



Systematic Review



Anatomical and Dermatologic Manifestations of Estrogen Deficiency in Postmenopausal Women: A Systematic Review

Anjum Mahmood¹, Shehryar Shah^{2*}, Naimat Ullah³, Rahmat Ullah Jan⁴, Muhammad Adnan Jan⁵ and Motasim Billah⁶¹Department of Obstetrics and Gynecology, Pak International Medical College, Peshawar, Pakistan²Department of Anatomy, Khyber Medical College, Peshawar, Pakistan³Department of Dermatology, Bannu Medical College Medical Teaching Institution, Bannu, Pakistan⁴Department of Anatomy, Muhammad College of Medicine, Peshawar, Pakistan⁵Department of Anatomy, Khyber Girls Medical College, Peshawar, Pakistan⁶Department of Anatomy, Gajju Khan Medical College, Sawabi, Pakistan

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*Corresponding Author:

Shehryar Shah
Department of Anatomy, Khyber Medical College,
Peshawar, Pakistan
dr.shehryar.shah@gmail.com

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ABSTRACT

Estrogen deficiency after menopause contributes to structural and symptomatic changes in genital, cutaneous, and adnexal tissues, yet available evidence remains scattered across clinical and imaging disciplines. Objectives: To summarize contemporary evidence on anatomical and dermatologic manifestations of estrogen deficiency in postmenopausal women and to evaluate the effects of local hormonal and device-based treatments. Methods: A systematic review following PRISMA 2020 guidelines. PubMed/MEDLINE, Scopus, Web of Science, and Google Scholar were searched for English-language studies from 1 January 2017 to 31 December 2024. Eligible designs included randomized controlled trials, observational and cross-sectional studies, imaging investigations, and pilot interventions involving naturally or surgically postmenopausal women. Outcomes included clinical signs, symptom scores, imaging parameters, and dermatologic manifestations. Risk of bias was assessed using the Cochrane RoB-2 tool for randomized trials and the Newcastle-Ottawa Scale for observational and imaging studies. Results: Eighteen studies met the inclusion criteria. Randomized trials of low-dose vaginal estradiol and selective estrogen receptor modulators improved vaginal pH, Vaginal Health Index, Vaginal Maturation Index, dryness, and dyspareunia with minimal systemic absorption. Dermatology-focused cohorts commonly reported xerosis, pruritus, dermatoses, nail fragility, and female-pattern hair loss. Imaging studies demonstrated reduced dermal and vaginal wall thickness and altered echogenicity. Evidence for fractional CO₂ laser and radiofrequency remained limited to small pilot studies with short follow-up. Conclusions: Estrogen deficiency is consistently associated with measurable structural and symptomatic changes in genital and cutaneous tissues. Local estrogen therapy offers reliable short-term benefits, whereas device-based interventions remain investigational and require larger controlled trials.

INTRODUCTION

Menopause represents a permanent cessation of ovarian follicular activity accompanied by a marked decline in circulating estrogen levels [1]. Although this transition is biologically universal, its structural and symptomatic consequences vary considerably across individuals and often remain under-recognized in routine clinical practice

[2]. Estrogen receptors are widely distributed in the vaginal epithelium, urogenital tract, skin, adnexal structures, and connective tissues, making these systems particularly sensitive to hormonal withdrawal. With reduced estrogenic stimulation, epithelial turnover slows, collagen synthesis declines, microvascular perfusion



decreases, and tissue moisture regulation becomes impaired, contributing to symptoms such as dryness, discomfort, impaired healing, and dermatologic changes [3, 4]. These manifestations collectively contribute to the clinical picture of Genitourinary Syndrome of Menopause (GSM) and Vulvovaginal Atrophy (VVA), conditions that significantly affect quality of life for many women [5]. Over the past decade, research exploring the anatomical and dermatologic effects of estrogen deficiency has expanded, supported by improved imaging technologies and controlled clinical studies [6, 7]. High-frequency ultrasound, elastography, and histopathological evaluations have demonstrated reduced dermal thickness, altered echogenicity, and diminished elasticity in estrogen-deprived tissues [8]. Clinical studies have further documented changes in hair density, nail integrity, and mucosal architecture, suggesting a broader spectrum of estrogen-related tissue vulnerability than previously recognized [9]. Despite this growing evidence base, substantial gaps persist, particularly regarding the integration of imaging findings with clinical manifestations, variability across populations, and the comparative benefits of emerging non-hormonal interventions. Therapeutic approaches have also evolved, with low-dose vaginal estradiol formulations, selective estrogen receptor modulators (SERMs), and non-hormonal modalities such as fractional CO₂ laser and radiofrequency being increasingly investigated [3]. While randomized controlled trials consistently show great improvements in Vaginal Health Index (VHI), Vaginal Maturation Index (VMI), pH, dryness, and dyspareunia, evidence for energy-based or device-based therapies remains limited and heterogeneous, highlighting the need for careful interpretation. Furthermore, cultural barriers and limited access to menopause-focused care continue to delay treatment seeking in many regions, underscoring the importance of comprehensive evidence synthesis. This systematic review consolidates the current literature describing structural, dermatologic, and mucosal manifestations of estrogen deficiency and evaluates therapeutic strategies aimed at restoring tissue health. This approach improves visibility of existing knowledge gaps and supports the development of more targeted and effective management strategies for postmenopausal women.

This study aims to clarify the breadth of estrogen-related anatomical changes and identify areas where evidence remains insufficient by integrating findings from clinical assessments, imaging modalities, and interventional studies.

METHODS

This systematic review was conducted according to the PRISMA 2020 guidelines, with the primary aim of summarizing contemporary clinical, dermatologic, anatomical, and imaging-based evidence regarding estrogen-deficiency manifestations in postmenopausal women. A comprehensive search was carried out in PubMed/MEDLINE, Scopus, Web of Science, and Google Scholar to identify eligible studies published between 1st January 2017 and 31st December 2024. The search strategy combined controlled vocabulary and keywords related to menopause, estrogen deficiency, genitourinary syndrome, vulvovaginal atrophy, skin aging, dermal thinning, and imaging modalities. A PubMed string was: ("menopause" OR "postmenopause" OR "post-menopausal") AND ("estrogen deficiency" OR "hypoestrogenism") AND ("genitourinary syndrome of menopause" OR "GSM" OR "vulvovaginal atrophy" OR "VVA") AND ("skin aging" OR "dermal thinning" OR "cutaneous changes") AND ("ultrasound" OR "imaging" OR "elastography" OR "histology"). In Google Scholar, searches were limited to results "since 2017", and only the first 200 records were screened, as recommended in high-yield search approaches. Reference lists of the included studies were also reviewed to ensure complete coverage of relevant literature. Eligibility criteria were defined using the PICOS framework. Studies were included if they involved naturally or surgically postmenopausal women and evaluated clinical, anatomical, or dermatologic outcomes associated with estrogen deficiency. Eligible designs consisted of randomized controlled trials, observational studies, cross-sectional surveys, imaging studies, and pilot interventional investigations. Only full-text publications available in English were considered. Reviews, case reports, animal studies, editorials, conference abstracts without full text, and studies lacking anatomical or dermatologic outcomes were excluded. To maintain consistency, all outcome measures were defined in advance. The Vaginal Health Index (VHI) was considered a five-domain clinical score assessing elasticity, moisture, fluid volume, pH, and epithelial integrity. The Vaginal Maturation Index (VMI) was defined as the percentage distribution of parabasal, intermediate, and superficial cells. Dyspareunia was accepted when measured by a visual analogue scale or as the Most Bothersome Symptom (MBS). Dermal thickness and elasticity were interpreted based on high-frequency ultrasound or elastography, while female-pattern hair loss was evaluated using trichoscopy or the Ludwig classification. Two independent reviewers screened all titles and abstracts retrieved from the search. Full-text articles were assessed separately by the same reviewers using the pre-specified criteria. Any disagreements were resolved through discussion, and

when consensus could not be reached, a senior reviewer served as an arbitrator. Inter-rater reliability for full-text screening was calculated using Cohen's kappa ($\kappa = 0.84$), demonstrating strong agreement. Data extraction was also performed independently by two reviewers using a structured extraction form that included study characteristics, sample features, outcome definitions, assessment tools, interventions, imaging parameters, and key findings. Extracted data were cross-checked to ensure accuracy before synthesis. Risk of bias assessment was conducted separately for randomized and non-randomized studies. Randomized trials were appraised using the Cochrane RoB-2 tool, which examines the randomization process, deviations from intended interventions, missing outcome data, measurement reliability, and selective reporting. Observational and imaging-based studies were evaluated using the Newcastle-Ottawa Scale, focusing on participant selection, comparability of groups, and outcome ascertainment. All assessments were completed independently by two reviewers, with discrepancies addressed through discussion. Due to substantial heterogeneity across study designs, populations, and measurement approaches, a meta-analysis was not feasible. Therefore, the findings were synthesized narratively, grouping results into anatomical, clinical, dermatologic, and imaging domains. This approach allowed integration of multidimensional evidence while acknowledging the variation in reported outcomes. Given the limited number of randomized trials and the heterogeneity in populations, interventions, and outcome measures, formal meta-analysis and funnel plots were not performed; instead, potential publication bias and small-study effects were considered qualitatively when interpreting the strength and consistency of findings. PRISMA 2020 flow diagram illustrating the identification, screening, eligibility assessment, and final inclusion of studies in the systematic review. A total of 466 records were identified through database searching, of which 78 duplicates were removed. After title and abstract screening, 83 full-text reports were reviewed, with 59 excluded for reasons including being reviews, lacking relevant outcomes, not primary studies, or non-English language. Ultimately, 18 studies met the inclusion criteria

and were included in the final synthesis (Figure 1).

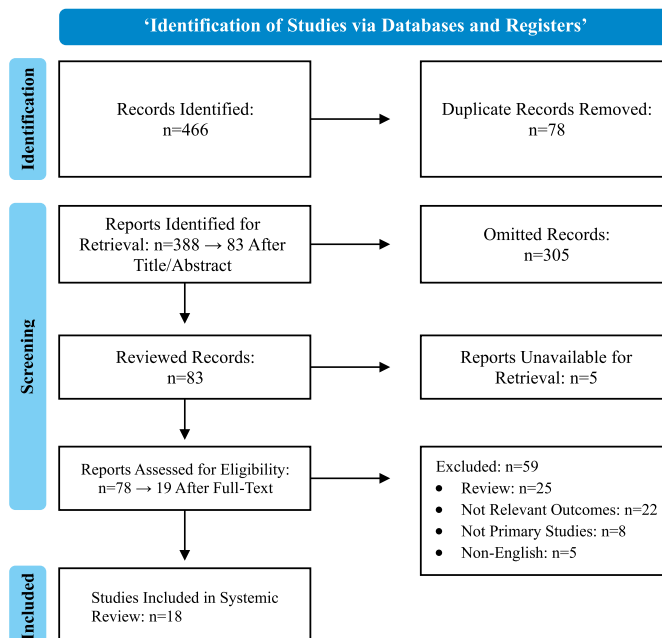


Figure 1: PRISMA 2020 Flow Diagram of Study Selection

RESULTS

A total of 18 primary studies published between 2017 and 2024 fulfilled the eligibility criteria. These included randomized controlled trials, cross-sectional studies, observational cohorts, and pilot imaging or interventional investigations, each contributing evidence on estrogen-deficiency-associated anatomical and dermatologic alterations in postmenopausal women. Across the randomized trials, consistent improvements were reported in vaginal pH, epithelial maturation, lubrication, and patient-reported symptoms, particularly dryness and dyspareunia, following local estrogen or SERM therapy. Dermatology-focused studies demonstrated a high frequency of xerosis, pruritus, infectious dermatoses, nail fragility, and female-pattern hair loss, confirming the broad cutaneous vulnerability associated with estrogen decline. Imaging-based studies using high-frequency ultrasound and elastography identified reductions in dermal thickness, altered echogenicity, and decreased skin stiffness, providing objective confirmation of estrogen-related atrophic changes (Table 1).

Table 1: Summary of Included Primary Studies (2017–2024)

Sr. No.	References	Design	n / Age	Menopause Criteria	Outcomes / Measures	Key Findings
1	[10]	Phase 3 RCT	764; 40–75 y	Postmenopausal with VVA	VHI, pH, Maturation Index, MBS Dyspareunia	Low-dose vaginal estradiol soft-gel provided rapid improvement in VVA symptoms with minimal systemic estradiol exposure.
2	[11]	RCT, Double-Blind	550; mid-50s to 70s	Postmenopausal with VVA	VHI, pH, MBS Dryness	Twice-weekly microdose estradiol cream significantly improved vaginal dryness and clinical signs compared with placebo.

3	[12]	RCT, Double-Blind	550	Postmenopausal with VVA	VHI, pH, Dyspareunia	Demonstrated efficacy and good tolerability of ultra-low-dose estradiol cream, especially for dyspareunia.
4	[13]	Phase 3 RCT	631; 40–80 y	Postmenopausal with VVA	MBS Dryness, VMI, pH	Oral SERM therapy improved vaginal dryness and epithelial parameters more effectively than placebo.
5	[14]	RCT, Post-Hoc Analyses	715	Postmenopausal with VVA	Dyspareunia/Dryness Response Thresholds	Clinically meaningful symptom responses were observed as early as week 2 and maintained across treatment.
6	[15]	Multicenter Cross-sectional	430; 30–75 y	≥12 Months Amenorrhea	GSM Prevalence, VHI, QoL	An estimated GSM prevalence of 70% a substantial impact on quality of life.
7	[16]	Cross-sectional	1,231; 45–75 y	Postmenopausal	Clinically Confirmed VVA, Symptom Scoring	VVA prevalence 75%; dryness and dyspareunia were the most prominent symptoms.
8	[17]	Cross-sectional	>3,000	Menopause by History	GSM Prevalence, Risk Factors	GSM was common; age, menopausal status, pelvic organ prolapses, and urinary incontinence were significantly associated factors.
9	[18]	Observational Cross-sectional	356; ≥45 y	Peri/Postmenopause	Daily Impact, Symptom Scoring	GSM symptoms significantly impaired daily functioning and overall well-being.
10	[19]	Cross-sectional	401; 45–75 y	Postmenopausal	DIVA, QoL	Women with GSM had markedly lower QoL scores compared with non-GSM participants.
11	[20]	Pilot Clinical	40	Postmenopausal	Vestibular epithelial thickness, trophism	Post-intervention increases in epithelial thickness and trophism were observed, indicating potential benefit.
12	[21]	Pilot Imaging	40	Postmenopausal	Transvaginal US of Vaginal Wall	Demonstrated feasibility of measuring vaginal wall thickness and differentiating between clinical groups.
13	[8]	Observational Imaging	118 adults	Age-Stratified	Epidermal/Dermal Thickness At 8 Sites	Dermal thickness decreased with age in women; high-frequency US is useful for menopausal skin evaluation.
14	[22]	Observational Imaging	600	Adult Cohort	US Thickness and Echo-Density Maps	Skin thickness and density were influenced by age, sex, and anatomical region; findings relevant for menopausal assessment.
15	[23]	Observational	196 women	Menopause Documented	Breast Skin Thickness and Stiffness	Menopausal women showed reduced breast tissue stiffness and altered skin thickness profiles.
16	[24]	Cross-sectional Dermatology	150; mean 61.5 y	Natural Menopause	Full Skin, Hair, Nail Examination	High burden of xerosis, pruritus, and infections; established dermatologic patterns of postmenopause.
17	[25]	Cross-sectional	200	Postmenopausal	Cutaneous, Hair, Nail Changes	Frequently observed xerosis, lichen sclerosus, and female-pattern hair loss with multi-site involvement.
18	[26]	Cross-sectional	178; mean 58.8 y	Postmenopausal	Trichoscopy, Ludwig Grading	FPHL prevalence was 52%, with grading

Following the overview of included studies, the study presents the major phenotypic patterns linked to estrogen deficiency across genital, cutaneous, breast, and adnexal structures. The most consistent observation was progressive dermal thinning and loss of elasticity, attributed to diminished collagen, elastin, and fibroblast activity. Clinically, this manifested as xerosis, pruritus, fragility, and accelerated photoaging. Genitourinary changes were more pronounced and included pale vaginal mucosa, loss of rugae, epithelial thinning, introital narrowing, dyspareunia, and reduced lubrication. These findings reflect decreased glycogen content, reduced superficial cell layers, and altered vascularity (Table 2).

Table 2: Anatomical and Dermatologic Manifestations of Estrogen Deficiency in Postmenopausal Women

Manifestation Category	Specific Findings	Underlying Mechanism	Assessment Tools	References
Skin thinning and elasticity loss	Wrinkles, laxity, ↓ dermal thickness	↓ Collagen I/III, ↓ elastin, ↓ fibroblasts	High-frequency US, elastography	[22]
Skin dryness and barrier dysfunction	Xerosis, pruritus, rough texture	↓ Sebum, ↓ natural moisturizing factors, impaired barrier	Clinical exam, corneometry	[23]
Pigmentation changes and photoaging	Hyperpigmentation, lentigines	Reduced the antioxidant effect of estrogen	Clinical exam, dermoscopy	[25]

Subcutaneous fat and facial contour changes	Facial fat loss, sagging	Estrogen decline → adipocyte remodeling	Clinical exam, imaging	[24]
Hair changes (FPHL)	Thinning, reduced density, widened part	↓ Estrogen → ↑ androgen influence, ↓ anagen phase	Trichoscopy, Ludwig scale	[26]
Nail fragility	Brittle nails, ridging	↓ Keratin support, ↓ microcirculation	Clinical exam	[24, 25]
Breast tissue changes	Atrophy, ↓ firmness	↓ Glandular tissue, ↓ collagen	US, skin stiffness device	[23]
Vulvovaginal atrophy (GSM)	Pale mucosa, loss of rugae, thin epithelium	↓ Glycogen, ↓ superficial cells, ↓ vascularity	VHI, pH, VMI	[10, 11]
Dyspareunia	Pain during intercourse	Epithelial thinning, ↓ lubrication, microtrauma	VAS, MBS	[14, 16]
Vulvar architecture changes	Labial thinning, introital narrowing	↓ Collagen & elasticity	Clinical exam, vestibular scoring	[20, 21]
Reduced epithelial thickness	Fragility, friability	↓ Estrogenic stimulation	Transvaginal US, histology	[20, 21]
Pelvic floor & urinary changes	Urinary symptoms, pelvic laxity	↓ Estrogen in urethral & pelvic fascia	POP-Q, pelvic exam	[17, 18]
Delayed wound healing	Slow repair, increased fragility	↓ Growth factors, ↓ angiogenesis	Clinical observation	[24, 25]
Microvascular changes	↓ Blood flow, pallor	↓ Endothelial support, ↓ capillary density	Doppler, US	[8]

Evidence regarding therapeutic options is summarized, presented after this paragraph. Across RCTs, low-dose vaginal estradiol demonstrated rapid and clinically meaningful improvements, with minimal systemic absorption and favorable safety profiles. Ospemifene produced comparable symptom relief but with slightly higher vasomotor side effects. Limited pilot studies of fractional CO₂ laser or radiofrequency suggested preliminary benefit in vestibular epithelial thickness; however, small sample sizes, lack of controls, and short follow-up periods restrict firm conclusions (Table 3).

Table 3: Therapeutic Interventions and Outcomes in Estrogen-Deficiency Manifestations (2017-2024)

References	Population	Intervention	Comparator	Duration	Outcomes	Key Results	Safety
[6]	Postmenopausal VVA (40-75 y)	Vaginal estradiol soft-gel 4-10 µg	Placebo	12 weeks	VHI, pH, VMI, MBS dyspareunia	Rapid and clinically meaningful improvement, early symptom relief	Low systemic absorption; mild Aes
[7]	VVA with dryness as MBS	Estradiol 0.003% cream twice weekly	Placebo	12 weeks	VHI, pH, MBS dryness	Significant improvement in dryness & objective signs	Mild local Aes
[9]	Moderate-severe dryness	Ospemifene 60 mg oral	Placebo	12 weeks	MBS dryness, VMI, pH	Improved dryness & epithelial maturation	More hot flashes; acceptable overall
[10]	Postmenopausal VVA	Vaginal estradiol soft-gel	Placebo	12 weeks	Response thresholds, VHI, pH	Symptom relief by week 2, sustained response	Low systemic E2
[16]	Postmenopausal GSM	Fractional CO ₂ laser / Radio frequency / Topical estrogen	None (within-study comparison)	Short-term	Epithelial thickness, trophism, symptoms	Increased epithelial thickness; early symptom improvement	No serious Aes; transient discomfort

AEs: adverse events; E2: estradiol; GSM: genitourinary syndrome of menopause; MBS: Most Bothersome Symptom; VHI: Vaginal Health Index; VMI: Vaginal Maturation Index.

The methodological quality of included studies is summarized, which follows this paragraph to maintain proper sequencing. Most RCTs demonstrated low risk of bias across assessed domains. Observational studies showed mixed quality, with some rated moderate risk due to sampling limitations and incomplete adjustment for confounders. One pilot interventional study demonstrated a high risk due to the absence of randomization and short follow-up (Table 4).

Table 4: Risk of Bias Assessment for Included Primary Studies (2017-2024)

Sr. No.	References	Design	Tool Used	Key Domains Evaluated	Score / Judgment	Overall Risk of Bias
1	[10]	RCT	Cochrane RoB-2	Randomization, Deviations, Missing Data, Outcomes, Reporting	All domains are low risk	Low
2	[11]	RCT	Cochrane RoB-2	Randomization, Deviations, Missing Data, Outcomes, Reporting	All domains are low risk	Low
3	[12]	RCT	Cochrane RoB-2	Randomization, Deviations, Missing Data, Outcomes, Reporting	All domains are low risk	Low
4	[13]	RCT	Cochrane RoB-2	Randomization, Deviations, Missing Data, Outcomes, Reporting	All domains are low risk	Low
5	[14]	RCT (Post-Hoc Analysis)	Cochrane RoB-2	Randomization, Analytic Deviations, and Reporting	Some concerns (post-hoc)	Some Concerns

6	[15]	Cross-sectional	NOS	Selection, Comparability, Outcome	6/9	Moderate
7	[16]	Cross-sectional	NOS	Selection, Comparability, Outcome	6/9	Moderate
8	[17]	Cross-sectional	NOS	Selection, Comparability, Outcome	8/9	Low
9	[18]	Cross-sectional	NOS	Selection, Comparability, Outcome	6/9	Moderate
10	[19]	Cross-sectional	NOS	Selection, Comparability, Outcome	6/9	Moderate
11	[20]	Pilot Interventional (Non-Randomized)	NOS	Selection, Comparability, Outcome	4/9	High
12	[21]	Pilot Imaging	NOS	Selection, Comparability, Outcome	5/9	Moderate
13	[8]	Imaging Observational	NOS	Selection, Comparability, Outcome	7/9	Low
14	[22]	Imaging Observational	NOS	Selection, Comparability, Outcome	7/9	Low
15	[23]	Observational	NOS	Selection, Comparability, Outcome	6/9	Moderate
16	[24]	Cross-sectional Dermatology	NOS	Selection, Comparability, Outcome	5/9	Moderate
17	[25]	Cross-sectional Dermatology	NOS	Selection, Comparability, Outcome	5/9	Moderate
18	[26]	Cross-sectional Hair	NOS	Selection, Comparability, Outcome	7/9	Low

DISCUSSION

This review highlights that estrogen deficiency in postmenopausal women is associated with consistent anatomical and dermatologic alterations, including vaginal epithelial thinning, elevated pH, dryness, dyspareunia, and cutaneous atrophy. These findings represent associations rather than established causation, but the repeated patterns across the included studies strengthen their clinical relevance. Imaging-based evidence further supports these associations. For example, Bosio *et al.* demonstrated reproducible measurements of vaginal wall thickness using transvaginal ultrasound [27], while Wang *et al.* provided histology-based percentile data on vaginal mucosa thickness [22]. These methods offer objective markers for detecting atrophic changes, although their integration into routine practice requires broader validation. The symptomatic burden observed in this review aligns with global and regional data on Genitourinary Syndrome of Menopause (GSM). Mahmoudian *et al.* in Ismail and Bibi, reported high frequencies of dryness, irritation, and sexual discomfort in Pakistan, paralleling the multi-country findings summarized here [28, 29]. These similarities across diverse healthcare systems suggest that GSM remains under-recognized and undertreated, potentially due to cultural taboos, limited awareness, and restricted access to menopause-focused services [30]. Evidence from randomized trials indicates that ultra-low-dose vaginal estradiol and selective estrogen receptor modulators (SERMs) improve vaginal hydration, epithelial maturation, and dyspareunia [31, 12]. These findings are consistent with recent mechanistic work. For example, Srinivasan *et al.* showed that low-dose estradiol can modify the vaginal microbiota and metabolome [32]. Additionally, Pérez-López *et al.* also reported improved *Lactobacillus* dominance and reduced vaginal pH following estriol therapy [3]. Although these improvements support the

physiological basis of symptom relief, most trials had short follow-up periods, limiting firm conclusions about long-term safety and durability. Non-hormonal and device-based interventions remain an evolving but uncertain area. Cruff *et al.* reported no meaningful superiority of CO₂ laser therapy over sham treatment [33], and Mension *et al.* demonstrated similar findings in breast cancer survivors [34]. Segnanfredo *et al.* reported improvements with CO₂ laser, radiofrequency, and promestriene [35], although the mixed-modality design limits interpretation. As such, energy-based treatments appear promising but remain investigational, with insufficient placebo-controlled evidence to support routine clinical use. Cutaneous and adnexal manifestations, including xerosis, pruritus, reduced dermal elasticity, brittle nails, and female-pattern hair loss, were consistently noted in dermatology-focused studies [24-26]. High-frequency ultrasound findings by Czajkowska *et al.* demonstrated reductions in dermal thickness and collagen echogenicity [36], while Pagac *et al.* showed distinct facial microbiome patterns in postmenopausal women [37]. These results reinforce the broader systemic involvement of estrogen-deficient tissues, though the observational nature of most dermatologic studies limits causal interpretation. Potential publication bias cannot be excluded, particularly for device-based interventions and industry-supported hormonal trials. A funnel plot was not feasible due to the absence of meta-analysis and the small number of randomized trials. Still, qualitative assessment suggested that small, positive trials may be more visible in the literature. Narrative sensitivity checks were performed by down-weighting high-risk studies, such as Campos *et al.* [20] and considering cohort-specific variability (Peru [18], Pakistan [19], Italy [16]). These adjustments did not materially change the conclusions: evidence supporting

local estrogen therapy is consistent and robust, whereas evidence for device-based therapies remains limited and uncertain. Future research should prioritize long-term comparative trials, standardized imaging biomarkers, and safe non-hormonal alternatives, which may broaden treatment accessibility and strengthen confidence in therapeutic decisions.

CONCLUSIONS

This review demonstrates that estrogen deficiency is consistently associated with structural and symptomatic changes involving the genital tract, skin, and adnexal structures in postmenopausal women. Across controlled trials, local estrogen therapy remains the most effective first-line option, providing improvements in epithelial maturation, lubrication, dyspareunia, and overall symptom burden. Device-based therapies are emerging, but current evidence is insufficient to support their routine use, particularly in the absence of robust placebo-controlled trials. Understanding menopause-related tissue changes as a multisystem process underscores the need for timely assessment, individualized management, and sensitive, culturally informed counselling.

Authors Contribution

Conceptualization: AM

Methodology: AM, SS

Formal analysis: SS

Writing review and editing: AM, UN, MUJ, MAJ, MB

All authors have read and agreed to the published version of the manuscript

Conflicts of Interest

All the authors declare no conflict of interest.

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REFERENCES

- [1] Lephart ED and Naftolin F. Menopause and the Skin: Old Favorites and New Innovations in Cosmeceuticals for Estrogen-Deficient Skin. *Dermatology and Therapy*. 2021 Feb; 11(1): 53-69. doi: 10.1007/s13555-020-00468-7.
- [2] Abdalla ZA, Elabbas SF, Saeed L, ME EE, Mohamed HE. The Effect of Topical Estrogen in Skin Aging Process in Estrogen Deficiency Skin. *Clinical Research and Clinical Trials*. 2024; 9(6). doi: 10.31579/2693-4779/182.
- [3] Pérez-López FR, Vieira-Baptista P, Phillips N, Cohen-Sacher B, Fialho SC, Stockdale CK. Clinical Manifestations and Evaluation of Postmenopausal Vulvovaginal Atrophy. *Gynecological Endocrinology*. 2021 Aug; 37(8): 740-5. doi: 10.1080/09513590.2021.1931100.
- [4] Lephart ED. Bioactives for Estrogen-Deficient Skin: Topical and Oral Supplement Clinical Studies. A Narrative Review. *Dermatology and Therapy*. 2025 May: 1-23. doi: 10.1007/s13555-025-01413-2.
- [5] Cucinella L, Tiranini L, Cassani C, Martini E, Cumetti A, Memoli S et al. Insights into the Vulvar Component of the Genitourinary Syndrome of Menopause (GSM). *Maturitas*. 2024 Aug; 186: 108006. doi: 10.1016/j.maturitas.2024.108006.
- [6] Lephart ED and Naftolin F. Factors Influencing Skin Aging and the Important Role of Estrogens and Selective Estrogen Receptor Modulators (Serms). *Clinical, Cosmetic and Investigational Dermatology*. 2022 Dec: 1695-709. doi: 10.2147/CCID.S333663.
- [7] Melody KT, Kendall AC, Wray JR, Foster AR, Langton AK, Costello P et al. Influence of Menopause and Hormone Replacement Therapy on Epidermal Ageing and Skin Biomechanical Function. *Journal of the European Academy of Dermatology and Venereology*. 2022 Mar; 36(7): e576. doi: 10.1111/jdv.18071.
- [8] Meng Y, Feng L, Shan J, Yuan Z, Jin L. Application of High-Frequency Ultrasound to Assess Facial Skin Thickness in Association with Gender, Age, and BMI In Healthy Adults. *BioMed Central Medical Imaging*. 2022 Jun; 22(1): 113. doi: 10.1186/s12880-022-00839-w.
- [9] Artar G, Tas B, Turan G, Uckan HH. Evaluation of Androgen-Dependent Skin Findings of Polycystic Ovary Syndrome (PCOS). *Gynecological Endocrinology*. 2022 Dec; 38(12): 1104-8. doi: 10.1080/09513590.2022.2162496.
- [10] Constantine GD, Simon JA, Pickar JH, Archer DF, Kushner H, Bernick B et al. The REJOICE Trial: A Phase 3 Randomized, Controlled Trial Evaluating the Safety and Efficacy of A Novel Vaginal Estradiol Soft-Gel Capsule for Symptomatic Vulvar and Vaginal Atrophy. *Menopause*. 2017 Apr; 24(4): 409-16. doi: 10.1097/GME.0000000000000786.
- [11] Archer DF, Kimble TD, Lin FY, Battucci S, Sniukiene V, Liu JH. A Randomized, Multicenter, Double-Blind, Study to Evaluate the Safety and Efficacy of Estradiol Vaginal Cream 0.003% in Postmenopausal Women with Vaginal Dryness as the Most Bothersome Symptom. *Journal of Women's Health*. 2018 Mar; 27(3): 231-7. doi: 10.1089/jwh.2017.6515.
- [12] 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 Feb; 25(2): 133-8. doi: 10.1097/GME.

- 0000000000000985.
- [13] Archer DF, Goldstein SR, Simon JA, Waldbaum AS, Sussman SA, Altomare C et al. Efficacy and Safety of Ospemifene in Postmenopausal Women with Moderate-To-Severe Vaginal Dryness: A Phase 3, Randomized, Double-Blind, Placebo-Controlled, Multicenter Trial. *Menopause*. 2019 Jun; 26(6): 611-21. doi: 10.1097/GME.0000000000001292.
 - [14] Simon JA, Kagan R, Archer DF, Constantine GD, Bernick B, Graham S et al. TX-004HR Clinically Improves Symptoms of Vulvar and Vaginal Atrophy in Postmenopausal Women. *Climacteric*. 2019 Jul; 22(4): 412-8. doi: 10.1080/13697137.2019.1577379.
 - [15] Moral E, Delgado JL, Carmona F, Caballero B, Guillán C, González PM et al. The Impact of Genitourinary Syndrome of Menopause on Well-Being, Functioning, and Quality of Life in Postmenopausal Women. *Menopause*. 2018 Dec; 25(12): 1418-23. doi: 10.1097/GME.0000000000001148.
 - [16] Nappi RE, Seracchioli R, Salvatore S, Cagnacci A, Di Paolantonio T, Busacca M et al. Impact of Vulvovaginal Atrophy of Menopause: Prevalence and Symptoms in Italian Women According to the EVES Study. *Gynecological Endocrinology*. 2019 May; 35(5): 453-9. doi: 10.1080/09513590.2018.1563883.
 - [17] Zhu Y, Wei J, Yang X, Zhu W, Zhang W. Investigation on Prevalence and Risk Factors Associated with Genitourinary Syndrome of Menopause in Middle-Aged and Older Women in Beijing Community: A Cross-Sectional Study. *BioMed Central Women's Health*. 2022 Dec; 22(1): 558. doi: 10.1186/s12905-022-02099-w.
 - [18] Kasano JP, Crespo HF, Arias RA, Alamo I. Genitourinary Syndrome in Menopause: Impact of Vaginal Symptoms. *Turkish Journal of Obstetrics and Gynecology*. 2023 Mar; 20(1): 38. doi: 10.4274/tjod.galenos.2023.50449.
 - [19] Batool A, Amin N, Yazdani T, Zaheer F. Impact of Genitourinary Syndrome of Menopause on Wellbeing, Functioning and Quality of Life in Postmenopausal Women: A Cross-Sectional Survey. *Pakistan Armed Forces Medical Journal*. 2024 Feb; 74(1). doi: 10.51253/pafmj.v74i1.5402.
 - [20] Campos ML, Bianchi-Ferraro AM, de Oliveira CD, Nogueira MC, Sartori MG, Fusco I et al. Fractional CO₂ Laser, Radiofrequency and Topical Estrogen for Treating Genitourinary Syndrome of Menopause: A Pilot Study Evaluating the Vulvar Vestibule. *Medicina*. 2023 Dec; 60(1): 80. doi: 10.3390/medicina60010080.
 - [21] Ros C, Mension E, Rius M, Munmany M, De Guirior C, Espuña-Pons M et al. Assessing Vaginal Wall Thickness by Transvaginal Ultrasound in Breast Cancer Survivors: A Pilot Study. *Maturitas*. 2023 May; 171: 7-12. doi: 10.1016/j.maturitas.2023.02.001.
 - [22] Wang S, Yu RX, Fan W, Li CX, Fei WM, Li S et al. Detection of Skin Thickness and Density in Healthy Chinese People by Using High-Frequency Ultrasound. *Skin Research and Technology*. 2023 Jan; 29(1): e13219. doi: 10.1111/srt.13219.
 - [23] Duraes M, Briot N, Connesson N, Chagnon G, Payan Y, Duflos C et al. Evaluation of Breast Skin and Tissue Stiffness Using A Non-Invasive Aspiration Device and Impact of Clinical Predictors. *Clinical Anatomy*. 2024 Apr; 37(3): 329-36. doi: 10.1002/ca.24134.
 - [24] Pariath K and Nair PA. A Cross-Sectional Study on the Dermatoses in Postmenopausal Patients at A Rural-Based Tertiary Health Care Center. *Indian Journal of Dermatology*. 2019 Sep; 64(5): 360-5. doi: 10.4103/ijd.IJD_204_19.
 - [25] Pallavi UK, Sinha R, Jaykar KC, Sarkar S, Yasmeen T, Prasad D. Dermatoses in Postmenopausal Women in A Tertiary Health Care Center of Bihar: A Prospective Cross-Sectional Study. *Cureus*. 2023 Jul; 15(7). doi: 10.7759/cureus.41587.
 - [26] Chaikittisilpa S, Rattanasirisin N, Panchaprateep R, Orprayoon N, Phutrakul P, Suwan A et al. Prevalence of Female Pattern Hair Loss in Postmenopausal Women: A Cross-Sectional Study. *Menopause*. 2022 Apr; 29(4): 415-20. doi: 10.1097/GME.0000000000001927.
 - [27] Bosio S, Barba M, Vigna A, Cola A, De Vicari D, Costa C et al. A Novel Method for the Measurement of the Vaginal Wall Thickness by Transvaginal Ultrasound: A Study of Inter-and Intra-Observer Reliability. *Medicina*. 2024 Feb; 60(3): 370. doi: 10.3390/medicina60030370.
 - [28] Mahmoudian A, Zamani Z, Mohammadzadeh F, Bahri N. The Prevalence and Predictive Factors of Genitourinary Syndrome of Menopause in Postmenopausal Women: A Cross-sectional Study. *International Journal of Community-Based Nursing and Midwifery*. 2025 Mar.
 - [29] Ismail A and Bibi I. Exploring Genitourinary Syndrome of Menopause: Analysis of Prevalence, Determinants, and Health Impacts in Pakistani Women: Genitourinary Syndrome of Menopause. *Pakistan BioMedical Journal*. 2024 Feb: 16-20. doi: 10.54393/pbmj.v7i02.1035.
 - [30] Palacios S, Sánchez-Borrego R, Álvarez BS, Salcedo FL, Calvo AJ, Martín JJ et al. Impact of Vulvovaginal Atrophy Therapies on Postmenopausal Women's Quality of Life in the CRETA Study Measured by the Cervantes Scale. *Maturitas*. 2023 Jun; 172: 46-51. doi: 10.1016/j.maturitas.2023.03.007.

- [31] Archer DF, Simon JA, Portman DJ, Goldstein SR, Goldstein I. Ospemifene for the Treatment of Menopausal Vaginal Dryness, A Symptom of the Genitourinary Syndrome of Menopause. *Expert Review of Endocrinology and Metabolism*. 2019 Sep; 14(5): 301-14. doi: 10.1080/17446651.2019.1657008.
- [32] Srinivasan S, Hua X, Wu MC, Proll S, Valint DJ, Reed SD *et al*. Impact of Topical Interventions on the Vaginal Microbiota and Metabolome in Postmenopausal Women: A Secondary Analysis of A Randomized Clinical Trial. *Journal of the American Medical Association Network Open*. 2022 Mar; 5(3): e225032-. doi: 10.1001/jamanetworkopen.2022.5032.
- [33] Cruff J and Khandwala S. A Double-Blind Randomized Sham-Controlled Trial to Evaluate the Efficacy of Fractional Carbon Dioxide Laser Therapy on Genitourinary Syndrome of Menopause. *The Journal of Sexual Medicine*. 2021 Apr; 18(4): 761-9. doi: 10.1016/j.jsxm.2021.01.188.
- [34] Mension E, Alonso I, Anglès-Acedo S, Ros C, Otero J, Villarino Á *et al*. Effect of Fractional Carbon Dioxide Vs Sham Laser on Sexual Function in Survivors of Breast Cancer Receiving Aromatase Inhibitors for Genitourinary Syndrome of Menopause: The LIGHT Randomized Clinical Trial. *Journal of the American Medical Association Network Open*. 2023 Feb; 6(2): e2255697-. doi: 10.1001/jamanetworkopen.2022.55697.
- [35] Seganfredo IB, Bianchi C, Tacla M, Chedraui P, Haddad JM, Simoes R *et al*. Comparison of Promestriene with Vaginal Fractional CO2 Laser and Radiofrequency Treatments of Genitourinary Syndrome of Menopause. *Maturitas*. 2024 Aug; 186: 108008. doi: 10.1016/j.maturitas.2024.108008.
- [36] Czajkowska J, Juszczuk J, Bugdol MN, Glenc-Ambroży M, Polak A, Piejko L *et al*. High-Frequency Ultrasound in Anti-Aging Skin Therapy Monitoring. *Scientific Reports*. 2023 Oct; 13(1): 17799. doi: 10.1038/s41598-023-45126-y.
- [37] Pagac MP, Stalder M, Campiche R. Menopause and Facial Skin Microbiomes: A Pilot Study Revealing Novel Insights into Their Relationship. *Frontiers in Aging*. 2024 Mar; 5: 1353082. doi: 10.3389/fragi.2024.1353082.