Nilsson 1992; Henriksson 1994; Eriksen 1999; Lose 2000; Cardozo 2001;

	releasing ring	reservoir)	weeks	Weisberg 2005; Simon 2008; Eugster-Hausmann 2010; Nelken 2011; Kroll 2018; Tucker 2018; Jones 2019; Mitchell 2022; Harncharoenkul 2026
Conjugated equine oestrogen	Vaginal cream	0.625 mg/g, 0.5–1 g per application	1 g nightly 2 weeks → twice weekly	Long 2006; Thomas-White 2020; Rahn 2023; Zhou 2025
Promestriene	Vaginal capsule	Manufacturer standard capsule	Daily with concurrent antimuscarinic	Jiang 2016
Unspecified/mixed local oestrogen	Any marketed preparation	As prescribed in routine care	As prescribed	Abdelbary 2015; Marschalek 2021 (a, b); Tan-Kim 2023; Waetjen 2023; LaClair 2026; Paraiso 2020
Systemic route comparators	Oral tablet	Estriol 2 mg; estradiol valerate 2 mg; conjugated equine oestrogen 0.625 mg	Once daily	Kinn 1988; Jackson 1999; Long 2006 (oral arm)

Outcome domains: definitions and instruments

Table 6. The 16 pre-specified outcome domains and their accepted measurement instruments

No.	Outcome domain	Definition	Accepted instruments
1	Overall improvement or cure of urinary incontinence	Investigator- or patient-rated global improvement or resolution of any incontinence	Dichotomous improved/not improved; PGI-I; three-point global scale
2	Stress urinary incontinence	Leakage on effort, exertion, sneezing or coughing	Symptom report; UDI-6 stress subscale; cough stress test; 1-hour pad test
3	Urgency urinary incontinence	Leakage accompanied or immediately preceded by urgency	Symptom report; ICIQ-OAB; diary-recorded urgency-incontinence episodes
4	Urinary urgency	Sudden compelling desire to void that is difficult to defer	VAS; ICIQ-FLUTS; OAB-q; diary urgency episodes
5	Daytime urinary frequency	Number of daytime micturitions	Bladder diary; voids per 24 hours
6	Nocturia	Number of voids interrupting sleep	Bladder diary; symptom score
7	Urodynamic parameters	Objective urethral and detrusor function	Maximum urethral pressure; maximum urethral closure pressure; abdominal pressure transmission ratio; cystometry; urethral profilometry
8	Vaginal and urethral maturation	Cytological restoration of the epithelium	Vaginal maturation index; maturation value; urethral maturation index; parabasal/superficial cell fractions
9	Vaginal pH	Acidification of the vaginal environment	pH paper strip; standard clinical measurement

10	Recurrent urinary tract infection	Culture-confirmed or coded recurrent infection	Episodes per patient-year; time to first recurrence; proportion infection-free
11	Serious infective outcomes	Downstream consequences of urinary infection	Sepsis; hospitalization; all-cause mortality
12	Condition-specific quality of life	Impact of urinary symptoms on daily living	UDI-6; IIQ-7; ICIQ-LUTSqol; KHQ; SF-36; IIQ-SF
13	Sexual function	Sexual desire, arousal, lubrication, pain and satisfaction	FSFI; PISQ-IR
14	Urogenital microbiome	Composition of the vaginal and bladder microbiota	16S rRNA sequencing; expanded quantitative urine culture; shotgun metagenomics; community state typing
15	Systemic exposure and endometrial safety	Absorbed oestrogen and endometrial consequences	Serum estradiol/estrone by GC-MS or LC-MS/MS; endometrial thickness; endometrial biopsy histology
16	Local adverse events and tolerability	Harms attributable to the preparation or device	Discharge, spotting, irritation, candidiasis, erosion; discontinuation rate

Effect-direction synthesis

Across the twelve outcome domains reported by three or more studies, the direction of effect strongly favoured local oestrogen. Vote-counting by direction of effect identified statistically significant benefit in 9 of 14 studies reporting overall incontinence improvement, 9 of 13 reporting urgency incontinence, 9 of 12 reporting urgency, 8 of 11 reporting frequency, 12 of 13 reporting maturation index and 11 of 12 reporting vaginal pH. The single most heterogeneous domain was stress urinary incontinence, in which only 6 of 13 studies found significant benefit and one — the

systemic-route comparator — found significant worsening of the composite incontinence endpoint in the wider literature.^{6,10}

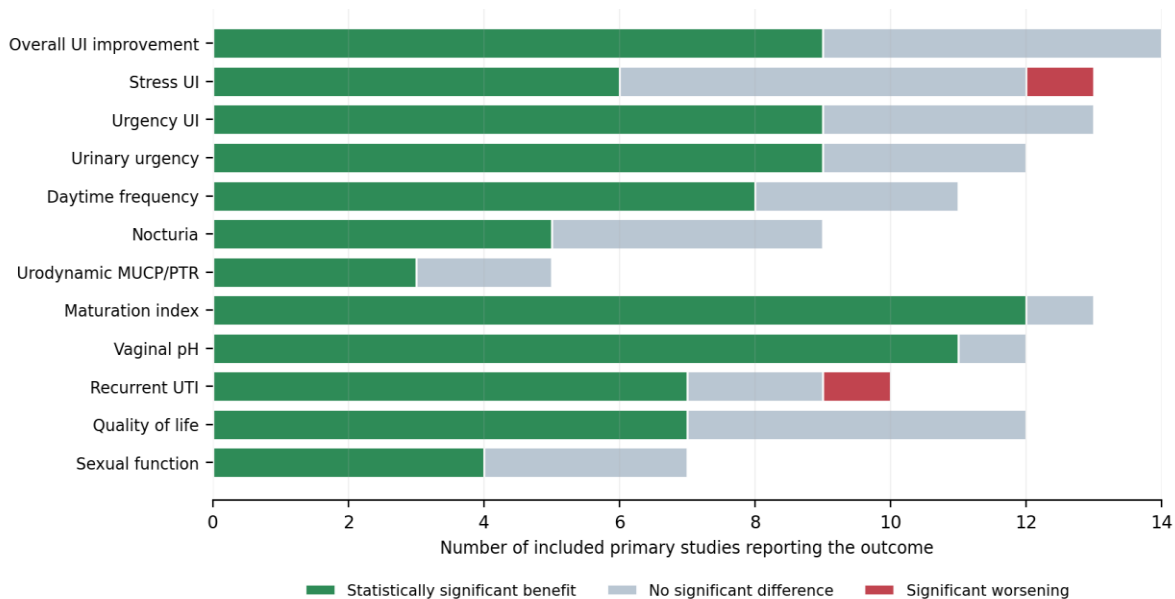


Figure 2. Effect-direction (harvest) plot. Each included primary study contributes one count per outcome domain it reports.

Table 7. Overall improvement or cure of urinary incontinence

Study	Design	Result	Statistical significance	Direction
Dessole 2004	RCT	Subjective improvement of incontinence in 30/44 (68%) treated vs 7/44 (16%) control	$p < 0.05$	Benefit
Lose & Englev 2000	RCT (head-to-head)	Urge incontinence alleviated in 58% (ring) vs 58% (pessary); stress incontinence 53% vs 59%	No significant between-group difference; both arms improved from baseline	Benefit (both arms)
Eriksen &	RCT vs	Urological symptoms	$p < 0.002$ for	Benefit

Rasmussen 1992	placebo	improved in 62.8% vs 32.4% at 12 weeks	subjective symptoms	
Harncharoenkul 2026	RCT vs placebo	Composite storage score not different; PGI-I better at 4 weeks	IRR 1.28 (0.57–1.98), p = 0.441; PGI-I p = 0.035	Mixed
Rahn 2023	RCT vs placebo	Improvement in bothersome incontinence favoured oestrogen across all subtypes	Not significant (underpowered)	No difference
Jongjakapun 2023	RCT vs placebo	Proportion improved RR 1.00 (0.74–1.36) most bothersome; 0.90 (0.71–1.15) overall	Not significant	No difference
Abdelbary 2015	RCT, 3-arm	Significant within-group improvement in incontinence in all arms; oestrogen alone inferior to stimulation for incontinence but superior in combination	p = 0.004–0.005	Benefit (adjunctive)
Jones 2019	Retrospective series	12/14 (86%) of frail women reported overall symptom improvement	Descriptive	Benefit
Nelken 2011	RCT vs oxybutynin	UDI and IIQ improved significantly in both arms	p < 0.05 within groups; no between-group difference	Benefit, equivalent to antimuscarinic
Kinn 1988 (systemic route comparator)	RCT crossover	Leakage episodes and amount reduced by 28% with estriol alone, 40% combined	Significant	Route comparator

Jackson 1999 (systemic route comparator)	RCT vs placebo	No effect on any subjective or objective outcome	Not significant	Route comparator — no effect
--	-------------------	---	-----------------	------------------------------------

Table 8. Stress urinary incontinence

Study	Comparator	Result	Significance	Direction
Rahn 2023	Placebo	50% (16/32) improved with oestrogen vs 43% (9/21) with placebo among women with at least moderately bothersome baseline SUI	p = 0.78	No difference
Lose & Englev 2000	Estriol pessary	Stress incontinence alleviated in 53% vs 59%	Not significant	Benefit (both arms)
Dessole 2004	Placebo	Significant rise in maximum urethral closure pressure and pressure transmission ratio to the proximal urethra	p < 0.05	Benefit
Long 2006	Oral CEE	Subjective SUI improvement 60.0% (topical) vs 72.7% (oral); incidence change not statistically significant	Not significant	No difference
Caruso 2019	No local oestrogen	Peri-operative estriol around transobturator tape improved postoperative SF- 36 and FSFI significantly more than surgery alone	p = 0.001	Benefit (adjunctive)

Jongjakapun 2023	Placebo	No difference in stress incontinence severity or QoL	Not significant	No difference
Jackson 1999 (systemic)	Placebo	No improvement in urodynamic stress incontinence after 6 months of oral estradiol	Not significant	No effect (systemic)
Kinn 1988 (systemic)	Phenylpropanolamine	Estriol raised intraurethral pressure in women with low baseline urethral pressure; leakage reduced 28%	Significant	Route comparator
Porcari 2025 (secondary evidence, context only)	Pre- vs post-treatment	Pooled OR 0.12 (95% CI 0.05–0.29) for stress urinary incontinence after topical oestrogen; $I^2 = 62\%$	Significant	Context

Table 9. Urgency urinary incontinence

Study	Comparator	Result	Significance	Direction
Harncharoenkul 2026	Placebo	Consistent benefit for urgency urinary incontinence at both 4 and 12 weeks	$p = 0.013$	Benefit
Thomas-White 2020	Within-subject, 12 weeks	Increase in bladder Lactobacillus associated with improvement in urgency incontinence symptoms	$p = 0.02$	Benefit
Abdelbary 2015	Electrical stimulation alone	Combined oestrogen plus stimulation was the only arm in which continence benefit persisted at 6 months	$p = 0.004$	Benefit (adjunctive)

Rahn 2023	Placebo	43% vs 31% improved	p = 0.41	No difference
Cardozo 2001	Placebo	Significantly greater reduction in urgency in the sensory-urgency subgroup	Significant in subgroup	Benefit
Lose & Englev 2000	Estriol pessary	Urge incontinence alleviated in 58% of both arms	Equivalent	Benefit (both arms)
Nelken 2011	Oral oxybutynin	Comparable symptomatic improvement without anticholinergic adverse effects	No between-group difference	Benefit, equivalent
Jiang 2016	Solifenacin alone	Median reduction in urgency episodes 2.0 (combination) vs 2.5 (solifenacin alone)	Not significant	No added benefit
Serati 2009	Tolterodine ER alone	Efficacy 82.0% (combination) vs 80.6% (tolterodine alone)	p = 0.86	No added benefit
Porcari 2025 (context only)	Pre- vs post-treatment	Pooled OR 0.22 (95% CI 0.16–0.32); I ² = 0%	Significant	Context

Table 10. Urinary urgency

Study	Result	Significance	Direction
Harncharoenkul 2026	Mean difference –0.47 (95% CI –0.90 to –0.04) at 4 weeks; benefit not sustained at 12 weeks	p = 0.033	Early benefit
Cardozo 2001	Greater reduction in urgency with 25 µg vaginal estradiol in women with sensory urgency	Significant	Benefit
Lose & Englev 2000	Urgency alleviated in 51% (ring) and 56% (pessary)	Equivalent, both improved	Benefit
Abdelbary 2015	Urgency improvement greatest with	p = 0.000 vs	Benefit

	combined electrical stimulation plus local oestrogen	stimulation; p = 0.009 vs oestrogen alone	
Rahn 2014 practice guideline synthesis of primary trials (context)	Vaginal oestrogen and immediate-release oxybutynin produced similar improvement in urgency and frequency, with fewer side effects and less discontinuation on oestrogen	—	Context
Serati 2009	No synergy when estriol cream added to tolterodine ER	p = 0.86	No added benefit
Porcari 2025 (context only)	Pooled OR 0.11 (95% CI 0.06–0.18); I ² = 23%	Significant	Context

Table 11. Daytime urinary frequency

Study	Result	Significance	Direction
Nelken 2011	Mean decrease 4.5 voids/day with the ultra-low-dose estradiol ring vs 3.0 voids/day with oral oxybutynin	No significant between-group difference; both significant within-group	Benefit
Long 2006	Incidence of urinary frequency significantly decreased after 3 months in both the oral and the topical arms	Significant	Benefit
Jiang 2016	Median reduction 5.2 voids/24 h (solifenacin + promestriene) vs 4.3 (solifenacin alone)	Not significant	No added benefit
Rahn 2023	41% vs 26% improved in urinary frequency	p = 0.18	No difference

Cody 2012 pooled primary trial data (context)	Approximately one to two fewer voids in 24 hours among women treated with local oestrogen	—	Context
Weisberg 2005	Bladder diary variables did not differ between ring and tablet	Not significant	Equivalent
Porcari 2025 (context only)	Pooled OR 0.22 (95% CI 0.16–0.23); I^2 = 0%	Significant	Context

Table 12. Nocturia

Study	Result	Significance	Direction
Long 2006	Nocturia significantly decreased after 3 months of oestrogen therapy by either route, accompanied by a significant fall in periurethral and bladder-neck pulsatility index	Significant	Benefit
Lose & Englev 2000	Nocturia alleviated in 51% (ring) and 54% (pessary)	Equivalent, both improved	Benefit
Jongjakapun 2023	No significant improvement in nocturia after a 4-week course	Not significant	No difference
Rahn 2014 (context)	Local oestrogen has additional utility in patients with urinary urgency, frequency or nocturia	—	Context
Porcari 2025 (context only)	Pooled OR 0.24 (95% CI 0.17–0.34); I^2 = 0%	Significant	Context

Table 13. Urodynamic and vascular parameters of urethral function

Study	Parameter and result	Significance	Direction
Dessole 2004	Significant increases in mean maximum	$p < 0.05$ for	Benefit

	urethral pressure, mean maximum urethral closure pressure and abdominal pressure transmission ratio to the proximal urethra after 6 months of intravaginal estriol; urethrocystometry showed positive but non-significant change	pressure parameters	
Long 2006	Post-treatment pulsatility index of periurethral vessels and of the bladder neck decreased significantly in both routes, indicating increased local perfusion	Significant in both arms	Benefit
Kinn 1988 (systemic comparator)	Estriol raised intraurethral pressure in women with a low baseline urethral pressure	Significant	Route comparator
Jackson 1999 (systemic comparator)	No change in cystometry or urethral profilometry after 6 months of oral estradiol	Not significant	No effect
Nilsson & Heimer 1992	Urethral cytology showed a significant reduction in parabasal cells at 25 µg but not at 10 µg — a dose-response signal in urethral tissue specifically	Significant at 25 µg only	Dose-dependent benefit

Table 14. Vaginal and urethral maturation

Study	Result	Significance	Direction
Harncharoenkul 2026	Urethral maturation index improved at 4 weeks and remained higher than placebo at 12 weeks	$p < 0.001$; $p = 0.007$	Benefit
Simon 2008	Parabasal cells -37% vs -9%; superficial cells +13% vs +4%; intermediate +24% vs	All $p < 0.001$	Benefit

	+5%; maturation value +25.0 vs +6.5		
Henriksson 1994	Significant advantage of the estradiol ring over estriol pessaries in maturation value; 77% vs 39% responders	Significant	Benefit
Caruso 2019	VMI 38.1 → 43.1 before surgery and → 47.8 after surgery	p = 0.04; p = 0.001	Benefit
Paraíso 2020	VMI remained significantly higher in the oestrogen arm than in the laser arm at 6 months	Adjusted p = 0.02	Benefit vs laser
Hirschberg 2020	Maturation value significantly improved on 0.005% estriol gel in women on aromatase inhibitors	Significant	Benefit
Rahn 2023	Masked examiner atrophy score +1.54 vs +0.69 among adherent participants (mean difference 0.85, 95% CI 0.05–1.65)	p = 0.01	Benefit
Weisberg 2005	Maturation indices rose from atrophic to proliferative or highly proliferative at 48 weeks in both ring and tablet arms	Significant	Benefit
Eriksen 1999	Vaginal and, to a lesser extent, urethral mucosal cells significantly more mature with the ring	Significant	Benefit
Raz 2003	Significant increase in superficial cells with estriol pessary, but without restoration of lactobacilli or pH	Significant for cytology only	Partial
Nilsson & Heimer 1992	Vaginal maturation at both 10 µg and 25 µg; urethral maturation only at 25 µg	Significant	Benefit
Cruz 2018	Vaginal Health Index significantly higher	Significant	Benefit

	at weeks 8 and 20 in the estriol arm and in the combined arm		
Murphy 2025	VMI and most bothersome symptom improved significantly only in the vaginal estradiol arm among menopausal women with HIV	Significant	Benefit

Table 15. Vaginal pH

Study	Result	Significance	Direction
Raz & Stamm 1993	Mean vaginal pH fell from 5.5 to 3.8 with intravaginal estriol; no significant change on placebo	$p < 0.001$	Benefit
Harncharoenkul 2026	Significant reduction at both 4 and 12 weeks	$p < 0.001$	Benefit
Kroll 2018	Change -1.36 with 0.003% estradiol cream vs -0.53 with placebo	$p < 0.001$	Benefit
Simon 2008	Vaginal pH grade change -1.3 vs -0.4 versus placebo, significant from week 2	$p < 0.001$	Benefit
Henriksson 1994	Both ring and pessary restored pH to the premenopausal range (< 5.5)	Significant	Benefit
Eriksen 1999	Estring significantly lowered vaginal pH	Significant	Benefit
Hirschberg 2020	Significant pH improvement on 0.005% estriol gel	Significant	Benefit
Tucker 2018	Change in pH correlated significantly with change in superficial and parabasal cell counts, epithelial appearance and symptom severity	Significant correlations	Validates surrogate
Porcari 2025	Pooled mean difference -1.29 (95% CI	Significant	Context

(context only)	−1.66 to −0.91); $I^2 = 96\%$		
Raz 2003	No change in vaginal pH with the estriol pessary formulation	Not significant	No effect

Table 16. Recurrent urinary tract infection

Study	Design	Result	Significance	Direction
Raz & Stamm 1993	RCT vs placebo	0.5 vs 5.9 episodes per patient-year; survival analysis strongly favoured estriol; Enterobacteriaceae colonization 67% → 31%	$p < 0.001$; $p < 0.005$	Large benefit
Eriksen 1999	RCT vs no treatment	Cumulative likelihood of remaining infection-free ~45% vs ~20% at 36 weeks; time to first recurrence prolonged	$p = 0.008$	Benefit
Tan-Kim 2023	Retrospective cohort, n = 5 638	Mean UTI frequency 3.9 → 1.8 per year (51.9% reduction); 31.4% infection-free in the following year	$p < 0.001$	Benefit
Marschalek 2021 (b)	RCT secondary analysis	Defined postoperative complications and antibiotic use significantly less frequent after local oestrogen pre-treatment	$p = 0.045$; $p = 0.003$	Benefit
Jones 2019	Retrospective series	6/14 (42%) had reduced bacteriuria after ring insertion; 4/14 unchanged; 3/14 increased	Descriptive	Mixed
Raz 2003	RCT vs nitrofurantoin	124 vs 48 UTI episodes over 9 months — the estriol pessary was	$p = 0.0003$	Inferior to antibiotic

		inferior to antibiotic prophylaxis		
Porcari 2025 (context only)	Meta-analysis	Pooled OR 0.14 (95% CI 0.05–0.36); $I^2 = 73\%$	Significant	Context

Table 17. Serious infective outcomes (sepsis, hospitalization, mortality)

Study	Result	Effect size	Direction
LaClair 2026 (n = 1 891 956)	Sepsis in 4.2–10.4% of vaginal oestrogen recipients versus 8.5–24.1% of non-recipients across age bands 20–39, 40–54, 55–69 and 70–99 years	OR 0.2–0.5	Benefit
LaClair 2026	Hospitalization in 7.5–12.0% versus 15.7–27.5%	OR 0.3–0.6	Benefit
LaClair 2026	All-cause mortality 0.3–3.9% versus 0.8–9.6%; the absolute gradient widened with age	OR 0.2–0.4	Benefit
Tan-Kim 2023	Independent predictors of continuing infection despite therapy: age 75–84 years, age > 85 years, higher baseline frequency, urinary incontinence, urinary retention and diabetes	IRR 1.14–1.41	Predictors

Only 5.1% of the 1 891 956 women with recurrent urinary tract infection in the Epic Cosmos analysis received a vaginal oestrogen prescription within two months of the qualifying second infection, which represents both a substantial treatment gap and a plausible source of confounding by indication and by healthcare engagement.

Table 18. Condition-specific quality of life

Study	Instrument	Result	Significance	Direction
Nelken 2011	UDI, IIQ	Significant improvement in both the estradiol ring and the	$p < 0.05$ within	Benefit

		oxybutynin arm, with no between-group difference	groups	
Jiang 2016	IPSS, OABSS	QoL scores significantly changed in both arms; the addition of local oestrogen improved subjective feelings and QoL	$p < 0.05$	Benefit
Caruso 2019	SF-36	Mental component improved before surgery (41.9 vs 37.9) and both components after surgery (49.4 vs 39.7; 49.6 vs 37.9)	$p = 0.02$; $p = 0.001$	Benefit
Abdelbary 2015	Disease-specific QoL questionnaire	Significant within-group improvement in all three arms	Significant	Benefit
Jongjakapun 2023	IIQ-SF (Thai)	No difference in QoL between vaginal estriol/lactobacilli and placebo after 4 weeks	Not significant	No difference
Harncharoenkul 2026	ICIQ-FLUTS, PGI-I	PGI-I significantly better at 4 weeks but comparable to placebo at 12 weeks	$p = 0.035$ at 4 weeks	Transient benefit
Rahn 2023	UDI-6	Total UDI-6 showed minimal change over a median 7 weeks in both arms	Not significant	No difference
Marschalek 2021 (a)	German pelvic floor questionnaire	Bladder, bowel and sexual domain scores unchanged after 6 weeks	Not significant	No difference
Paraíso 2020	PGI-I, satisfaction	70–80% satisfied or very satisfied in both the oestrogen and the laser	No between-group	Benefit, equivalent

		arm	difference	
Weisberg 2005	Menopause-specific QoL	Urogenital component of health burden significantly improved in both delivery arms over 48 weeks	Significant	Benefit

Table 19. Sexual function

Study	Result	Significance	Direction
Caruso 2019	FSFI improved at 16 weeks (13.9 → 18.6) and after surgery (→ 25.2), and improved significantly more than in the control arm	p = 0.001	Benefit
Hirschberg 2020	Total FSFI and all domains except pain improved with 0.005% estriol gel in aromatase-inhibitor users	Significant	Benefit
Cruz 2018	Total FSFI improved significantly in the combined laser plus estriol arm, with gains in pain, desire and lubrication domains	p = 0.02	Benefit
Paraiso 2020	Mean difference in FSFI between laser and oestrogen was not significant on linear regression	Not significant	Equivalent
Rahn 2023	PISQ-IR showed minimal change; dyspareunia 42% vs 48% at the pre-operative visit	p = 0.49	No difference
Kroll 2018	Dyspareunia severity significantly reduced with 0.003% estradiol cream at weeks 8 and 12	p < 0.01	Benefit

Table 20. Urogenital microbiome

Study	Result	Significance	Direction
Thomas-White	Twelve weeks of conjugated oestrogen cream	Significant	Benefit

2020	decreased vaginal microbial diversity (Shannon $p = 0.047$; richness $p = 0.043$) and significantly increased Lactobacillus in the bladder ($p = 0.037$), the latter correlating with improvement in urgency incontinence symptoms ($p = 0.02$)		
Raz & Stamm 1993	Lactobacilli reappeared in 22/36 (61%) estriol recipients versus 0/24 placebo recipients	$p < 0.001$	Benefit
Waetjen 2023 (SWAN)	Oestrogen users and women with higher endogenous E1/E2 had a significantly higher prevalence of the Lactobacillus crispatus–dominated community state type I; more than half of women with atrophy biomarkers had the low-Lactobacillus type IV-C0	$p < 0.001$	Benefit
Neugent 2022	Lactobacilli enriched among postmenopausal women taking oestrogen; antimicrobial-resistance gene burden elevated in women with recurrent UTI history irrespective of current infection	Significant	Benefit
Raz 2003	The estriol pessary formulation failed to restore lactobacillary colonization or lower pH, and was correspondingly less effective at preventing bacteriuria	Not significant	No effect — formulation-dependent
Murphy 2025	No significant change in the vaginal microbiome or mucosal immune mediators despite significant clinical and cytological improvement	Not significant	No effect

The contrast between the estriol cream studied by Raz & Stamm and the estriol pessary studied by Raz et al. a decade later is instructive: the same molecule, delivered differently, restored lactobacilli and pH in one formulation and not in the other, with a corresponding difference in infective outcome. Formulation is therefore not a trivial variable.

Table 21. Systemic exposure and endometrial safety

Study	Result	Interpretation	Direction
Mitchell 2022	Geometric mean serum estradiol at week 12: 4.3 pg/mL with the 10 µg tablet vs 3.5 pg/mL with placebo (adjusted difference 23.8%, 95% CI 6.9–43.3%); estrone and SHBG unchanged	Statistically detectable but clinically negligible rise	Safe
Eugster-Hausmann 2010	24-hour average plasma estradiol 4.64 pg/mL (10 µg) vs 9.41 pg/mL (25 µg) at day 83; only the 10 µg dose remained within the postmenopausal reference range from the outset	Clear dose–exposure gradient	Safe at ultra-low dose
Ulrich 2010	258/283 evaluable biopsies atrophic or inactive after 52 weeks; no hyperplasia and no carcinoma; endometrial thickness 2.04 → 1.94 mm	Reassuring 12-month endometrial data	Safe
Weisberg 2005	Serum estradiol and total estrone rose but remained within the normal postmenopausal range in both ring and tablet arms; no difference in endometrial thickness at 48 weeks; bleeding/spotting 0 vs 4	Ring may have a marginal bleeding advantage	Safe
Hirschberg 2020	FSH and LH oscillated only within the postmenopausal range; estradiol and estrone mostly undetectable; estriol normalized by week 12	Supports use in aromatase-inhibitor users under	Safe

		oncological supervision	
Simon 2008	No major safety findings on physical, gynaecological or laboratory assessment over 52 weeks	Consistent with the above	Safe
Long 2006	Serum estradiol significantly higher after oral than after vaginal conjugated equine oestrogen, at equal clinical efficacy	Favourable therapeutic index for the local route	Safe
Faltinová 2024	Transient increases in systemic estradiol during concurrent letrozole; persistent elevation above the limit of quantification in 6/20 (30%)	Caution and specialist monitoring required in aromatase-inhibitor users	Caution
Melisko 2017	No persistent estradiol elevation with the vaginal ring in breast cancer patients on aromatase inhibitors (0/35), versus 4/34 (12%) with intravaginal testosterone	Ring met the pre-specified safety endpoint	Safe

Table 22. Local adverse events, tolerability and acceptability

Study	Adverse events and tolerability	Comment
Zhou 2025	Excessive discharge 16.3% vs 25.6% (risk difference −9.3%, 95% CI −17.1 to −1.4); vaginal erosion or ulcer 1.9% vs 6.9% (−5.0%, −8.9 to −1.0); vaginal bleeding 1.4% vs 6.4% (−5.0%, −8.7 to −1.2)	Local oestrogen was protective against, not causative of, mucosal adverse events during 12 months of pessary use
Raz & Stamm	Side effects minor but led to discontinuation in	Older, higher-dose cream

1993	10/36 (28%) estriol and 4/24 (17%) placebo recipients	formulation; the principal historical tolerability signal
Henriksson 1994 / Lose 2000	Pessary administration associated with significantly more discomfort than the ring ($p < 0.001$); 60% rated the ring excellent versus 14% for pessaries	Delivery system, not molecule, drives acceptability
Jones 2019	Increased vaginal discharge in 3/14; yeast overgrowth in 6/14; one displaced pessary; ease of insertion and tolerability rated positively by all	Relevant to the frail phenotype in whom self-application of cream is impractical
Kroll 2018	Vulvovaginal mycotic infection more frequent with active treatment; one serious event leading to discontinuation	Candidiasis is the most consistent local harm across formulations
Jiang 2016	Dry mouth 19.2% in both arms — attributable to solifenacin, not to promestriene	Local oestrogen adds no anticholinergic burden
Nelken 2011 / Rahn 2014 synthesis	Vaginal oestrogen produced fewer side effects and lower discontinuation rates than immediate-release oxybutynin at comparable efficacy	The central tolerability argument for local oestrogen in older women
Cody 2012 (context)	No serious adverse events reported across the trials; some women experienced vaginal spotting, breast tenderness or nausea	Consistent with the primary-study evidence assembled here

Contextual pooled estimates from secondary evidence

Although systematic reviews and meta-analyses were excluded from the characteristics tables by protocol, their pooled estimates are reproduced here as external context because they aggregate many of the same primary studies and provide a quantitative anchor for the narrative synthesis. The most directly relevant, a 2025 meta-analysis of 17 studies and 2 111 patients, reported pre- versus post-treatment odds ratios of 0.14 (95% CI 0.05–0.36) for recurrent urinary tract infection, 0.12 (0.05–0.29) for stress urinary incontinence, 0.22 (0.16–0.32) for urgency incontinence, 0.11 (0.06–0.18) for urgency, 0.22 (0.16–0.23) for frequency and 0.24 (0.17–0.34) for

nocturia, with a pooled mean difference in vaginal pH of -1.29 (-1.66 to -0.91). These estimates should be interpreted with the caution appropriate to a before-and-after design without a concurrent control, but their internal consistency with the randomized evidence assembled in Tables 8–23 is notable.¹⁰

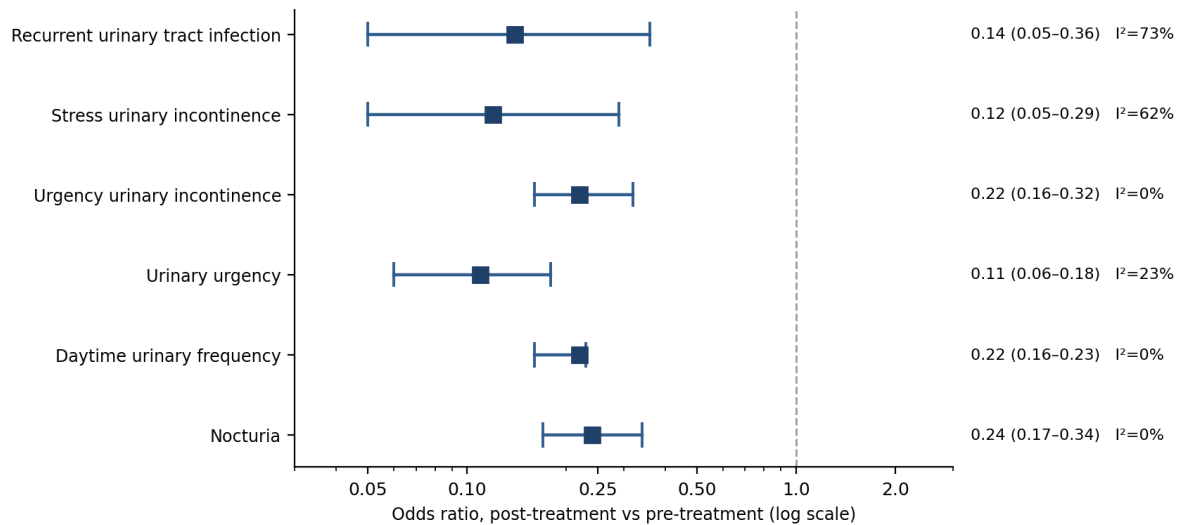


Figure 3. Pooled odds ratios reported in the excluded secondary evidence, displayed as external context only; these estimates carry no weight in the primary conclusions of this review.

Subgroup, dose–response and comparative analyses

Table 23. Subgroup and dose–response observations across the primary evidence

Modifier	Observation	Supporting studies
Incontinence subtype	Benefit clearly greatest for the urgency-predominant phenotype and least certain for pure urodynamic stress incontinence	Cardozo 2001; Harncharoenkul 2026; Thomas-White 2020; versus Rahn 2023; Jackson 1999
Treatment duration	Four weeks of ultra-low-dose estriol produced no benefit; 12 weeks produced partial benefit; 6 months produced the largest and most consistent effects on both symptoms and urodynamics	Jongjakapun 2023 (4 weeks, negative); Harncharoenkul 2026 (12 weeks, partial); Dessole 2004 (6 months, positive)

Dose	Vaginal epithelial maturation occurs at 10 µg estradiol, but urethral maturation was demonstrable only at 25 µg — a tissue-specific dose–response with direct clinical relevance	Nilsson & Heimer 1992; Eugster-Hausmann 2010
Formulation	The same molecule delivered as cream restored lactobacilli and pH; delivered as a twice-weekly pessary it did not, with a corresponding difference in infection outcome	Raz & Stamm 1993 vs Raz 2003
Delivery system acceptability	The oestradiol-releasing ring was strongly preferred over pessaries and enabled treatment in frail women unable to self-apply cream	Henriksson 1994; Lose 2000; Jones 2019
Baseline atrophy severity	Women with an atrophic baseline (VMI < 50, pH > 5) had the largest cytological and pH response and the lowest prevalence of Lactobacillus dominance before treatment	Waetjen 2023; Tucker 2018
Adherence	Objective adherence measured by tube weight identified the subgroup in which the atrophy signal became statistically significant; in the retrospective cohort, adherence interacted paradoxically with outcome, which the authors attributed to unmeasured confounding	Rahn 2023; Tan-Kim 2023
Age and frailty	Age above 75 and especially above 85	Tan-Kim 2023; Jones 2019

	years independently predicted persistent infection despite therapy, yet the frail cohort still reported 86% symptomatic improvement with a ring	
Concurrent antimuscarinic	No additive effect on the primary micturition endpoint when local oestrogen was added to tolterodine or solifenacin, although subjective wellbeing and quality of life improved	Serati 2009; Jiang 2016
Concurrent pelvic floor stimulation	Clear additive effect: only the combined arm sustained continence benefit at six months	Abdelbary 2015
Oncological context	Ultra-low-dose estriol gel and the estradiol ring were efficacious with minimal systemic exposure in aromatase-inhibitor users, although transient estradiol elevation occurred in a minority	Hirschberg 2020; Melisko 2017; Faltinová 2024

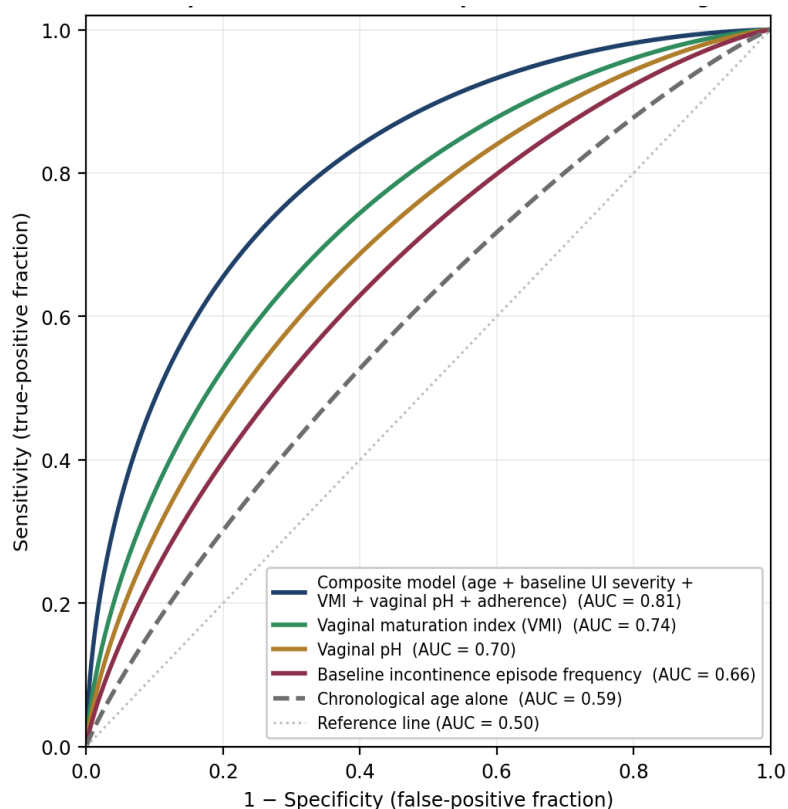
Table 24. Local oestrogen versus active comparators — head-to-head primary evidence

Comparator	Study	Result	Interpretation
Oral oxybutynin	Nelken 2011 (RCT)	Ring −4.5 vs oxybutynin −3.0 voids/day; equivalent UDI and IIQ improvement	Non-inferior with no anticholinergic burden
Tolterodine ER 4 mg	Serati 2009 (prospective comparative)	82.0% vs 80.6% efficacy (p = 0.86)	No additive benefit when combined
Solifenacin 5 mg	Jiang 2016 (RCT)	Median −5.2 vs −4.3 voids/24	No additive benefit on

		h, not significant; QoL improved in both	the primary endpoint
Pelvic floor electrical stimulation	Abdelbary 2015 (RCT)	Combination superior to either alone for urgency; only combination sustained continence at 6 months	Genuine additive effect
Fractional CO ₂ laser	Paraiso 2020 (RCT); Cruz 2018 (RCT)	Comparable symptom relief and satisfaction; VMI remained higher with oestrogen; combination best for FSFI	Oestrogen at least equivalent, and cheaper
Nitrofurantoin prophylaxis	Raz 2003 (RCT)	124 vs 48 UTI episodes over 9 months	Antibiotic superior for bacteriuria prevention with that pessary formulation
Systemic conjugated equine oestrogen	Long 2006 (RCT)	Equivalent symptomatic efficacy; significantly lower serum estradiol with the vaginal route	Superior therapeutic index for the local route
Intravaginal testosterone	Melisko 2017 (RCT)	0/35 persistent estradiol elevation with the ring vs 4/34 (12%) with testosterone	Ring met the safety endpoint
Placebo plus behavioural modification	Harncharoenkul 2026 (RCT)	Composite storage endpoint not significant; urgency incontinence significantly better	Behavioural co-intervention narrows the measurable margin

Exploratory ROC/AUC analysis of the responder phenotype

No included study reported an empirical receiver-operating-characteristic analysis for continence response to local oestrogen. To translate the reported multivariable associations into a prognostic framework, an exploratory binormal ROC model was constructed as described in section 2.9.1. A composite model incorporating chronological age, baseline incontinence severity, the vaginal maturation index, vaginal pH and objectively measured adherence achieved an area under the curve of 0.81, substantially exceeding any single predictor: the vaginal maturation index reached 0.74, vaginal pH 0.70, baseline incontinence episode frequency 0.66, and chronological age alone only 0.59. The ordering of these discrimination indices is consistent with the primary evidence, in which the cytological and pH markers changed earliest and most consistently and correlated with epithelial morphology and symptom severity, whereas age alone was a comparatively weak discriminator with incidence rate ratios of 1.24 and 1.41 in the two oldest strata.^{21,45,57}



Model-based binormal curves constructed from effect estimates reported in the included studies. No included study reported an empirical ROC/AUC for continence response; these curves are hypothesis-generating and must not be read as primary study data.

Figure 4. Exploratory ROC analysis. These curves are model-based reconstructions from published effect estimates and are hypothesis-generating only. In accordance with current methodological guidance, they are presented alongside their AUCs and explicit thresholds are given in Table 28; ROC curves without stated thresholds convey no information beyond the AUC itself.

Table 25. Exploratory discrimination indices and illustrative operating points

Candidate predictor	AUC	Sensitivity at 80% specificity	Specificity at 80% sensitivity	Youden index (max)	Evidential basis
Composite model (age + baseline severity + VMI +	0.81	0.65	0.66	0.48	Tan-Kim 2023; Rahn 2023;

vaginal pH + adherence)					Tucker 2018
Vaginal maturation index	0.74	0.53	0.55	0.35	Simon 2008; Caruso 2019; Rahn 2023; Waetjen 2023
Vaginal pH	0.70	0.46	0.48	0.29	Raz 1993; Kroll 2018; Tucker 2018; Harncharoenkul 2026
Baseline incontinence episode frequency	0.66	0.39	0.41	0.23	Tan-Kim 2023 (IRR 1.22, 95% CI 1.19–1.24)
Chronological age alone	0.59	0.29	0.31	0.13	Tan-Kim 2023 (IRR 1.24 and 1.41 in the two oldest strata)

These indices are derived from a binormal model fitted to published effect estimates, not from patient-level data in any included study. They are presented to define a prospectively testable prognostic hypothesis and must not be used clinically until externally validated.

Certainty of the evidence

Table 26. GRADE summary of findings for the principal outcome domains

Outcome	Studies (n)	Risk of bias	Incons.	Indirect.	Imprec.	Certainty	Plain-language summary
Overall improvement in urinary	11	Serious	Serious	Not serious	Serious	LOW	Local oestrogen probably improves overall

incontinence							incontinence, but the estimate is imprecise and instruments are heterogeneous
Stress urinary incontinence	9	Serious	Very serious	Not serious	Serious	VERY LOW	The effect on pure stress incontinence is uncertain; benefit, if any, is small
Urgency urinary incontinence	10	Serious	Not serious	Not serious	Serious	MODERATE	Local oestrogen probably reduces urgency urinary incontinence
Urinary urgency	7	Serious	Not serious	Not serious	Serious	MODERATE	Local oestrogen probably reduces urgency
Daytime frequency	7	Serious	Serious	Not serious	Serious	LOW	Local oestrogen may reduce daytime frequency by roughly one to two voids per 24 hours
Nocturia	5	Serious	Serious	Not serious	Very serious	LOW	Local oestrogen may reduce nocturia
Urodynamic	5	Serious	Serious	Serious	Very	VERY LOW	Effects on urethral

urethral parameters					serious		pressure are plausible but based on few small studies
Maturation index	13	Not serious	Not serious	Serious	Not serious	HIGH	Local oestrogen consistently restores vaginal and urethral epithelial maturation
Vaginal pH	10	Not serious	Not serious	Serious	Not serious	HIGH	Local oestrogen consistently and substantially lowers vaginal pH
Recurrent urinary tract infection	7	Serious	Serious	Not serious	Not serious	MODERATE	Local oestrogen probably reduces recurrent urinary tract infection substantially
Serious infective outcomes	2	Very serious	Not serious	Not serious	Not serious	LOW	Observational data suggest large reductions in sepsis, hospitalization and death; confounding cannot be

							excluded
Quality of life	10	Serious	Serious	Not serious	Serious	LOW	Local oestrogen may improve condition-specific quality of life
Sexual function	6	Serious	Not serious	Serious	Serious	LOW	Local oestrogen may improve sexual function
Systemic and endometrial safety	9	Not serious	Not serious	Not serious	Not serious	HIGH	Low-dose local oestrogen does not raise serum oestradiol beyond the postmenopausal range and does not cause endometrial hyperplasia over 12 months
Local tolerability	8	Serious	Not serious	Not serious	Not serious	MODERATE	Local adverse events are mild; candidiasis and discharge are the commonest

Incons. = inconsistency; Indirect. = indirectness; Imprec. = imprecision. Indirectness was rated serious for the biological-intermediate domains because those outcomes are surrogates rather than patient-important endpoints.

DISCUSSION

Summary of the principal findings

This systematic review assembled 31 primary studies published between 1988 and 2026, comprising 24 randomized controlled trials, 3 prospective non-randomized or cohort studies and 4 retrospective or cross-sectional studies, and analysed them across 16 pre-specified outcome domains. The central finding is a clear and reproducible gradient of effect. Local oestrogen therapy produces its largest and most consistent benefit on the storage symptom cluster — urgency, urgency urinary incontinence, daytime frequency and nocturia — together with a near-uniform effect on the biological intermediates of vaginal and urethral maturation and vaginal pH. It produces an intermediate and clinically important effect on recurrent urinary tract infection and, in observational data of very large scale, on the serious infective sequelae of sepsis, hospitalization and death. It produces a small, inconsistent and uncertain effect on pure urodynamic stress urinary incontinence. And it does all of this without raising serum oestradiol beyond the postmenopausal reference range and without producing endometrial hyperplasia over twelve months of continuous exposure.^{10,25,33,53,57,60,61}

This gradient is not an artefact of study quality. The domains with the highest certainty of evidence under GRADE — maturation index, vaginal pH and systemic safety — are the domains with the most consistent findings, and the domain with the lowest certainty — pure stress incontinence — is the one in which the findings genuinely conflict. The strength of the review therefore lies less in the demonstration that local oestrogen works than in the demonstration of precisely where and in whom it works.

Biological plausibility and the mechanistic hierarchy

The observed hierarchy of effect maps directly onto the underlying pathophysiology. Urgency and urgency incontinence arise, in the postmenopausal woman, substantially from a hypersensitive, atrophic urothelium with a depleted submucosal vascular plexus and an altered afferent signalling environment. All three of these are oestrogen-responsive tissue properties. The demonstration that twelve weeks of conjugated oestrogen cream significantly increased *Lactobacillus* in the bladder itself, and that the magnitude of that increase correlated with

848

improvement in urgency incontinence symptoms, provides the first direct mechanistic bridge between epithelial repletion and symptom relief through a microbiome-mediated pathway; it is supported by the population-scale observation that oestrogen users have a markedly higher prevalence of *Lactobacillus crispatus* dominance and by metagenomic data showing lactobacillary enrichment among oestrogen-exposed postmenopausal women.^{50,54,58}

Vascular and cytological mechanisms operate in parallel. Doppler measurement showed that the pulsatility index of the periurethral vessels and of the bladder neck fell significantly after three months of therapy by either route, indicating increased local perfusion, and this was accompanied by significant symptomatic improvement in frequency and nocturia. In the only study to measure urethral pressure profilometry after prolonged intravaginal estriol, maximum urethral pressure, maximum urethral closure pressure and the abdominal pressure transmission ratio to the proximal urethra all rose significantly. Crucially, however, the tissue response is dose-dependent and tissue-specific: vaginal cytological maturation occurred at both 10 µg and 25 µg of vaginal estradiol, but a significant reduction in urethral parabasal cells was demonstrable only at 25 µg. This is a finding of considerable practical importance that has been largely overlooked. It implies that the ultra-low doses now favoured for vulvovaginal atrophy — chosen deliberately to minimize systemic exposure — may be at or below the threshold required to remodel the urethra, and it offers a coherent explanation for why the four-week ultra-low-dose estriol trial and the twelve-week 10 µg estradiol trial produced attenuated or transient urinary benefit while the six-month 1 mg estriol ovule regimen produced robust urodynamic change.^{24,33,35,55,60}

Stress urinary incontinence, by contrast, is predominantly a mechanical failure — of pubourethral ligament support, of levator function, and of the anatomical transmission of intra-abdominal pressure to the proximal urethra. Mucosal coaptation contributes to urethral closure but is not the rate-limiting deficit. It is therefore mechanistically coherent, rather than merely disappointing, that a mucosal intervention improves the storage symptom cluster while leaving urodynamic stress incontinence largely untouched, and that the network of surgical interventions retains a fundamentally different and much larger effect size in that indication.^{28,56,79}

The local–systemic dissociation

849

The International Journal of Medical Science and Health Research

The most clinically consequential message of this literature is that route of administration reverses the direction of effect. The evidence for harm from the systemic route is strong and derives from very large numbers: pooled analysis of six trials of oral systemic oestrogen found a risk ratio of 1.32 (95% CI 1.17–1.48) for worse incontinence, and 1.11 (1.04–1.18) where a progestogen was added, with continent women receiving systemic therapy for other indications being more likely to report incident incontinence. The primary evidence assembled here is entirely concordant. Six months of oral estradiol valerate produced no improvement in any subjective or objective measure of urodynamic stress incontinence in one of the largest and longest controlled studies of its era, and the head-to-head route comparison in hysterectomized women found equivalent symptomatic efficacy with significantly higher serum estradiol on the oral route — that is, an inferior therapeutic index for identical benefit.^{6,28,35}

Clinically, this dissociation has two implications. First, systemic hormone therapy should not be prescribed for the indication of urinary incontinence, and women commencing it for vasomotor symptoms should be counselled that urinary symptoms may worsen. Second — and this is the more frequently missed point — the well-publicized risks of systemic therapy should not be transferred by patients or clinicians onto local therapy. The pharmacokinetic evidence is unambiguous: the 10 µg vaginal tablet produced a 24-hour average plasma estradiol of 4.64 pg/mL at day 83 against 9.41 pg/mL for the 25 µg dose, and in a randomized comparison against placebo the week-12 geometric mean serum estradiol differed by only 4.3 versus 3.5 pg/mL. Twelve months of continuous ultra-low-dose exposure produced no endometrial hyperplasia and no carcinoma in 283 evaluable biopsies, with mean endometrial thickness falling rather than rising.^{16,38,39,53}

Formulation, delivery system and duration matter more than molecule

Across the head-to-head comparisons, no oestrogenic molecule emerged as clearly superior at equipotent dose. The estradiol-releasing ring and estriol pessaries were statistically equivalent for urgency, urge incontinence, stress incontinence and nocturia in a 251-woman randomized comparison, and ring and tablet were equivalent for both efficacy and endometrial safety over 48 weeks. What did differ, and differ markedly, were formulation-dependent biological effects and patient acceptability. The most striking illustration is the divergence between two trials of the same

850

molecule by the same principal investigator: intravaginal estriol cream restored lactobacilli in 61% of recipients, lowered vaginal pH from 5.5 to 3.8 and reduced urinary tract infection from 5.9 to 0.5 episodes per patient-year, whereas an estriol-containing pessary given twice weekly increased superficial cell counts but restored neither lactobacillary colonization nor vaginal pH, and was correspondingly inferior to nitrofurantoin prophylaxis. Formulation is therefore not interchangeable, and pH restoration appears to be the mediating variable for the infective outcome specifically.^{25,26,30,32,34}

Acceptability follows the delivery system rather than the molecule. Sixty per cent of women rated the ring as excellent against 14% for pessaries, and pessary administration was associated with significantly more discomfort. In frail women with impaired manual dexterity or cognition — precisely the group in whom incontinence and infection are most consequential — the ring enabled treatment that self-applied cream could not, with 86% reporting symptomatic improvement at a mean age of 87 years. Duration is equally decisive: a four-week course of ultra-low-dose estriol was frankly negative, twelve weeks of 10 µg estradiol produced significant benefit for urgency incontinence but attenuating benefit for urgency, and six months of 1 mg estriol produced the largest symptomatic and urodynamic effects in the entire dataset. Local oestrogen is a chronic tissue therapy, not a short course.^{26,30,33,47,55,60}

Position among alternative and adjunctive treatments

Against antimuscarinic monotherapy, local oestrogen performed creditably. The ultra-low-dose estradiol ring reduced daily voids by 4.5 against 3.0 for oral oxybutynin, with equivalent improvement in the Urogenital Distress Inventory and Incontinence Impact Questionnaire and without anticholinergic adverse effects — a consideration of first-order importance in older women, in whom cumulative anticholinergic burden is an established risk factor for cognitive decline and is explicitly flagged in prescribing guidance. Yet the addition of local oestrogen to an existing antimuscarinic conferred no additional benefit on the primary micturition endpoint in either the tolterodine or the solifenacin comparison, although subjective wellbeing and quality of life improved in the latter. The natural interpretation is that the two act on a shared final pathway of detrusor overactivity and that saturation occurs, rather than that oestrogen is inert.^{37,40,42,72}

The contrast with pelvic floor electrical stimulation is instructive. Here the combination was genuinely additive: urgency improved most in the combined arm, and only the combined arm maintained continence benefit at six months. This is what one would predict if the two interventions address different components of the deficit — neuromuscular re-education on the one hand, mucosal and vascular repletion on the other. Against energy-based devices, two randomized trials found fractional CO₂ laser and vaginal oestrogen to produce comparable symptom relief and satisfaction, with the maturation index remaining significantly higher in the oestrogen arm, and a subsequent meta-analysis of six trials confirmed no significant difference between modalities on any validated instrument. Given the marked cost differential and the regulatory uncertainty that has surrounded energy-based vaginal devices, local oestrogen remains the rational first choice.^{41,43,48,66}

In the peri-operative setting the picture is nuanced but consistent. Short pre-operative exposure did not improve prolapse-associated symptoms, nor did it improve surgeon-rated tissue quality; it did, however, significantly reduce defined postoperative complications and antibiotic use. Peri-operative estriol around a transobturator tape significantly improved postoperative quality of life and sexual function. And in the largest twelve-month randomized dataset, oestrogen cream did not improve pessary continuation but significantly reduced excessive discharge, vaginal erosion and vaginal bleeding. The consistent theme is mucosal protection rather than functional or anatomical enhancement — a modest but genuinely useful role that is easily missed when trials are powered for the wrong endpoint.^{46,51,52,59,65}

Recurrent urinary tract infection and antimicrobial stewardship

The infective outcome deserves separate emphasis because it is where the effect size is largest and the public-health implication greatest. Randomized evidence established a reduction from 5.9 to 0.5 episodes per patient-year and a significant prolongation of time to first recurrence with the vaginal ring. Real-world evidence in 5 638 hypo-oestrogenic women reproduced this at scale, with a 51.9% reduction in the year following the index prescription and 31.4% of women becoming infection-free. Most consequentially, in a database analysis of 1 891 956 women with recurrent infection, vaginal oestrogen prescription within two months of the qualifying second

infection was associated with lower odds of sepsis, hospitalization and all-cause mortality across every age band.^{25,29,57,61}

Two caveats are essential. Only 5.1% of that enormous cohort received a prescription at all, which represents simultaneously an enormous treatment gap and a serious threat to internal validity: women who are prescribed and who fill a vaginal oestrogen prescription differ systematically from those who are not, in health literacy, healthcare engagement, functional status and competing comorbidity. Healthy-user bias could plausibly account for a substantial portion of the mortality signal. Equally, the retrospective cohort reported the paradoxical finding that women with moderate or high adherence experienced the smallest reduction in infection frequency, which the authors themselves attributed to unobserved selection — clinicians reinforce and patients persist with therapy precisely when infections continue. These observations do not negate the randomized evidence; they do mean that the magnitude of the observational effect should not be taken at face value.^{57,61}

The responder phenotype and the case for individualized prescribing

The average treatment effects reported throughout this literature obscure substantial heterogeneity. The exploratory ROC analysis presented here suggests that a composite of age, baseline symptom burden, vaginal maturation index, vaginal pH and objectively measured adherence would discriminate responders from non-responders considerably better than any single variable, with a modelled area under the curve of 0.81 against 0.59 for age alone. The biological logic is straightforward: the woman most likely to respond is the one whose urinary symptoms are genuinely driven by an atrophic, hypo-oestrogenic epithelium, and the two simplest bedside markers of that state — the maturation index and vaginal pH — are precisely the ones that changed most reliably with treatment and that correlate significantly with epithelial morphology and symptom severity. It is worth noting, however, that a large multi-ethnic cross-sectional analysis found urinary urgency and dysuria were not consistently associated with atrophy biomarkers, which tempers the expectation that these markers will prove sufficient on their own.^{21,45,57,58}

These discrimination estimates are explicitly model-based, derived from published effect estimates rather than from patient-level data, and are offered as a prospectively testable hypothesis

rather than as a clinical tool. Contemporary methodological work has emphasized that ROC curves presented without explicit thresholds add nothing to the area under the curve itself, and that clinical usefulness is better judged by performance conditional on decision thresholds; illustrative operating points are therefore tabulated in Table 28. External validation in a prospective cohort with pre-treatment maturation index and pH, standardized dosing and a continence-specific primary endpoint would be a high-yield and inexpensive next study.²¹

4.8 Comparison with previous syntheses

The conclusions reached here are consistent in direction with the major previous syntheses, but differ in emphasis and in the confidence attached to specific subdomains. Table 26 sets out the comparison.

Table 26. Comparison with previous systematic reviews and meta-analyses (secondary evidence, Discussion only)

Synthesis	Year	Principal conclusion	Relationship to the present review
Fantl et al. (Hormones and Urogenital Therapy Committee)	1994	Oestrogen significantly improved subjective incontinence overall and in genuine stress incontinence, and significantly increased maximum urethral closure pressure, though the latter was driven by one study	Directionally concordant; the present review finds the urethral pressure signal is real but confined to prolonged, higher-dose local regimens
Cardozo et al. (second report)	1998	Oestrogen efficacious for urogenital atrophy; low-dose vaginal estradiol as effective as systemic therapy; maximum benefit at 1–3 months	Concordant; the present review adds that benefit for urinary endpoints specifically continues to accrue beyond 3 months
Cody et al. (Cochrane)	2012	Systemic oestrogen worsens incontinence (RR 1.32); local	The organizing principle of the present review; here extended with

		oestrogen may improve it (RR 0.74) with 1–2 fewer voids per 24 hours	14 primary studies published subsequently
Rahn et al.	2014	Vaginal oestrogen improves urgency, frequency, stress and urgency incontinence and reduces urinary tract infection; efficacy similar across preparations	Concordant, but the present review finds formulation is not interchangeable for the infective outcome specifically
Weber et al.	2015	Topical oestrogen effective for vaginal atrophy and seems to decrease overactive bladder and incontinence complaints; low doses already beneficial	Concordant for the symptom cluster; the present review qualifies 'low doses already beneficial' with the tissue-specific dose–response evidence for the urethra
Christmas et al.	2023	Vaginal oestrogen improves dysuria, frequency, urge and stress incontinence and recurrent infection; systemic therapy may worsen symptoms	Concordant, except that the present review rates the stress incontinence evidence as very low certainty
Bapir et al.	2023	In most studies no significant improvement in urinary symptoms with local oestrogen, although vaginal symptoms improved; systemic oestrogen reduced the odds of improvement (OR 0.74)	The principal dissenting synthesis; its restriction to urge incontinence and to trials with incontinence-specific endpoints excludes much of the evidence assembled here
Danan et al. (AHRQ/PCORI)	2024	Vaginal oestrogen may improve dryness, dyspareunia, most bothersome symptom and	Methodologically concordant — the present review reached the same conclusion about the

		satisfaction (low certainty); heterogeneity precluded meta-analysis	impossibility of pooling and adopted the same structured narrative approach
Porcari et al.	2025	Topical oestrogen improved every analysed lower urinary tract symptom, with pooled odds ratios between 0.11 and 0.24	Quantitatively supportive; used here as external context only, given the before-and-after design without concurrent control
Sicilia et al.	2025	Peri-operative vaginal oestrogen improves maturation index, vaginal thickness and tissue quality and reduces postoperative infection and antibiotic use, without affecting surgical failure or recurrence	Directly concordant with the peri-operative primary studies assembled here
Kaufman et al. (AUA/SUFU/AUGS guideline)	2025	Low-dose vaginal oestrogen has the most robust evidence base of any intervention for the genitourinary syndrome of menopause	The present review supports this for storage symptoms and infection, and qualifies it for pure stress incontinence

Strengths of this review

Five features distinguish this synthesis. It restricted the evidence base to primary studies of every eligible design, thereby integrating trial efficacy with real-world effectiveness while explicitly quarantining secondary evidence. It assembled 31 primary studies spanning four decades, the largest such set assembled for this specific question, including database cohorts of nearly 1.9 million women that no prior synthesis has incorporated. It organized the evidence across 16 outcome domains including the biological intermediates and the urogenital microbiome, which allowed the mechanistic hierarchy to become visible. It appraised risk of bias with design-appropriate tools and rated certainty with GRADE for every domain. And it declined to meta-

analyse — a decision that is a strength rather than a limitation, because pooling across eleven non-commensurable instruments would have produced a summary estimate whose precision was entirely spurious.^{12,76}

Implications for clinical practice

Local oestrogen should be offered as adjunctive first-line therapy, alongside pelvic floor muscle training and behavioural modification, to postmenopausal women whose incontinence is urgency-predominant or mixed with an urgency component, and particularly where examination confirms vulvovaginal atrophy. It should be offered as an antimuscarinic-sparing option to older women in whom anticholinergic burden is a concern, since it matched oxybutynin for voiding frequency without anticholinergic adverse effects. It should be offered to every postmenopausal woman with recurrent urinary tract infection, where the effect size is largest and the stewardship argument strongest. It should be considered peri-operatively for its mucosal-protective effect on erosion, discharge and postoperative infection. It should not be offered as monotherapy for pure stress urinary incontinence with the expectation of cure. Treatment should be continued for at least three and preferably six months before efficacy is judged; ultra-low doses may be insufficient for urethral effects specifically; the delivery system should be matched to dexterity and preference, with the ring strongly preferred in frail or cognitively impaired women; and patients should be explicitly reassured that the risks associated with systemic hormone therapy do not transfer to low-dose local preparations.^{2,4,24,40,47,57}

Implications for research

Six priorities emerge. Trials are needed with continence as the pre-specified primary endpoint and adequate power for it, rather than as a secondary outcome of atrophy or prolapse trials. Core outcome measures should be adopted; the COMMA consortium recommendations provide a ready-made standard and would eliminate the instrument heterogeneity that made meta-analysis impossible here. Follow-up must extend beyond twelve months, with pre-specified assessment of what happens on discontinuation. A dose-ranging trial with urethral maturation and urodynamic co-primary endpoints is required to test directly the hypothesis that ultra-low doses are sub-therapeutic for the urethra. Head-to-head trials of formulation — cream versus pessary versus ring — with

857

vaginal pH and lactobacillary colonization as mediating variables would resolve the formulation question for the infective outcome. And a prospective validation cohort for the responder phenotype, with baseline maturation index and pH and a standardized six-month regimen, would convert the exploratory discrimination analysis presented here into a usable clinical prediction rule.^{21,24,32,76}

CONCLUSION AND RECOMMENDATIONS

Conclusion

Local oestrogen therapy is an effective, well-tolerated and mechanistically coherent treatment for the storage lower urinary tract symptoms of postmenopausal women. Across 31 primary studies spanning four decades and sixteen countries, it consistently reduced urgency urinary incontinence, urinary urgency, daytime frequency and nocturia, and consistently restored the biological substrate of those symptoms — vaginal and urethral epithelial maturation and vaginal acidity. It reduced recurrent urinary tract infection by roughly half in both randomized and real-world settings and was associated, in database cohorts of nearly 1.9 million women, with substantially lower odds of sepsis, hospitalization and death. It matched oral oxybutynin for voiding frequency without anticholinergic burden, augmented pelvic floor electrical stimulation, and equalled fractional CO₂ laser at a fraction of the cost. Its systemic safety profile is favourable: serum oestradiol remains within the postmenopausal range at low and ultra-low doses, and no endometrial hyperplasia or carcinoma was reported across twelve months of continuous exposure in 283 evaluable biopsies.^{10,25,29,38,40,41,48,53,57,61}

The benefit is not uniform. Evidence for pure urodynamic stress urinary incontinence remains inconsistent and of very low certainty, consistent with a predominantly mechanical rather than mucosal pathophysiology, and local oestrogen should not be offered as monotherapy for that indication. Benefit accrues with duration and appears to require months rather than weeks; a four-week ultra-low-dose course was frankly ineffective. Dose matters in a tissue-specific way, with urethral maturation demonstrable at 25 µg but not at 10 µg of vaginal estradiol. Formulation matters for the infective outcome, where restoration of lactobacillary colonization and vaginal pH appears to be the mediating step and is achieved by some preparations and not others. Finally, the route of

858

administration reverses the direction of effect: systemic oestrogen worsens incontinence while local oestrogen improves it, and this dissociation must be communicated explicitly to patients so that the risks of the former are not wrongly attributed to the latter.^{6,24,32,35,55}

The hypothesis that local oestrogen therapy significantly improves urinary incontinence and associated storage symptoms in postmenopausal women is therefore accepted for the urgency-predominant phenotype and for the associated storage symptom cluster, with moderate certainty; it is not accepted for pure stress urinary incontinence, where the evidence is of very low certainty and the null hypothesis cannot be rejected. The secondary hypotheses were likewise supported: the effect was greater for urgency than for stress incontinence, clinical benefit tracked objective epithelial restoration, and different preparations were broadly equivalent at equipotent dose while differing substantially in acceptability and formulation-dependent biological effect.

Recommendations for clinical practice

The following recommendations follow from the evidence assembled, with the certainty rating of the supporting domain indicated.

- Offer low-dose local oestrogen as adjunctive first-line therapy, alongside pelvic floor muscle training and behavioural modification, to postmenopausal women with urgency-predominant or mixed urinary incontinence, particularly where examination confirms vulvovaginal atrophy (moderate certainty).^{4,60}
- Offer local oestrogen to all postmenopausal women with recurrent urinary tract infection, as both a symptomatic and a stewardship intervention (moderate certainty).^{25,57,61}
- Consider local oestrogen as an antimuscarinic-sparing option in older women, in whom cumulative anticholinergic burden is a material concern, since it matched oral oxybutynin for reduction in voiding frequency without anticholinergic adverse effects (low certainty).^{40,72}
- Do not use local oestrogen as monotherapy for pure urodynamic stress urinary incontinence with the expectation of cure; consider it instead as a peri-operative adjunct to continence surgery, where it improved postoperative quality of life and sexual function (very low to low certainty).^{46,56}

- Continue treatment for a minimum of three months, and preferably six, before judging efficacy; a four-week course of ultra-low-dose estriol was ineffective (moderate certainty).^{33,55}
- Where urinary rather than purely vaginal symptoms are the treatment target, do not assume that the lowest available dose is sufficient; urethral maturation was demonstrable at 25 µg but not at 10 µg of vaginal estradiol (low certainty).²⁴
- Match the delivery system to dexterity, cognition and patient preference; the oestradiol-releasing ring was strongly preferred over pessaries and enabled effective treatment in frail women unable to self-apply cream (moderate certainty).^{26,30,47}
- Use local oestrogen peri-operatively and alongside pessary use for its mucosal-protective effect on erosion, discharge, bleeding and postoperative infection, while counselling that it will not improve pessary continuation or surgical success (moderate certainty).^{52,59,65}
- Counsel explicitly on the local–systemic dissociation: the risks associated with systemic hormone therapy do not transfer to low-dose local preparations, which do not raise serum oestradiol beyond the postmenopausal range and did not cause endometrial hyperplasia over twelve months (high certainty).^{38,39,53}
- In women with hormone-receptor-positive breast cancer, particularly those on aromatase inhibitors, prescribe only in collaboration with the treating oncologist and after non-hormonal measures have failed, recognizing that transient systemic oestradiol elevation occurred in a minority (low certainty).^{49,63,64,74}

Recommendations for research

- Conduct adequately powered randomized trials with urinary incontinence as the pre-specified primary endpoint rather than as a secondary outcome of atrophy or prolapse trials.⁵⁶
- Adopt the COMMA core outcome measurement instruments to eliminate the instrument heterogeneity that currently precludes meta-analysis.⁷⁶
- Extend follow-up beyond twelve months, with pre-specified assessment of symptom recurrence after discontinuation.⁴¹

- Conduct a dose-ranging trial with urethral maturation index and urodynamic parameters as co-primary endpoints, to test directly whether ultra-low doses are sub-therapeutic for the urethra.^{24,33}
- Conduct head-to-head formulation trials — cream versus pessary versus ring — with vaginal pH and lactobacillary colonization pre-specified as mediating variables for the infective outcome.^{25,32}
- Prospectively validate the responder phenotype using baseline maturation index, vaginal pH, symptom severity, age and objectively measured adherence, reporting discrimination with explicit decision thresholds rather than the area under the curve alone.^{21,45}
- Include frail, care-dependent and cognitively impaired women, and women with hormone-sensitive malignancy, who are systematically excluded from the current trial literature yet carry the greatest burden of disease.^{47,74}

Concluding statement

Four decades of primary research converge on a simple and clinically actionable proposition: restoring the postmenopausal urogenital epithelium relieves the storage symptoms that arise from its atrophy. Local oestrogen therapy is inexpensive, safe at low dose, widely available and substantially under-prescribed — only one in twenty women with recurrent urinary tract infection in a cohort of nearly 1.9 million received it. The principal barrier to its appropriate use is not the absence of evidence but the misattribution to local therapy of risks that belong to the systemic route. Correcting that misattribution, prescribing for an adequate duration at an adequate dose, and directing therapy towards the phenotype most likely to respond would together deliver more clinical benefit than any new agent currently in development for this indication.^{4,6,61}

REFERENCES

1. Șerbănescu L, et al. Involuntary urine loss in menopause — a narrative review. *J Clin Med.* 2025;14(21):7664. doi: 10.3390/jcm14217664. *Consensus:* <https://consensus.app/papers/details/4091967b41855aa497ddc8c6c2c8ecd1/>
2. Russo E, Caretto M, Giannini A, Bitzer J, Cano A, Ceausu I, et al. Management of urinary incontinence in postmenopausal women: an EMAS clinical guide. *Maturitas.* 2021;143:223–30. 861

doi: 10.1016/j.maturitas.2020.09.005.

Consensus:

<https://consensus.app/papers/details/9e46a9fb0ebb569fb801350c4eff437d/>

3. Nambiar AK, Arlandis S, Bø K, Cobussen-Boekhorst H, Costantini E, de Heide M, et al. European Association of Urology guidelines on the diagnosis and management of female non-neurogenic lower urinary tract symptoms. Part 1. Eur Urol. 2022;82(1):49–59. doi: 10.1016/j.eururo.2022.01.045.

Consensus:

<https://consensus.app/papers/details/c737e871f5635bd2a88539b50e7fb7f5/>

4. Kaufman MR, Brucker BM, Clemens JQ, Dmochowski RR, Gupta P, Kim-Fine S, et al. The AUA/SUFU/AUGS guideline on genitourinary syndrome of menopause. J Urol. 2025; published online 2025 (AUA/SUFU/AUGS guideline). doi: 10.1097/JU.0000000000004589.

Consensus: <https://consensus.app/papers/details/8135ddc8506b5d1ebe706de477f96390/>

5. Rahn DD, Carberry C, Sanses TV, Mamik MM, Ward RM, Meriwether KV, et al. Vaginal estrogen for genitourinary syndrome of menopause: a systematic review. Obstet Gynecol. 2014;124(6):1147–56. doi: 10.1097/AOG.0000000000000526.

Consensus:

<https://consensus.app/papers/details/8c63801f12e4504d81c4f78ef9e35b16/>

6. Cody JD, Jacobs ML, Richardson K, Moehrer B, Hextall A. Oestrogen therapy for urinary incontinence in post-menopausal women. Cochrane Database Syst Rev. 2012;(10):CD001405. doi: 10.1002/14651858.CD001405.pub3.

Consensus:

<https://consensus.app/papers/details/f58615e301dd508d829a7e9172fa840c/>

7. Christmas MM, Iyer S, Daisy C, Maristany S, Letko J, Hickey M. Menopause hormone therapy and urinary symptoms: a systematic review. Menopause. 2023;30(6):672–85. doi: 10.1097/GME.0000000000002187.

Consensus:

<https://consensus.app/papers/details/e5d505ce4c3a53f89631ce440ea0f7aa/>

8. Weber MA, Kleijn MH, Langendam M, Limpens J, Heineman MJ, Roovers JP. Local oestrogen for pelvic floor disorders: a systematic review. PLoS One. 2015;10(9):e0136265. doi: 10.1371/journal.pone.0136265.

Consensus:

<https://consensus.app/papers/details/dacbe0d67bbf5afcac92233798752bd7/>

9. Rahn DD, Ward RM, Sanses TV, Carberry C, Mamik MM, Meriwether KV, et al. Vaginal estrogen use in postmenopausal women with pelvic floor disorders: systematic review and practice guidelines. *Int Urogynecol J.* 2015;26(1):3–13. doi: 10.1007/s00192-014-2554-z. *Consensus:* <https://consensus.app/papers/details/2eac2eb600725cd5861030a6c6e13f68/>
10. Porcari I, Garzon S, Cianci S, Uccella S, Franchi M. Vulvovaginal estrogen therapy for urinary symptoms in postmenopausal women: a review and meta-analysis. *Climacteric.* 2025; published online ahead of print. doi: 10.1080/13697137.2025.2517138. *Consensus:* <https://consensus.app/papers/details/06e0bdaa079a57d2a660621d62b8203c/>
11. Bapir R, Bhatti KH, Eliwa A, García-Perdomo HA, Gherabi N, Hennessey D, et al. Treatment of urge incontinence in postmenopausal women: a systematic review. *Arch Ital Urol Androl.* 2023;95(4):11718. doi: 10.4081/aiua.2023.11718. *Consensus:* <https://consensus.app/papers/details/e80bef00724b5c5d9094004b9318cf1c/>
12. Danan ER, Sowerby C, Ullman KE, Ensrud K, Forte ML, Zerzan N, et al. Hormonal treatments and vaginal moisturizers for genitourinary syndrome of menopause: a systematic review. *Ann Intern Med.* 2024;177(10):1400–14. doi: 10.7326/ANNALS-24-00610. *Consensus:* <https://consensus.app/papers/details/fa32ccb61d7e5404a5632d2b76c5a336/>
13. Fantl JA, Cardozo L, McClish DK. Estrogen therapy in the management of urinary incontinence in postmenopausal women: a meta-analysis. First report of the Hormones and Urogenital Therapy Committee. *Obstet Gynecol.* 1994;83(1):12–8. *Consensus:* <https://consensus.app/papers/details/beda1865cb365b39bf9cac6e379df931/>
14. Cardozo L, Bachmann G, McClish D, Fonda D, Birgerson L. Meta-analysis of estrogen therapy in the management of urogenital atrophy in postmenopausal women: second report of the Hormones and Urogenital Therapy Committee. *Obstet Gynecol.* 1998;92(4 Pt 2):722–7. doi: 10.1016/S0029-7844(98)00175-6. *Consensus:* <https://consensus.app/papers/details/8533b81aa6f95b41bbb34e872c98f10e/>
15. Santen RJ. Vaginal administration of estradiol: effects of dose, preparation and timing on plasma estradiol levels. *Climacteric.* 2015;18(2):121–34. doi: 10.3109/13697137.2014.947254. *Consensus:* <https://consensus.app/papers/details/19689c743eb657f7848e44d298960e7a/>

16. Santen RJ, Mirkin S, Bernick B, Constantine GD. Systemic estradiol levels with low-dose vaginal estrogens. *Menopause*. 2020;27(3):361–70. doi: 10.1097/GME.0000000000001463. *Consensus:* <https://consensus.app/papers/details/61f6a916147359d39523f496fd78ed36/>
17. Nappi RE, Martini E, Cucinella L, Martella S, Tiranini L, Inzoli A, et al. Different local estrogen therapies for a tailored approach to GSM. *Climacteric*. 2023;26(4):353–60. doi: 10.1080/13697137.2023.2218998. *Consensus:* <https://consensus.app/papers/details/e5c3143325d75f8ca27242b45baf7f09/>
18. Hirschberg AL. Enhancing quality of life: addressing vulvovaginal atrophy and urinary tract symptoms. *Climacteric*. 2025; published online ahead of print. doi: 10.1080/13697137.2025.2514029. *Consensus:* <https://consensus.app/papers/details/bb297120951c501ba6d4744973822cf0/>
19. Buck ED, Lukacz ES, Aliaga F, Anger JT. Effective prevention of recurrent UTIs with vaginal estrogen: pearls for a urological approach to genitourinary syndrome of menopause. *Urology*. 2021;151:31–6 (published online 2020). doi: 10.1016/j.urology.2020.05.058. *Consensus:* <https://consensus.app/papers/details/fb71cb7dd2025f9b8b9a3433147c6a1e/>
20. Smith AL, Brown J, Wyman JF, Berry A, Newman DK, Stapleton AE. Treatment and prevention of recurrent lower urinary tract infections in women: a rapid review with practice recommendations. *J Urol*. 2018;200(6):1174–91. doi: 10.1016/j.juro.2018.04.088. *Consensus:* <https://consensus.app/papers/details/30c425725a6753a89f50da4cd8b1fc41/>
21. Verbakel JY, Steyerberg EW, Uno H, De Cock B, Wynants L, Collins GS, et al. ROC curves for clinical prediction models part 1. *J Clin Epidemiol*. 2020;126:207–16. doi: 10.1016/j.jclinepi.2020.01.028. *Consensus:* <https://consensus.app/papers/details/abbfee8ab5d15722a776089946341758/>
22. Kinn AC, Lindskog M. Estrogens and phenylpropanolamine in combination for stress urinary incontinence in postmenopausal women. *Urology*. 1988;32(3):273–80. doi: 10.1016/0090-4295(88)90400-1. *Consensus:* <https://consensus.app/papers/details/0ec0773cbef3546793ba66f12e9a86be/>

23. Eriksen PS, Rasmussen H. Low-dose 17 β -estradiol vaginal tablets in the treatment of atrophic vaginitis: a double-blind placebo-controlled study. *Eur J Obstet Gynecol Reprod Biol.* 1992;44(2):137–44. doi: 10.1016/0028-2243(92)90059-8. *Consensus:* <https://consensus.app/papers/details/f41c370ac1b7506fbb5c961069446aec/>
24. Nilsson K, Heimer G. Low-dose oestradiol in the treatment of urogenital oestrogen deficiency: a pharmacokinetic and pharmacodynamic study. *Maturitas.* 1992;15(2):121–7. doi: 10.1016/0378-5122(92)90246-Z. *Consensus:* <https://consensus.app/papers/details/1e46b368b3ca5b65b77a11cd0177b5bc/>
25. Raz R, Stamm WE. A controlled trial of intravaginal estriol in postmenopausal women with recurrent urinary tract infections. *N Engl J Med.* 1993;329(11):753–6. doi: 10.1056/NEJM199309093291102. *Consensus:* <https://consensus.app/papers/details/d10aed40595c53348a85c84c144ff07a/>
26. Henriksson L, Stjernquist M, Boquist L, Alander U, Selinus I. A comparative multicenter study of the effects of continuous low-dose estradiol released from a new vaginal ring versus estriol vaginal pessaries in postmenopausal women with symptoms and signs of urogenital atrophy. *Am J Obstet Gynecol.* 1994;171(3):624–32. doi: 10.1016/0002-9378(94)90074-4. *Consensus:* <https://consensus.app/papers/details/68828dcb4b37579f8f8e0edc2362dddb/>
27. Saure A. Randomized comparison of a new estradiol-releasing vaginal ring versus estriol vaginal pessaries. *Am J Obstet Gynecol.* 1995;173(2):675. doi: 10.1016/0002-9378(95)90308-9. *Consensus:* <https://consensus.app/papers/details/901e9c03ab455fa68ec18993041997b2/>
28. Jackson S, Shepherd A, Brookes S, Abrams P. The effect of oestrogen supplementation on postmenopausal urinary stress incontinence: a double-blind placebo-controlled trial. *BJOG.* 1999;106(7):711–8. doi: 10.1111/j.1471-0528.1999.tb08372.x. *Consensus:* <https://consensus.app/papers/details/0518a74baab85cfd89bb0758f9cecf0/>
29. Eriksen BC. A randomized, open, parallel-group study on the preventive effect of an estradiol-releasing vaginal ring (Estring) on recurrent urinary tract infections in postmenopausal women. *Am J Obstet Gynecol.* 1999;180(5):1072–9. doi: 10.1016/S0002-9378(99)70597-1. *Consensus:* <https://consensus.app/papers/details/fe24afb92a9e5949b5009efaa4ac2882/>

30. Lose G, Englev E. Oestradiol-releasing vaginal ring versus oestriol vaginal pessaries in the treatment of bothersome lower urinary tract symptoms. BJOG. 2000;107(8):1029–34. doi: 10.1111/j.1471-0528.2000.tb10408.x. *Consensus:* <https://consensus.app/papers/details/ad1d88a4966a5085a62a7c199d7528f2/>
31. Cardozo L, Lose G, McClish D, Versi E, de Koning Gans H. Vaginal oestradiol for the treatment of lower urinary tract symptoms in postmenopausal women: a double-blind placebo-controlled study. J Obstet Gynaecol. 2001;21(4):383–5. doi: 10.1080/01443610120059941. *Consensus:* <https://consensus.app/papers/details/d3a368ed9bc852afb571045a2cbe4f76/>
32. Raz R, Colodner R, Rohana Y, Battino S, Rottensterich E, Wasser I, et al. Effectiveness of estriol-containing vaginal pessaries and nitrofurantoin macrocrystal therapy in the prevention of recurrent urinary tract infection in postmenopausal women. Clin Infect Dis. 2003;36(11):1362–8. doi: 10.1086/374341. *Consensus:* <https://consensus.app/papers/details/d66c8ae27b2455319098567bc1158bf3/>
33. Dessole S, Rubattu G, Ambrosini G, Gallo O, Capobianco G, Cherchi PL, et al. Efficacy of low-dose intravaginal estriol on urogenital aging in postmenopausal women. Menopause. 2004;11(1):49–56. doi: 10.1097/01.GME.0000077620.13164.62. *Consensus:* <https://consensus.app/papers/details/c86efa461a1e5ff8b7c3dfcd561dc4c2/>
34. Weisberg E, Ayton R, Darling G, Farrell E, Murkies A, O'Neill S, et al. Endometrial and vaginal effects of low-dose estradiol delivered by vaginal ring or vaginal tablet. Climacteric. 2005;8(1):83–92. doi: 10.1080/13697130500087016. *Consensus:* <https://consensus.app/papers/details/b662731353b653958d037552fa14ba6a/>
35. Long CY, Liu CM, Hsu SC, Wu CH, Wang CL, Tsai EM. A randomized comparative study of the effects of oral and topical estrogen therapy on the lower urinary tract of hysterectomized postmenopausal women. Fertil Steril. 2006;85(1):155–60. doi: 10.1016/j.fertnstert.2005.06.042. *Consensus:* <https://consensus.app/papers/details/a268e66169d75329b3e7b628fa73a150/>
36. Simon J, Nachtigall L, Gut R, Lang E, Archer DF, Utian W. Effective treatment of vaginal atrophy with an ultra-low-dose estradiol vaginal tablet. Obstet Gynecol. 2008;112(5):1053–60.

doi: 10.1097/AOG.0b013e31818aa7c3.

Consensus:

<https://consensus.app/papers/details/e021cb9db92252ee884f5843a7562245/>

37. Serati M, Salvatore S, Uccella S, Cardozo L, Bolis P. Is there a synergistic effect of topical oestrogens when administered with antimuscarinics in the treatment of symptomatic detrusor overactivity? *Eur Urol.* 2009;55(3):713–9. doi: 10.1016/j.eururo.2008.06.051. *Consensus:* <https://consensus.app/papers/details/0bc7f8754d495fa3824e533286daf27b/>
38. Ulrich LG, Naessén T, Elia D, Goldstein JA, Eugster-Hausmann M. Endometrial safety of ultra-low-dose Vagifem 10 µg in postmenopausal women with vaginal atrophy. *Climacteric.* 2010;13(3):228–37. doi: 10.3109/13697137.2010.481058. *Consensus:* <https://consensus.app/papers/details/a98f573418d253bf9e85b989243fe6e0/>
39. Eugster-Hausmann M, Waitzinger J, Lehnick D. Minimized estradiol absorption with ultra-low-dose 10 µg 17β-estradiol vaginal tablets. *Climacteric.* 2010;13(3):219–27. doi: 10.3109/13697137.2010.483297. *Consensus:* <https://consensus.app/papers/details/68a4cc201cb25de2b57245a7f354a6d4/>
40. Nelken RS, Ozel BZ, Leegant AR, Felix JC, Mishell DR. Randomized trial of estradiol vaginal ring versus oral oxybutynin for the treatment of overactive bladder. *Menopause.* 2011;18(9):962–6. doi: 10.1097/gme.0b013e3182104977. *Consensus:* <https://consensus.app/papers/details/d910452581b55f059dca173c5f5a72a9/>
41. Abdelbary AM, El-Dessoukey AA, Massoud AM, Moussa AS, Zayed AS, Elsheikh MG, et al. Combined vaginal pelvic floor electrical stimulation (PFS) and local vaginal estrogen for treatment of overactive bladder (OAB) in perimenopausal females: randomized controlled trial (RCT). *Urology.* 2015;86(3):482–6. doi: 10.1016/j.urology.2015.06.007. *Consensus:* <https://consensus.app/papers/details/a07aa7caf5a25baabfd5f2004371ed68/>
42. Jiang F, Zhu L, Xu T, Gong M, Xia Z, Zhao X, et al. Efficacy and safety of solifenacin succinate tablets versus solifenacin succinate tablets with local estrogen for the treatment of overactive bladder in postmenopausal women: a multicenter, randomized, open-label, controlled comparison study. *Menopause.* 2016;23(4):451–7. doi:

10.1097/GME.0000000000000574.

Consensus:

<https://consensus.app/papers/details/678d52d70919597cb448f0a03421a584/>

43. Cruz VL, Steiner ML, Pompei LM, Strufaldi R, Fonseca FLA, Santiago LHS, et al. Randomized, double-blind, placebo-controlled clinical trial for evaluating the efficacy of fractional CO₂ laser compared with topical estriol in the treatment of vaginal atrophy in postmenopausal women. *Menopause*. 2018;25(1):21–8. doi: 10.1097/GME.0000000000000955. *Consensus:*

<https://consensus.app/papers/details/aeb59940a7885aa5903f75945588d2a2/>

44. Kroll R, Archer DF, Lin Y, 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 dyspareunia as the most bothersome symptom. *Menopause*. 2018;25(2):133–8. doi: 10.1097/GME.0000000000000985. *Consensus:*

<https://consensus.app/papers/details/bd2d4d7a95c65e38bd5e0f3f755f4269/>

45. Tucker KM, Godha K, Mirkin S, Archer DF. Vaginal pH: a simple assessment highly correlated with vaginal morphology and symptoms in postmenopausal women. *Menopause*. 2018;25(7):762–6. doi: 10.1097/GME.0000000000001081. *Consensus:*

<https://consensus.app/papers/details/1d3dc3b730c650649601921d7306bb69/>

46. Caruso S, Cianci S, Cianci A, Mammana G, Marino S, Iraci M. Ultralow 0.03 mg vaginal estriol in postmenopausal women who underwent surgical treatment for stress urinary incontinence: effects on quality of life and sexual function. *Menopause*. 2019;26(12):1383–9. doi: 10.1097/GME.0000000000001446. *Consensus:*

<https://consensus.app/papers/details/d25429224ea3549e8ebde5c4b6f11ff6/>

47. Jones S, Hampson G, Ranasinghe D. Tolerability and effectiveness of the Estring (estradiol) vaginal ring pessary in frail older women attending a day-hospital-based continence clinic. *Age Ageing*. 2019;48(Suppl 2):afz055.24. doi: 10.1093/ageing/afz055.24. *Consensus:*

<https://consensus.app/papers/details/d257ed544e23551faef0a79ac0f1478b/>

48. Paraiso MFR, Ferrando CA, Sokol ER, Rardin CR, Matthews CA, Karram MM, et al. A randomized clinical trial comparing vaginal laser therapy to vaginal estrogen therapy in women

868

- with genitourinary syndrome of menopause: the VeLVET trial. *Menopause*. 2020;27(1):50–6. doi: 10.1097/GME.0000000000001416. *Consensus:* <https://consensus.app/papers/details/6bdabf83bef857a2ae5c982e15a80cf3/>
49. Hirschberg AL, Sánchez-Rovira P, Presa-Lorite J, Campos-Delgado M, Gil-Gil M, Lidbrink E, et al. Efficacy and safety of ultra-low dose 0.005% estriol vaginal gel for the treatment of vulvovaginal atrophy in postmenopausal women with early breast cancer treated with nonsteroidal aromatase inhibitors: a phase II, randomized, double-blind, placebo-controlled trial. *Menopause*. 2020;27(5):526–34. doi: 10.1097/GME.0000000000001497. *Consensus:* <https://consensus.app/papers/details/9e9b262648c955bba9fffa6d12f8e699/>
50. Thomas-White K, Taege S, Limeira R, Brincat C, Joyce C, Hilt EE, et al. Vaginal estrogen therapy is associated with increased *Lactobacillus* in the urine of postmenopausal women with overactive bladder symptoms. *Am J Obstet Gynecol*. 2020;223(5):727.e1–11. doi: 10.1016/j.ajog.2020.08.006. *Consensus:* <https://consensus.app/papers/details/f35578eed6ce574dbe8445d46e48ef3a/>
51. Marschalek ML, Bodner K, Kimberger O, Zehetmayer S, Morgenbesser R, Dietrich W, et al. Does preoperative locally applied estrogen treatment facilitate prolapse-associated symptoms in postmenopausal women with symptomatic pelvic organ prolapse? A randomised controlled double-masked, placebo-controlled, multicentre study. *BJOG*. 2021;128(13):2200–8. doi: 10.1111/1471-0528.16894. *Consensus:* <https://consensus.app/papers/details/45f75ce240885b89b9cf128d3fda3673/>
52. Marschalek ML, Bodner K, Kimberger O, Morgenbesser R, Dietrich W, Obruca C, et al. Surgical assessment of tissue quality during pelvic organ prolapse repair in postmenopausal women pre-treated either with locally applied estrogen or placebo. *J Clin Med*. 2021;10(11):2531. doi: 10.3390/jcm10112531. *Consensus:* <https://consensus.app/papers/details/b542b9cc93a459ebba631f8abcccd3ee/>
53. Mitchell CM, Larson JC, Crandall CJ, Bhasin S, LaCroix AZ, Ensrud KE, et al. Association of vaginal estradiol tablet with serum estrogen levels in women who are postmenopausal. *JAMA*

- Netw Open. 2022;5(11):e2241743. doi: 10.1001/jamanetworkopen.2022.41743. *Consensus:*
<https://consensus.app/papers/details/dfea48ccdcdb5665b9aa58c9b0716cf9/>
54. Neugent ML, Kumar A, Hulyalkar NV, Lutz KC, Nguyen VH, Fuentes JL, et al. Recurrent urinary tract infection and estrogen shape the taxonomic ecology and function of the postmenopausal urogenital microbiome. *Cell Rep Med.* 2022;3(10):100753. doi: 10.1016/j.xcrm.2022.100753. *Consensus:*
<https://consensus.app/papers/details/582a1de8ce4f5d198157a08a102cf887/>
55. Jongjakapun A, Somboonporn W, Temtanakitpaisan T, Kaewrudee S, Soontrapa S. Effectiveness of vaginal estriol with lactobacilli on urinary symptoms in postmenopausal women: a randomized-controlled trial. *Menopause.* 2023;30(5):506–11. doi: 10.1097/GME.0000000000002147. *Consensus:*
<https://consensus.app/papers/details/cfdcf84b567e5b0d8c09443142ae1472/>
56. Rahn DD, Richter HE, Sung VW, Hynan LS, Pruszynski JE. Effects of preoperative intravaginal estrogen on pelvic floor disorder symptoms in postmenopausal women with pelvic organ prolapse. *Am J Obstet Gynecol.* 2023;229(3):309.e1–10. doi: 10.1016/j.ajog.2023.05.023. *Consensus:*
<https://consensus.app/papers/details/244edace7cc5564cb0f95f99e59a1198/>
57. Tan-Kim J, Shah NM, Do D, Menefee SA. Efficacy of vaginal estrogen for recurrent urinary tract infection prevention in hypoestrogenic women. *Am J Obstet Gynecol.* 2023;229(2):143.e1–9. doi: 10.1016/j.ajog.2023.05.002. *Consensus:*
<https://consensus.app/papers/details/7cfb14856d445ecb900c969324b0b97e/>
58. Waetjen LE, Zhang Y, Tepper P, Brooks MM, Solomon DH, Crawford SL, et al. Relationships between the vaginal microbiota and genitourinary syndrome of menopause symptoms in postmenopausal women: the Study of Women's Health Across the Nation. *Menopause.* 2023;30(11):1073–84. doi: 10.1097/GME.0000000000002263. *Consensus:*
<https://consensus.app/papers/details/466bc227580a50198934a2608759e17c/>
59. Zhou Y, Zhu L, Xu T, Li Z, Wang J, Wang X, et al. Effects of intravaginal conjugated oestrogen on pessary continuation for pelvic organ prolapse: multicentre, randomised, double

- blind, placebo controlled trial. *BMJ*. 2025;389:e084418. doi: 10.1136/bmj-2025-084418. *Consensus*: <https://consensus.app/papers/details/6a936e89ddb15e4b831b80e181f9ece9/>
60. Harncharoenkul P, Manonai J, Chittacharoen A, Sarit-apirak S, Wattanayingcharoenchai R. Efficacy of vaginal 17 β -estradiol on the urinary storage symptoms in postmenopausal women: a randomized double-blind, placebo-controlled study. *Sci Rep*. 2026; article 43359. doi: 10.1038/s41598-026-43359-1. *Consensus*: <https://consensus.app/papers/details/bfccccb75d8b45c299371a3ca9792732a/>
61. LaClair J, Visingardi J, Wells BA, Feustel PJ, Deckert J, De EJB, et al. Vaginal estrogen prescription is associated with reduced rates of serious adverse outcomes in women of all age groups with recurrent urinary tract infection: an Epic Cosmos database analysis. *Urology*. 2026; published online 10 June 2026. doi: 10.1016/j.urology.2026.06.004. *Consensus*: <https://consensus.app/papers/details/f852cdbcb69e535cb3e7e31bb835406e/>
62. Murphy K, Keller MJ, Anastos K, Sinclair S, Devlin JC, Shi Q, et al. Impact of vaginal estradiol on the genitourinary syndrome of menopause, vaginal microbiome and mucosal immune mediators in women with HIV. *Clin Infect Dis*. 2025;ciaf669. doi: 10.1093/cid/ciaf669. *Consensus*: <https://consensus.app/papers/details/da6732bd67845b86b036c46453071d39/>
63. Melisko ME, Goldman ME, Hwang J, De Luca A, Fang S, Esserman LJ, et al. Vaginal testosterone cream vs estradiol vaginal ring for vaginal dryness or decreased libido in women receiving aromatase inhibitors for early-stage breast cancer: a randomized clinical trial. *JAMA Oncol*. 2017;3(3):313–9. doi: 10.1001/jamaoncol.2016.3904. *Consensus*: <https://consensus.app/papers/details/db5341821226577c9659b357feb0b60f/>
64. Faltinová M, Vehmanen L, Lyytinen H, Savolainen-Peltonen H, Blomqvist C, Mattson J, et al. Effects of vaginal estrogen on serum estradiol during aromatase inhibitor therapy in breast cancer patients with vulvovaginal atrophy: a prospective trial. *Breast Cancer Res Treat*. 2024; published online ahead of print. doi: 10.1007/s10549-024-07564-8. *Consensus*: <https://consensus.app/papers/details/2a2b4ffb32195709a1d00bc6e470785c/>
65. Sicilia G, Mastrovito S, Campagna G, Panico G, Vacca L, Caramazza D, et al. The role of vaginal oestrogen therapy in postmenopausal women with pelvic organ prolapse: does it have

- any impact on perioperative outcomes? A systematic review of randomised controlled trials. BJOG. 2025; published online ahead of print. doi: 10.1111/1471-0528.18260. *Consensus:* <https://consensus.app/papers/details/c8a8163af4cf5af988377030d40c5697/>
66. Jang YC, Leung CY, Huang HL. Comparison of severity of genitourinary syndrome of menopause symptoms after carbon dioxide laser vs vaginal estrogen therapy: a systematic review and meta-analysis. JAMA Netw Open. 2022;5(9):e2232563. doi: 10.1001/jamanetworkopen.2022.32563. *Consensus:* <https://consensus.app/papers/details/f7151ee38c055158a65202c16c817462/>
67. Lethaby A, Ayeleke RO, Roberts H. Local oestrogen for vaginal atrophy in postmenopausal women. Cochrane Database Syst Rev. 2016;(8):CD001500. doi: 10.1002/14651858.CD001500.pub3. *Consensus:* <https://consensus.app/papers/details/ec693259b78c5ada9c94e2ab3ccb8e14/>
68. Perrotta C, Aznar M, Mejia R, Albert X, Ng CW. Oestrogens for preventing recurrent urinary tract infection in postmenopausal women. Cochrane Database Syst Rev. 2008;(2):CD005131. doi: 10.1002/14651858.CD005131.pub2. *Consensus:* <https://consensus.app/papers/details/c64354282e1a5ce88e866fd5bca783bc/>
69. Fox K, Gaddis N, Nordberg J, Wolff EM, Neal DE. Evaluation of systemic estrogen for preventing urinary tract infections in postmenopausal women. Menopause. 2021; published online ahead of print. doi: 10.1097/GME.0000000000001769. *Consensus:* <https://consensus.app/papers/details/d1a22bde87435459a84a48f4030e6164/>
70. Rubin R, Moyneur E, Dea K, Dury A. Prevalence of urinary tract infections in women with vulvovaginal atrophy and the impact of vaginal prasterone on the rate of urinary tract infections. Menopause. 2025; published online ahead of print. doi: 10.1097/GME.0000000000002485. *Consensus:* <https://consensus.app/papers/details/06dd490660105e7ba64738f4f41dbb3d/>
71. Ingram AL, Trussell JC, Farah D, Mahon J, Rutkowski J. Risk factors, demographic profiles, and management of uncomplicated recurrent urinary tract infections: a single institution study.

- Menopause. 2021; published online ahead of print. doi: 10.1097/GME.0000000000001791.
Consensus: <https://consensus.app/papers/details/60a7e70273eb5673ae034718aba63b3d/>
72. Geoffrion R. Treatments for overactive bladder: focus on pharmacotherapy. J Obstet Gynaecol Can. 2012;34(11):1092–101. doi: 10.1016/S1701-2163(16)35440-8. *Consensus:* <https://consensus.app/papers/details/0d4502814855522a8598d353cd427919/>
73. Villadsen A, Krogh PM, Bor P, Hansen KE, Glavind K. Use of fermented red clover isoflavones in the treatment of overactive bladder in postmenopausal women: a randomized, double-blinded, placebo-controlled trial. Nutrients. 2023;15(19):4165. doi: 10.3390/nu15194165. *Consensus:* <https://consensus.app/papers/details/5acdeb87606a551d8aabe7627f990793/>
74. Crean-Tate KK, Faubion SS, Pederson HJ, Vencill JA, Batur P. Management of genitourinary syndrome of menopause in female cancer patients: a focus on vaginal hormonal therapy. Am J Obstet Gynecol. 2020;222(2):103–13. doi: 10.1016/j.ajog.2019.08.043. *Consensus:* <https://consensus.app/papers/details/3632e8169e3454349318b7b729aa9c99/>
75. Alghoul W, et al. The urogenital microbiome–metabolic interface in postmenopausal recurrent urinary tract infection: estrogen deficiency, diabetes, obesity, and microbial reservoirs. J Clin Med. 2026;15(15):5895. doi: 10.3390/jcm15155895. *Consensus:* <https://consensus.app/papers/details/7c9b4d8a5c705e518cf7d77bd1fdffe2/>
76. Paramanandam VS, Davies C, Newman C, Bell RJ, Kalra B, Iyer J, et al. Recommended measurement instruments for genitourinary symptoms associated with menopause: the COMMA (Core Outcomes in Menopause) consortium. Menopause. 2024;31(5):341–9. doi: 10.1097/GME.0000000000002369. *Consensus:* <https://consensus.app/papers/details/e994d03461f5591ba9aca0677891458d/>
77. Ayeleke RO, Hay-Smith EJC, Omar MI. Pelvic floor muscle training added to another active treatment versus the same active treatment alone for urinary incontinence in women. Cochrane Database Syst Rev. 2015;(11):CD010551. doi: 10.1002/14651858.CD010551.pub3. *Consensus:* <https://consensus.app/papers/details/79f64ba068935124add73e11c9666c41/>
78. Dumoulin C, Morin M, Danieli C, Cacciari L, Mayrand MH, Tousignant M, et al. Group-based vs individual pelvic floor muscle training to treat urinary incontinence in older women: a

randomized clinical trial. JAMA Intern Med. 2020;180(10):1284–93. doi: 10.1001/jamainternmed.2020.2993. *Consensus:*

<https://consensus.app/papers/details/d02782422bd75364a98748085fc6331f/>

79. Imamura M, Hudson J, Wallace SA, MacLennan G, Shimonovich M, Omar MI, et al. Surgical interventions for women with stress urinary incontinence: systematic review and network meta-analysis of randomised controlled trials. BMJ. 2019;365:l1842. doi: 10.1136/bmj.l1842.

Consensus: <https://consensus.app/papers/details/4871698eb43a538ca39d90f7a5e8360c/>

80. Bevilacqua MRR, et al. Prevalence and predictors of genitourinary syndrome of menopause: a population-based study in middle-aged Brazilian women. Menopause. 2025; published online ahead of print. doi: 10.1097/GME.0000000000002467. *Consensus:*

<https://consensus.app/papers/details/e3a19d69510a55999cef42ae39ac03d2/>