(International Print/Online Journal)

SJIF IMPACT FACTOR: 6.829
PUBMED-National Library of Medicine ID-101739732

ISSN (Print): 2209-2870
ISSN (Online): 2209-2862

International Journal of Medical Science and Current Research (IJMSCR)
Available online at: www.ijmscr.com
Volume 9, Issue 2 , Page No: 402-408
March-April 2026

IJMSCR

Comparison of Local Versus Oral Estrogen Therapy in Postmenopausal Women with Vulvovaginal Atrophy: A Randomized Controlled Trial

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Type of Publication: Original Research Paper
Conflicts of Interest: Nil

Abstract

Introduction: Vulvovaginal atrophy (VVA), now encompassed within the genitourinary syndrome of menopause, is a common but underreported consequence of estrogen deficiency in postmenopausal women, leading to vaginal dryness, dyspareunia, irritation and urinary complaints, with significant impact on quality of life. Both local and systemic estrogen are effective, but their comparative benefit–risk profile in women with predominantly VVA symptoms remains clinically relevant.

Aim: To compare the efficacy and adverse effect profile of local versus oral estrogen therapy in postmenopausal women with vulvovaginal atrophy.

Materials and Methods: Eighty postmenopausal women (40–65 years) with symptoms of VVA and biochemical confirmation of menopause were randomized into two groups (n=40 each). Group A received local estriol cream (0.625 mg) twice weekly for 6 weeks; Group B received oral conjugated estrogen 0.625 mg daily for 6 weeks. Symptoms (vaginal dryness, dyspareunia, vaginal irritation) were assessed using a 0–10 Visual Analogue Scale (VAS) at baseline, 2, 4 and 6 weeks. Adverse drug reactions (ADRs) and safety investigations (LFT, USG abdomen-pelvis, mammography) were monitored. Data were analysed using chi-square and unpaired t-tests; $p<0.05$ was considered significant.

Results: At baseline, almost all women had vaginal dryness (97.5% vs 95.0%), dyspareunia (100% vs 100%) and vaginal irritation (100% vs 100%). All symptoms improved progressively in both groups. By 6 weeks, vaginal dryness persisted in 70.0% vs 55.0%, dyspareunia in 65.0% vs 60.0%, and vaginal irritation in 75.0% vs 77.5% (local vs oral); between-group differences were not statistically significant. Mean VAS scores for dryness declined from 6.53 to 2.85 (local) and from 6.22 to 1.99 (oral; $p=0.09$ at 6 weeks). Dyspareunia scores fell from 6.13 to 2.28 vs 6.38 to 1.58 ($p=0.08$), and irritation from 5.93 to 2.10 vs 6.43 to 2.20 ($p=0.75$). Systemic ADRs were significantly more frequent with oral therapy: nausea/vomiting (12.5%), headache (12.5%) and weight gain (10.0%) (all $p<0.01$), while the local group showed only mild vaginal discharge (5.0%) and minimal vaginal bleeding (2.5%) without statistical significance.

Conclusion: Both local and oral estrogen therapies provide clinically meaningful symptomatic relief in postmenopausal vulvovaginal atrophy, with no significant difference in efficacy over 6 weeks. However, oral estrogen is associated with a higher burden of systemic adverse effects, whereas local estrogen demonstrates a more favourable safety profile. Local estrogen therapy should be preferred as the first-line option in postmenopausal women presenting predominantly with vulvovaginal symptoms.

Keywords: Vulvovaginal atrophy, genitourinary syndrome of menopause, local estrogen, oral estrogen, postmenopausal women, randomized controlled trial

Introduction

Menopause is a universal physiological transition characterised by cessation of menstruation for 12 months and a decline in ovarian estrogen production, leading to multisystemic effects involving bone, cardiovascular system, skin and urogenital tract.[1,2] The genitourinary syndrome of menopause encompasses vulvovaginal atrophy, urogenital atrophy and lower urinary tract symptoms resulting from chronic hypoestrogenism.[3,4]

Vulvovaginal atrophy (VVA) affects approximately 40–50% of postmenopausal women, though only a minority actively seek medical care.[5–7] Estrogen deficiency leads to thinning of the vaginal epithelium, loss of rugae, reduced lubrication, elevated vaginal pH and altered vaginal microbiota, culminating in symptoms such as vaginal dryness, pruritus, dyspareunia, urinary urgency, frequency and recurrent infections.[3,8–10] These symptoms significantly impair sexual function, emotional well-being and overall quality of life.

Non-hormonal therapies including lubricants and moisturisers may provide transient relief but are generally less effective than estrogen-based therapy for established VVA.[11–13] Systemic hormone therapy (HT) improves both vasomotor and genitourinary symptoms but is limited by safety concerns, particularly in women without indications beyond urogenital complaints.[14,15] Local vaginal estrogen (creams, tablets, pessaries, rings) restores vaginal epithelium, normalises pH and improves symptoms with minimal systemic absorption when used at low doses.[16–18] Current consensus statements recommend local estrogen as the preferred option when genitourinary symptoms are the sole indication for treatment.[15,19,20]

However, in routine clinical practice, oral estrogen is still frequently prescribed for postmenopausal complaints, and comparative data on symptom control and adverse effects in women with predominant VVA symptoms remain of practical interest. Against this background, the present randomized controlled trial was conducted to compare the efficacy and safety of local versus oral estrogen therapy in postmenopausal women with vulvovaginal atrophy.

Materials And Methods

A hospital-based randomized controlled trial was conducted in the Department of Obstetrics and Gynaecology, MGM Women's and Child Hospital, Kalamboli, Navi Mumbai, over a total study duration of 18 months. The study protocol was approved by the Institutional Ethics Committee. Written informed consent (English/Hindi/Marathi) was obtained from all participants prior to enrolment. Confidentiality of patient data was maintained throughout.

Postmenopausal women aged 40–65 years presenting with symptoms of vulvovaginal atrophy (vaginal dryness, dyspareunia, vaginal irritation/itching and related complaints) were screened for eligibility. Menopause was defined as amenorrhoea for more than 12 months with serum FSH >40 IU/L.

Sample size and randomization

Based on an expected prevalence of VVA symptoms of 80%, a 95% confidence level (Z=1.96), 10% margin of error and 20% allowance for non-compliance, the calculated sample size was 80. Eligible and consenting women (n=80) were enrolled and allocated alternately to:

Group A (Local ET): Local estriol cream 0.625 mg intravaginally, twice weekly for 6 weeks.

Group B (Oral ET): Oral conjugated estrogen 0.625 mg once daily for 6 weeks.

Alternate allocation was used to achieve approximate randomization without bias regarding age or baseline clinical picture.

Inclusion Criteria

1. Women aged 40–65 years.
2. Natural menopause with amenorrhoea >12 months.
3. Serum FSH >40 IU/L.
4. Presence of VVA symptoms.
5. Willingness to provide written informed consent.

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Exclusion Criteria

1. Unexplained vaginal bleeding.
2. Known breast cancer or history of hormone-sensitive malignancy.
3. Active liver disease.
4. History of stroke, transient ischaemic attack or coronary artery disease.
5. Current use of hormone replacement therapy.
6. History of thrombotic peripheral vascular disease.
7. Anticipated non-compliance or refusal to consent.

All participants underwent detailed history and clinical examination, including age at menopause, duration of amenorrhoea, obstetric history, medical and surgical comorbidities and previous hormone use. Baseline investigations included complete blood count, liver function tests, thyroid profile (T3, T4, TSH), serum calcium, serum FSH/LH/estriol, ultrasound abdomen and pelvis, bone mineral density and breast sonomammography. Dilatation and curettage with cervical punch biopsy were performed when indicated to exclude premalignant/malignant pathology.

Vaginal examination documented mucosal pallor, atrophy, loss of rugosity, presence of discharge, petechiae or ulceration and vaginal pH.

Symptomatic severity was assessed at baseline using a 0–10 Visual Analogue Scale (VAS) for:

1. Vaginal dryness
2. Dyspareunia
3. Vaginal irritation/itching

Presence/Absence Of Each Symptom Was Also Recorded.

Intervention And Follow-Up

Day 0 was defined as the start of therapy. Participants in both groups received the assigned intervention for 6 weeks. Follow-up visits were scheduled at 2, 4 and 6 weeks. At each visit, symptom presence and VAS scores were recorded, and participants were evaluated for adverse events.

Participants were specifically monitored for:

1. Local estrogen group: vaginal irritation or pruritus, discharge, vaginal bleeding, pelvic pain, breast tenderness.
2. Oral estrogen group: breast tenderness, nausea/vomiting, bloating, abdominal cramps, headache, weight gain.

Liver function tests, ultrasound abdomen and pelvis and breast imaging were repeated at 6 weeks to assess short-term safety.

All adverse events were documented and managed as per clinical judgement. Serious or unexpected events were reported to the Institutional Ethics Committee (IEC).

Statistical analysis

Data were entered in a predesigned proforma and analysed using SPSS Version 26.0. Quantitative variables were expressed as mean ± standard deviation (SD) and compared between groups using unpaired t-test (for normally distributed data) or Mann–Whitney test (for non-normal data). Qualitative variables were expressed as frequencies and percentages, and associations between groups were tested using chi-square test. A p-value <0.05 was considered statistically significant.

Results

Eighty postmenopausal women with vulvovaginal atrophy were enrolled, with 40 allocated to local estrogen therapy and 40 to oral estrogen therapy. Baseline age and BMI were similar in both groups (Table 1). At baseline, nearly all participants reported vaginal dryness, dyspareunia and vaginal irritation, with no significant between-group differences in symptom prevalence.

Both groups demonstrated progressive reduction in symptom prevalence over the 6-week treatment period. By week 6, vaginal dryness persisted in 70.0% of women in the local group and 55.0% in the oral group. Dyspareunia persisted in 65.0% vs 60.0%, and vaginal irritation in 75.0% vs 77.5% (Table 2). None of these differences reached statistical significance.

Mean VAS scores for vaginal dryness, dyspareunia and vaginal irritation showed substantial improvement in both groups at 6 weeks (Table 3). Numerical reductions were slightly greater in the oral group, but between-group differences did not reach statistical significance.

Systemic adverse effects were predominantly observed in the oral estrogen group. Breast tenderness occurred in 5 (12.5%) women, nausea/vomiting in 5

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(12.5%), headache in 5 (12.5%), bloating in 3 (7.5%), abdominal cramps in 3 (7.5%) and weight gain in 4 (10.0%). Nausea/vomiting, headache and weight gain were significantly more frequent in the oral group ($p<0.01$).

In the local group, adverse events were limited to vaginal discharge in 2 (5.0%) women and mild vaginal bleeding in 1 (2.5%), none of which were statistically significant (Table 4). No abnormalities were detected on liver function tests, ultrasound abdomen and pelvis or breast imaging at baseline or 6 weeks in either group.

Discussion

Vulvovaginal atrophy is a chronic, progressive manifestation of estrogen deficiency and does not resolve spontaneously, in contrast to vasomotor symptoms that often regress over time.[3,4,8] In the present randomized controlled trial, both local and oral estrogen therapies provided clinically important symptomatic improvement over 6 weeks in postmenopausal women with VVA, with no statistically significant difference in efficacy between the two routes. However, the systemic side-effect burden was clearly higher with oral estrogen.

At baseline, almost all participants had vaginal dryness, dyspareunia and vaginal irritation, reflecting the high symptomatic load typical of untreated VVA.[5–7] Both groups showed progressive reduction in symptom prevalence and VAS scores, indicating that even a relatively short, 6-week course of therapy confers meaningful benefit.

Numerically, oral estrogen produced slightly greater reductions in VAS scores for dryness and dyspareunia, though between-group differences did not attain statistical significance ($p\approx0.08–0.09$). This suggests that, in women with VVA as the primary complaint, local estrogen is not inferior to oral estrogen in terms of symptom control over a short-to-medium time frame.

These findings are in agreement with previous randomized trials and meta-analyses showing that low-dose local vaginal estrogen preparations (creams, tablets, rings) are at least as effective as systemic estrogen for relief of vaginal dryness and dyspareunia, while offering lower systemic exposure.[16–18,21–23] Consensus statements from major menopause societies similarly emphasise that local estrogen therapy achieves robust symptomatic relief in the majority of women with genitourinary syndrome of menopause.[15,19,20]

A key differentiating feature in this study was the adverse event profile. The oral estrogen group experienced significant rates of systemic side effects including nausea, headache and weight gain, consistent with the known pharmacology and systemic actions of conjugated estrogen.[14,15,24] While these events were not severe, they are clinically relevant as they can impair adherence and long-term acceptability of therapy, particularly when the primary indication is localised urogenital symptoms.

In contrast, the local estrogen group demonstrated only mild, predominantly local adverse events (vaginal discharge and occasional minimal bleeding), none of which were statistically significant. No biochemical or imaging abnormalities were identified in either group during the 6-week follow-up, in keeping with reports that low-dose local estrogen has minimal impact on endometrium, liver function or breast tissue when appropriately used.[16–18,21,22]

The safety advantage of local estrogen observed in this trial supports current guideline recommendations that local vaginal estrogen be used preferentially when VVA is the sole or dominant indication, reserving systemic therapy for women who also require control of vasomotor or other systemic menopausal symptoms.[15,19,20,24]

Conclusion

Both local and oral estrogen therapy are effective in reducing vaginal dryness, dyspareunia and vaginal irritation in postmenopausal women with vulvovaginal atrophy over a 6-week treatment period. Although oral estrogen showed slightly greater numerical improvements in VAS scores, these differences were not statistically significant. In contrast, systemic adverse effects such as nausea, headache and weight gain were significantly more frequent with oral therapy, whereas local estrogen was associated only with mild and infrequent local side effects.

Given the comparable efficacy and superior safety profile, local vaginal estrogen should be prioritised as the first-line treatment for postmenopausal women with predominantly vulvovaginal atrophy symptoms,

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reserving systemic estrogen for those with additional indications for systemic hormone therapy.

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Tables

Table 1. Baseline characteristics and symptom prevalence in the two groups

Parameter	Local ET (n=40)	Oral ET (n=40)	p-value
Age (years), mean ± SD	52.08 ± 4.42	51.60 ± 4.46	0.55
BMI (kg/m²), mean ± SD	23.40 ± 4.18	23.54 ± 4.36	0.88
Baseline symptoms			
Vaginal dryness, n (%)	39 (97.5%)	38 (95.0%)	1.0
Dyspareunia, n (%)	40 (100.0%)	40 (100.0%)	–
Vaginal irritation, n (%)	40 (100.0%)	40 (100.0%)	–

Table 2. Symptom prevalence at baseline and at 6 weeks

Symptom	Time point	Local ET n (%) (n=40)	Oral ET n (%) (n=40)
Vaginal dryness	Baseline	39 (97.5%)	38 (95.0%)
	6 weeks	28 (70.0%)	22 (55.0%)
Dyspareunia	Baseline	40 (100.0%)	40 (100.0%)
	6 weeks	26 (65.0%)	24 (60.0%)
Vaginal irritation	Baseline	40 (100.0%)	40 (100.0%)
	6 weeks	30 (75.0%)	31 (77.5%)

* (Within-group reductions over time were clinically significant; between-group comparisons at 6 weeks were not statistically significant.)

Table 3. Mean VAS scores for symptoms at baseline and 6 weeks

Symptom / Time point	Group	Mean ± SD	p-value (between groups)
Vaginal dryness (VAS 0–10)			
Baseline	Local	6.53 ± 2.49	**0.54**

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Symptom / Time point	Group	Mean ± SD	p-value (between groups)
	Oral	6.22 ± 2.49	
6 weeks	Local	2.85 ± 1.70	**0.09**
	Oral	1.99 ± 1.50	
Dyspareunia (VAS 0–10)			
Baseline	Local	6.13 ± 1.34	**0.42**
	Oral	6.38 ± 1.43	
6 weeks	Local	2.28 ± 0.93	**0.08**
	Oral	1.58 ± 1.22	
Vaginal irritation (VAS 0–10)			
Baseline	Local	5.93 ± 1.75	**0.22**
	Oral	6.43 ± 1.85	
6 weeks	Local	2.10 ± 1.45	**0.75**
	Oral	2.20 ± 1.40	

Table 4. Comparison of adverse reactions between groups

Adverse reaction	Local ET (n=40)	Oral ET (n=40)	p-value
Breast tenderness	2 (5.0%)	5 (12.5%)	0.24
Nausea / vomiting	0 (0.0%)	5 (12.5%)	<0.01
Bloating	0 (0.0%)	3 (7.5%)	0.24
Abdominal cramps	0 (0.0%)	3 (7.5%)	0.24
Headache	0 (0.0%)	5 (12.5%)	<0.01
Weight gain	0 (0.0%)	4 (10.0%)	<0.01
Vaginal discharge	2 (5.0%)	0 (0.0%)	0.48
Vaginal bleeding	1 (2.5%)	0 (0.0%)	1.00

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