International Platform of Registered Systematic Review and Meta-analysis Protocols

INPLASY

Systemic Estradiol Levels Following Vaginal Estrogen Therapy: A Scoping Review Protocol Across Formulations and Measurement Methods

INPLASY202670107

doi: 10.37766/inplasy2026.7.0107

Received: 27 July 2026

Published: 28 July 2026

Rusk, K; Mallahan, S; Pesavento, K; Porter, K; Huggins, E; Acevedo-Alvarez, M.

Corresponding author:
Kimberly Rusk

krusk@luc.edu

Author Affiliation:
Loyola University Chicago.

ADMINISTRATIVE INFORMATION

Support - No support.

Review Stage at time of this submission - Preliminary searches.

Conflicts of interest - None declared.

INPLASY registration number: INPLASY202670107

Amendments - This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 28 July 2026 and was last updated on 28 July 2026.

INTRODUCTION

Review question / Objective Among peri and postmenopausal women using vaginal estrogen therapy, what is the extent and nature of the evidence on systemic estradiol concentrations following treatment, and how do reported levels vary by formulation, dose, duration, timing of measurement, patient population, and assay methodology? For studies using LC-MS/MS, do reported post treatment estradiol concentrations fall within the harmonized postmenopausal reference ranges established by Cui et al. (2026)?

Rationale Vaginal estrogen therapy is the recommended first line treatment for genitourinary syndrome of menopause, yet concerns about systemic estradiol absorption continue to influence clinical decision making, particularly among women with estrogen sensitive conditions such as breast cancer. Existing studies report highly variable systemic estradiol concentrations because they differ in vaginal estrogen formulation, dose, duration of therapy, timing of blood sampling, patient populations, and laboratory assay methodology. Interpretation is further complicated by historical reliance on immunoassays, which may overestimate estradiol concentrations at the low levels typical of postmenopausal women, whereas more recent studies increasingly use liquid chromatography tandem mass spectrometry (LC-MS/MS). The recent establishment of harmonized international LC-MS/MS reference ranges for postmenopausal estradiol provides, for the first time, a validated physiologic benchmark against which reported systemic estradiol levels can be interpreted. No published scoping review has comprehensively mapped the available evidence while evaluating reported LC-MS/MS measured estradiol concentrations against these reference ranges. A scoping review is therefore warranted to characterize the breadth of the evidence, identify sources of heterogeneity, and highlight gaps to inform clinical interpretation and future research.

Condition being studied Genitourinary syndrome of menopause (GSM) in peri and postmenopausal

women, with a focus on systemic estradiol exposure following vaginal estrogen therapy.

METHODS

Search strategy A comprehensive search strategy was developed in collaboration with a health sciences librarian and is designed to identify studies reporting systemic estradiol concentrations following vaginal estrogen therapy in peri and postmenopausal women. The initial search strategy was developed and executed in Embase (Elsevier) using a combination of controlled vocabulary (EMTREE terms) and free text keywords related to vaginal estrogen therapy, estradiol, and systemic estrogen concentrations. The Embase strategy used the "syn" field to search current and subordinate headings as well as indexed keywords. The strategy will be adapted, with appropriate controlled vocabulary and syntax modifications, for each additional database while maintaining the same conceptual framework.

Electronic database searches will be conducted in:
MEDLINE via PubMed
Embase (Elsevier)
Science Citation Index, Web of Science

The Embase search strategy forms the basis for all database searches:
('vaginal estrogen'/syn OR (('vagina'/syn OR 'intravaginal drug administration'/syn) AND 'estrogen therapy'/syn)) AND ('estradiol'/syn OR 'estrogen blood level'/syn)

The search will be limited to peer reviewed journal articles published in English within the last five years (2019 through 2026). This time frame was selected because recent studies are more likely to evaluate currently marketed low dose vaginal estrogen formulations and use contemporary laboratory methods, particularly liquid chromatography tandem mass spectrometry (LC-MS/MS), which provides greater analytical accuracy for measuring low postmenopausal estradiol concentrations.

To maximize retrieval, the reference lists of all included studies and relevant review articles will be manually searched for additional eligible studies. Citation tracking of key publications will also be performed to identify more recent articles citing seminal studies. Reviews identified during screening will be used for citation mining but will not be included as primary evidence unless they contain extractable original systemic estrogen outcome data.

All identified citations will be imported into Covidence for review management. Duplicate records will be removed automatically and verified manually. Following calibration exercises, two independent reviewers will screen titles and abstracts against the predefined inclusion criteria. Full text articles deemed potentially eligible will then undergo independent review by two reviewers. Reasons for exclusion at the full text stage will be documented, and disagreements at any stage will be resolved through discussion and consensus. The study selection process will be reported using a PRISMA Scoping Review (PRISMA ScR) flow diagram.

Studies will be eligible if they include peri or postmenopausal women receiving vaginal estrogen therapy of any formulation, dose, or schedule and report systemic serum estradiol or related estrogen measurements before treatment or at defined post treatment time points. Randomized controlled trials, nonrandomized trials, cohort studies, case control studies, cross sectional studies, and case series will be included. Narrative reviews, editorials, animal studies, and studies without systemic hormone measurements will be excluded.

Data extracted from eligible studies will include study characteristics, participant demographics, menopausal status, clinical setting, vaginal estrogen formulation, dose, frequency, duration of therapy, timing of blood sampling, assay methodology, detection limits, units of measurement, and reported systemic estradiol concentrations. Particular attention will be paid to the laboratory methods used to quantify estradiol, including LC-MS/MS, radioimmunoassay (RIA), enzyme linked immunoassay (ELISA), gas chromatography mass spectrometry (GC-MS), and other validated assays, because assay performance substantially influences interpretation of low postmenopausal estradiol concentrations. For studies using LC-MS/MS, reported post treatment estradiol concentrations will be compared with the harmonized international postmenopausal reference ranges established by Cui et al. (2026) to determine whether measured systemic concentrations remain within the expected physiologic range.

Participant or population Adult peri and postmenopausal women receiving vaginal estrogen therapy of any formulation, dose, or schedule. This includes women receiving endocrine therapy (including aromatase inhibitors) or with estrogen sensitive conditions, such as a history of breast cancer, provided systemic

estrogen outcomes are reported. Studies will be excluded if participants are not adult women or if menopausal status cannot be determined from the study context.

Intervention Vaginal estrogen therapy of any formulation, dose, or schedule, including estradiol, estriol, and conjugated estrogen preparations administered as creams, tablets, inserts, softgel capsules, or vaginal rings.

Comparator Not applicable.

Study designs to be included Experimental and quasi experimental studies (including randomized and nonrandomized controlled trials, before and after studies, and interrupted time series), analytical observational studies (prospective and retrospective cohort, case control, and analytical cross sectional studies), and descriptive observational studies (case series and descriptive cross sectional studies). Systematic reviews will be used for citation tracking only and will not be included as primary evidence unless they contain extractable original systemic estrogen outcome data.

Eligibility criteria Studies will be eligible if they include adult peri or postmenopausal women receiving vaginal estrogen therapy of any formulation, dose, or schedule and report systemic serum estradiol or related estrogen concentrations before treatment or at defined post treatment time points. Eligible study designs include randomized and nonrandomized trials, cohort studies, case control studies, cross sectional studies, and case series. Studies involving women receiving endocrine therapy or with a history of breast cancer will be included if systemic hormone outcomes are reported. Studies will be excluded if they involve nonhuman subjects, do not include adult peri or postmenopausal women, do not evaluate vaginal estrogen therapy, do not report systemic hormone measurements, or are narrative reviews, editorials, commentaries, conference abstracts without sufficient data, or other nonprimary research. Only English language, peer reviewed articles published between 2019 and 2026 will be included.

Information sources Electronic searches will be conducted in MEDLINE via PubMed, Embase (Elsevier), and Science Citation Index (Web of Science). Reference lists of included studies and relevant reviews will be hand searched, and citation tracking of key articles will be performed to identify additional eligible studies. All records will be imported into Covidence for deduplication and study selection. No direct author contact or grey literature searches are planned.

Main outcome(s) The primary outcome is reported systemic serum estradiol concentration following vaginal estrogen therapy. Data will be extracted on estradiol concentrations at baseline and post treatment, timing of blood sampling, vaginal estrogen formulation, dose, frequency, duration of therapy, assay methodology (e.g., LC-MS/MS, RIA, ELISA, GC-MS), detection limits, and units of measurement. For studies using LC-MS/MS, post treatment estradiol concentrations will be compared with the harmonized postmenopausal reference ranges established by Cui et al. (2026) to determine whether reported values remain within the physiologic postmenopausal range.

Additional outcome(s) Additional outcomes include study characteristics (design, country, sample size, participant characteristics, menopausal status, and breast cancer or endocrine therapy status), vaginal estrogen formulation, dose, frequency, duration of therapy, timing of serum sampling, assay methodology and analytical performance, reported adverse events, and authors' conclusions regarding systemic absorption and clinical safety. Patterns in reported estradiol concentrations across formulations, doses, patient populations, and assay methods will also be summarized.

Data management Search results will be imported into Covidence for deduplication, title and abstract screening, full text review, and data extraction. Two reviewers will independently screen studies against predefined eligibility criteria, with disagreements resolved through discussion or consultation with a third reviewer. A standardized data extraction form will be pilot tested and refined as needed. Extracted data will be exported from Covidence into Microsoft Excel for data management, synthesis, and reporting.

Quality assessment / Risk of bias analysis Consistent with JBI guidance for scoping reviews, formal risk of bias assessment is not planned because the objective is to map and characterize the available evidence rather than estimate pooled treatment effects. Methodological characteristics, including study design, sample size, assay methodology, completeness of outcome reporting, and other factors that may influence interpretation of reported systemic estradiol concentrations, will be extracted and summarized descriptively.

Strategy of data synthesis A narrative synthesis will be undertaken to map the available evidence

on systemic estradiol concentrations following vaginal estrogen therapy. Extracted data will be summarized in tables and descriptive figures by study design, participant characteristics, vaginal estrogen formulation, dose, duration of therapy, timing of serum sampling, assay methodology, and reported estradiol concentrations. Results will be grouped by formulation and assay type, with particular emphasis on studies using LC-MS/MS. Where sufficient data are available, reported post treatment estradiol concentrations measured by LC-MS/MS will be compared with the harmonized postmenopausal reference ranges established by Cui et al. (2026). No quantitative meta analysis is planned because substantial clinical and methodological heterogeneity is anticipated across study populations, interventions, outcome measurement, and laboratory methods.

Subgroup analysis Where sufficient data are available, findings will be summarized by vaginal estrogen formulation (cream, tablet, insert, softgel capsule, ring), estrogen type (estradiol, estriol, conjugated estrogens), dose, duration of therapy, timing of serum sampling, assay methodology (LC-MS/MS versus immunoassay based methods), menopausal status (peri versus postmenopausal), and patient population, including women with a history of breast cancer or receiving endocrine therapy. For studies using LC-MS/MS, reported serum estradiol concentrations will also be categorized according to whether values remain within the harmonized postmenopausal reference ranges established by Cui et al. (2026). Comparisons will be descriptive, and no formal statistical subgroup analyses are planned.

Sensitivity analysis No formal sensitivity analyses are planned because this review is designed to map and characterize the available evidence rather than quantitatively synthesize study results.

Language restriction English.

Country(ies) involved United States.

Other relevant information This review is designed to address an important clinical question regarding the extent of systemic estradiol exposure following vaginal estrogen therapy. A distinguishing feature of the review is the planned comparison of LC-MS/MS measured serum estradiol concentrations with the harmonized postmenopausal reference ranges established by Cui et al. (2026), providing a clinically relevant framework for interpreting systemic absorption. The review will also examine how reported estradiol concentrations vary according to formulation, dose, duration of therapy, timing of serum sampling, assay methodology, and patient population. Findings are intended to identify evidence gaps, inform future research, and support evidence based clinical decision making regarding the safety of vaginal estrogen therapy in peri and postmenopausal women, including those with a history of breast cancer or receiving endocrine therapy.

Keywords Vaginal estrogen; Estradiol; Genitourinary syndrome of menopause; LC-MS/MS; Systemic absorption; Postmenopause; Scoping review; Breast cancer survivors.

Dissemination plans Findings from this scoping review will be submitted for publication in a peer reviewed journal with a strong focus on women's health and menopause care. Results may also be presented at national or international scientific conferences to facilitate dissemination to clinicians, researchers, and other stakeholders involved in the care of peri and postmenopausal women.

Contributions of each author

Author 1 - Kimberly Rusk - Conceived the review, developed the protocol, designed the search strategy, drafted the manuscript, and will oversee study selection, data extraction, data synthesis, and manuscript preparation.
Email: krusk@luc.edu
Author 2 - Samantha Mallahan - Drafted the manuscript, and will assist in study selection, data extraction, data synthesis, and manuscript preparation.
Email: smallahan@luc.edu
Author 3 - Kristen Pesavento - Will assist in study selection, data extraction, data synthesis, manuscript preparation, and laboratory assessment.
Email: kpesavento@luc.edu
Author 4 - Kendall Porter - Will assist in study selection, data extraction, data synthesis, and manuscript preparation.
Email: kporter6@luc.edu
Author 5 - Elizabeth Huggins - Developed the protocol, designed the search strategy, drafted the manuscript, and manuscript preparation.
Email: ehuggins@luc.edu
Author 6 - Marian Acevedo-Alvarez - Drafted the manuscript, and clinical interpretation and manuscript preparation.
Email: marian.acevedoalvarez@lumc.edu