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Comparison of the effect of vaginal vitamin E cream with conjugated estrogen vaginal cream on vulvovaginal atrophy and overactive bladder syndrome: a randomized controlled trial

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Abstract

Objectives The present study aimed to investigate the effect of vitamin E on vulvovaginal atrophy (VVA) and overactive bladder syndrome (OABS).

Materials and methods This trial was conducted on 72 postmenopausal women referring to health centers. Participants were randomly divided into the intervention (vitamin E, vaginal cream) and control (conjugated estrogen, vaginal cream) groups. The duration of the intervention was eight weeks, as they took medicine every day in the first week and then, twice a week. The primary outcome is to compare the symptoms of VVA in the intervention and control groups, and the secondary outcome includes the comparison of the mean score of OABS, pH, vaginal health index (VHI), and side effects eight weeks after treatment.

Results The mean score of VVA in both groups improved significantly during eight-week, and the difference between the groups was not statistically significant [Adjusted mean difference (AMD): 0.63, 95% Confidence interval (CI) − 1.03–2.28, $p=0.449$]. The mean score of OABS decreased significantly in both groups, and the difference between the groups was not statistically significant [AMD: 0.261, 95% CI − 1.278–1.799, $p=0.736$]. The mean score of VHI increased significantly in both groups, and the difference between the groups was not significant [AMD: 0.64, 95% CI − 0.13–1.42, $p=0.101$].

Conclusion Vaginal vitamin E cream may be an alternative to vaginal estrogen in the symptom relief of vaginal atrophy and OABS among postmenopausal women, especially those who cannot use hormone therapy.

Keywords Atrophic vaginitis, Conjugated estrogen, Menopause, Overactive bladder, Vitamin E

1 Introduction

Vaginal atrophy is considered as the second most common complication of menopause after hot flash [1]. Several studies revealed the negative effects of vulvovaginal atrophy (VVA) on the quality of life, emotional health, self-esteem, sexual performance, body image, intimacy and relationship with spouse, and mood.

Approximately one-third of women reported that vaginal symptoms made them feel old [2]. The most common symptom of VVA is vaginal dryness (55%), followed by dyspareunia (pain during intercourse) (44%),

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and vaginal irritation (37%), affecting sexual pleasure in more than half of cases (59%) [3, 4]. In general, the symptoms of estrogen deficiency after menopause include dryness, burning, vaginal irritation, dyspareunia, bleeding after intercourse, incontinence, and frequent urinary tract infection [5].

Overactive bladder syndrome (OABS) is another issue associated with menopause. Given that estrogen and progesterone receptors are located in the trigone of the bladder and the lower urinary tract, the decrease in estrogen levels in menopause can lead to disorders of the bladder and the lower part of the urinary tract with symptoms indicating an overactive bladder (OAB) [6]. The different prevalence rate of OABS has been reported in different communities. The overall prevalence of OAB among postmenopausal women is 30.9% [7]. Almost all studies showed that the prevalence of OAB increases with age. Several demographic and clinical factors can directly cause OAB, influencing various aspects of quality of life, such as sexual function [8]. According to the widely accepted international standards for the treatment of mild and moderate manifestations of vaginal atrophy, the first-line of treatment is non-hormonal. After moisturizers and lubricants, estrogen therapy is regarded as a second-line treatment for most physicians and scientific communities. Some of the non-hormonal treatments include water-based lubricants, vaginal moisturizers, vitamin D, and vitamin E oil. Vitamin E is a fat-soluble vitamin with excellent antioxidant properties, and alpha-tocopherol is the most common and active form in human tissue and plasma [9, 10].

Considering the potential risks of menopausal systemic hormone replacement therapy, estrogen replacement therapy may not be accepted by many women [1]. The local estrogens should not be prescribed to women with a history of breast cancer, tumors, thromboembolism, and those who are sensitive to estrogen and the necessity of other treatment options should be emphasized [11].

Although vitamin E is a fat-soluble vitamin, excess alpha-tocopherols are expelled in the urine and bile, thereby reducing the accumulation of circulating alpha-tocopherols. Consequently, toxic effects are not observed in most healthy patients consuming less than 1000 mg of vitamin E per day [12, 13]. Little information is available about other potential functions of vitamin E, and the research has only been done on its antioxidant properties so far [14]. A study in Iran showed a significant decrease in vaginal pH and the improvement of vaginal atrophy symptoms in the group receiving vaginal vitamin E suppository by women with breast cancer taking tamoxifen compared to those in the placebo group [15]. In another study, the improvement of the quality of life was reported in patients with vaginal atrophy using vitamin E vaginal suppository [16].

Given the study gap about investigating the effects of vitamin E on the OABS and the opposite study results on the effect of estrogen treatment, the present study aimed to compare the impact of vitamin E with low-dose estrogen on OABS and VVA.

2 Materials and method

2.1 Study design

This triple-blind randomized controlled clinical trial (participants, researcher, and data analyzer) was conducted on 72 postmenopausal women with VVA and OABS referring to health centers of Ahar located in the northwest of Iran. The present study aimed at evaluating the effect of vitamin E vaginal cream with ultra-low dose estrogen on VVA among postmenopausal women. The hypothesis was that vitamin E vaginal cream is effective on the symptoms of VVA and OABS.

2.2 Participants

This study was conducted from June to November 2021. Participants were women with VVA and OABS. The inclusion criteria were postmenopausal women aged 45–56, having sexual activity, suffering from VVA (having 3 out of 5 symptoms), and OABS (scoring 3 or more from the overactive bladder symptom score questionnaire). Menopause following oophorectomy, vaginal bleeding, hormone therapy during the last 3 months, history of breast cancer or any type of estrogen-related cancer treated, history of breast cancer among family members (mother and sisters), and use of anticoagulants were considered as the exclusion criteria.

2.3 Recruitment, randomization, and data collection

The researcher attended the health centers and after preparing a list of eligible women covered by the center, called and invited them to participate in the study. The sampling was done from all eight health centers of Ahar city. Eligible women were precisely examined by clinical examination with a speculum and determination of vaginal pH using a paper pH meter. Participants completed questionnaires before and after the intervention, and written consent was obtained. Eligible women were assigned into the intervention (receiving vaginal vitamin E cream) and control (receiving conjugated estrogen vaginal cream) groups with a ratio of 1:1 by block randomization using Random Allocation Software with a block size of 4 and 6. The packages containing vaginal vitamin E cream and conjugated estrogen vaginal cream were placed in sequentially numbered opaque envelopes (prepared by a non-involved person in the sampling and data collection process) for the allocation concealment.

The envelopes were provided in the order in which the participants entered the study.

2.4 Data collection tool

The data were collected using the questionnaires of socio-demographic profile, symptoms of VVA, OABS, vaginal health index (VHI), and checklist of adverse events.

2.4.1 VVA questionnaire

It is a standard tool to check the symptoms of VVA and evaluate the vaginal health by measuring the symptoms of vaginal dryness, dyspareunia, itching, burning, and abnormal vaginal discharge. Items are scored on 4-point Likert scale (0 = no sign, 1 = low level of symptoms, 2 = average level of symptoms, 3 = severe level of symptoms). The total score range is between 0 and 15 [17].

2.4.2 VHI questionnaire

This instrument is used to evaluate elasticity, type and consistency of secretions, pH, epithelial mucus, and moisture. The severity of each characteristic is evaluated based on the 5-point Likert scale, ranging from 1 to 5. The total score of VHI varies from 5 to 25, and its cut-off point is less than 15, and a score less than 15 indicates atrophic vaginitis [18].

2.4.3 OABSS questionnaire

This 4-item scale was developed by Homma et al. [19] to assess the frequency of nocturia, daytime urinary frequency, sudden urge to urinate, and urinary incontinence. The scoring of item one is from 0 to 2, item two is 0–3, and item three and four are from 0 to 5. The score of each item is calculated separately, and a total score is obtained. A total score of three or more is the cut-off point for the diagnosis of OABS. The total score of 0–2 is considered for no OABS, 3–5 for mild severity, 6–11 for moderate severity, and 12 or more for severe [19]. This tool is translated by Hakimi, and its Cronbach's alpha coefficient was estimated to be 0.79 [20].

Inter-rater reliability was used to check the reliability of VHI questionnaire and vaginal symptoms. In the same vein, five participants were examined by two individuals and the questionnaire was completed. Cohen's kappa coefficient was calculated to assess the consistency of the examiners' opinions.

2.5 Intervention

The intervention group received vaginal vitamin E cream containing 100 international units of vitamin E in half of the applicator [16] and the control group received 0.3 mg of conjugated estrogen vaginal cream in half of the applicator [21].

A non-involved person in the study prepared the conjugated estrogen vaginal cream from a pharmacy, manufactured by Abidi factory, which is odorless and white color, and removed from the original tube and entered into a new tube similar to vitamin E in the formulation laboratory of the faculty of pharmacy observe the principles of blinding. Vaginal vitamin E cream is also white and odorless, which was prepared in the pharmaceutics laboratory of Tabriz University of Medical Sciences.

In the first visit, a vaginal cream was given to the participants along with the necessary instruction on how to use the cream. In the fourth week, the clients were contacted and given another tube of vaginal cream if needed. The whole treatment regimen was eight weeks. The patients were advised to use the drugs every night in the first week and twice a week for the next 7-week, and if possible side effects occur during the treatment, they should stop the intervention and return to complete the questionnaires.

2.6 Consequences

The comparison of the symptoms of VVA in the intervention and control groups eight-week after treatment is the primary outcome, and the secondary outcome includes the comparison of the mean scores of OABS, PH, VHI, and side effects.

2.7 Sample size

The sample size was calculated according to the study of Hakimi et al. using G-power software. Considering the score of symptoms of VVA, $M_1 = 7.42$, $SD_1 = 2.54$ and $M_2 = 5.9$, $SD_2 = 2.54$, $\beta = 0.2$, and $\alpha = 0.05$ assuming a 20% reduction in the score of symptoms of VVA, the sample size of 36 was obtained per group [21].

2.8 Statistical analysis

Statistical analysis was done using SPSS 18.0 (IBM Corp., Armonk, NY, USA). The normality of data distribution was assessed using Shapiro–Wilk test. Demographic characteristics between the two groups were compared using Chi-square test. The scores of VVA, VHI, and OABS were compared between the two groups before the intervention using the independent t-test and after the intervention using the ANCOVA test by adjusting the baseline score. For intra-group comparison, Wilcoxon test was used for VVA score and paired t-test was employed for VHI score.

3 Results

Initially, 300 postmenopausal women were screened for eligibility, of whom 228 (76%) women did not meet the inclusion criteria. Therefore, a total of 72 participants (36 participants in the intervention group and 36 in the

control group) completed the treatment (Fig. 1). The mean (SD) age of the participants was 54.4 (1.84), and the average duration of menopause was 4.3 (0.82) years. Table 1 indicates the socio-demographic characteristics of the participants.

The results of the ANCOVA test after adjusting the baseline values demonstrated no statistically significant difference in the scores of VVA, VHI, and OABS between the intervention and control groups after the intervention (Table 2). Based on the Wilcoxon test results, in the intra-group comparison, the mean score of VVA (SD) in the intervention group was 10.91 (1.5) before the intervention and 3.3 (3.8) after the intervention ($p < 0.001$) and in the control group was 10.5 (1.9) before the intervention and 3.9 (3.2) after the intervention ($p < 0.001$). Results of paired *t*- test showed that mean score of the VHI (SD) in the intervention group was 9.6 (2.8) before the intervention and 13.4 (2.6) after the intervention ($p < 0.001$) and in the control group was 9.8 (2.3) before the intervention and 13.6 (2.1) after the intervention ($p < 0.001$). The mean score of OABS (SD) in the intervention group was 10.33 (3.09) before the intervention and 5.38 (3.97) after the intervention and in the control group was 8.61 (1.96) before the intervention and 4.25 (3.21) after the intervention ($p < 0.001$).

Table 3 displays the frequency of the severity of OABS in the control and intervention groups. The results of the adjustment to the Mantel–Haenszel Chi-square statistics indicated no statistically significant difference between the intervention and control groups after the intervention [Odd ratio: 0.82, 95% CI 0.78–1.3]. Results of Mantel–Haenszel test demonstrated no statistical difference between two groups according to the vaginal pH after control of confounding effect (pH before intervention) (Table 3) [Odd ratio: 0.73, 95% CI 0.65–1.1].

In the control group (conjugated estrogen vaginal cream), eight subjects had abdominal pain in the first ten days of use, and three had itching immediately after use, and in the intervention group (vitamin E vaginal cream),

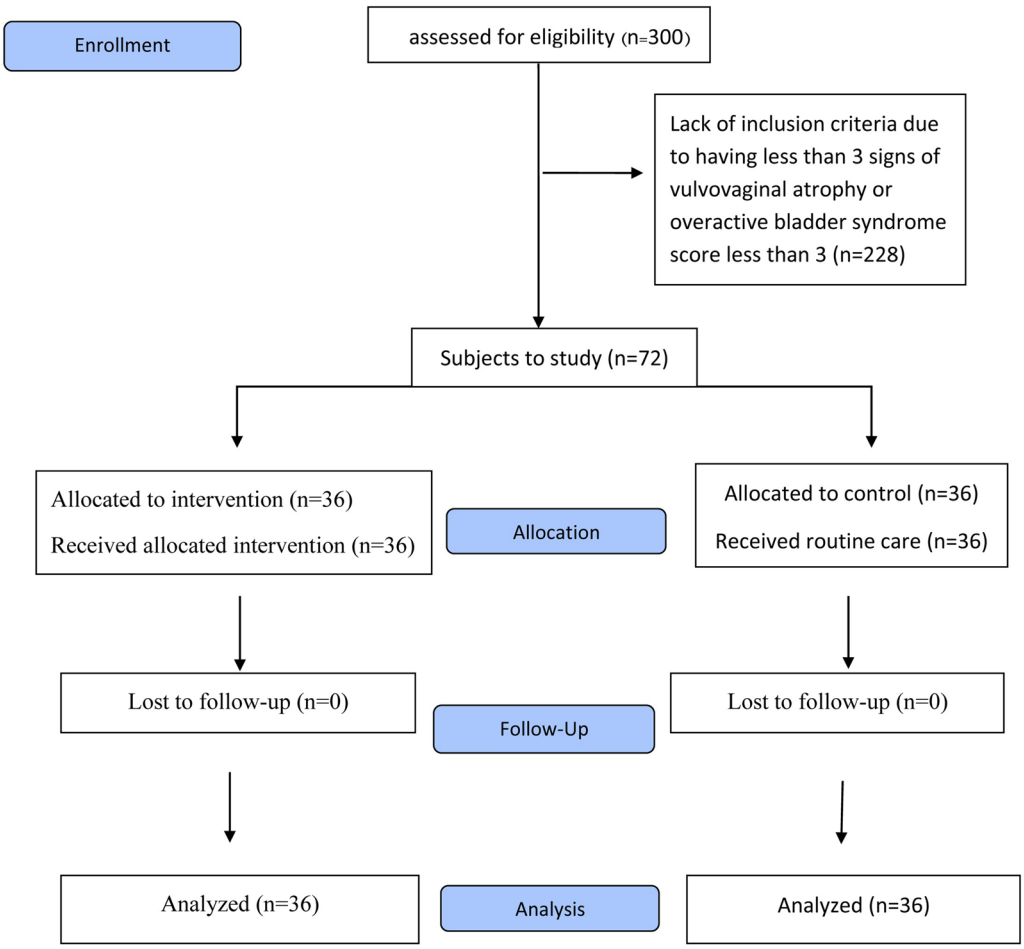

Fig. 1 Flowchart of the study

Table 1 Demographic characteristics of the samples in the study groups

Variable	Intervention $n=36$	Control $n=36$	P^a
Age (years)			0.339
50–53	12 (33.3)	10 (27.8)	
54–56	24 (66.7)	26 (72.2)	
Education			–
Illiterate/primary school	36 (100)	36 (100)	
Job			–
House wife	36 (100)	36 (100)	
Number of pregnancy (Gravid)			0.612
0–3	7 (19.4)	15 (41.7)	
4–6	19 (52.8)	17 (47.2)	
6 <	10 (27.8)	4 (11.1)	
Duration of menopause (years)			0.524
1–3	21 (58.3)	22 (61.1)	
4–5	15 (41.7)	14 (38.9)	

[a] Chi-square test

three had abdominal pain, one had mild itching, and one had mild burning. In all cases, side effects were tolerable.

4 Discussion

Overactive bladder and atrophic vaginitis have remarkable impact on menopausal women's quality of life. Menopausal women have negative feeling about urinary incontinence and vaginal dryness [22]. Based on the results, vitamin E, with the same effect as low-dose estrogen, is effective in reducing the clinical symptoms of VVA and OABS.

Vitamin E is antioxidant and anti-inflammatory and its healing properties highly influence the reduction in the vaginal infection-related symptoms, such as vaginal irritation, swelling, local redness, burning, and itching. The tissue is less irritated by reducing redness, swelling, and congestion [23]. This vitamin keeps the vessels flexible and facilitates blood circulation, and consequently, increases the metabolism of the vaginal connective tissues and enhances the moisture and flexibility of the vaginal walls [24].

Ziagham et al. [9] compared the effect of hyaluronic acid vaginal suppository with vitamin E on vaginal cell maturation index among 40 postmenopausal women in a double-blind clinical trial. They reported that hyaluronic acid and vitamin E relieved vaginal symptoms, decreased vaginal pH, and increased vaginal epithelium maturation [9]. In another study, the effect of vitamin E vaginal suppository on atrophic vaginitis of 42 postmenopausal women was assessed and finding showed a significant reduction in the symptoms of atrophy and vaginal pH [25]. Emamverdikhan et al. [24] found that the mean scores of libido, arousal, lubrication, and orgasm aspects of sexual functioning (abbreviated sexual function questionnaire) significantly increased in both vitamin E and estrogen groups in 12th week compared to the baseline and there was no significant difference between the overall score of the groups. Therefore, vaginal estrogen is not superior to vaginal vitamin E in improving the sexual function of postmenopausal women suffering from menopausal genitourinary syndrome [24]. The findings of two similar studies by Keshavarzi and Golmakani revealed the beneficial effects of vitamin E on the significant reduction in vaginal pH and improvement of the symptoms of vaginal atrophy and quality of life among postmenopausal women with vaginal atrophy [15, 16]. In the same vein, Ziaei and Carroll reported that vitamin E as a treatment can reduce hot flashes [26, 27].

Although vitamin E has been recognized as an essential nutrient since 1922, the exact mechanism of its physiological functions is still unknown [28]. Healthy adults

Table 2 Comparison of mean score of VVA and VHI and OABS between study groups

Variable	Intervention mean (SD)	Control mean (SD)	AMD (95%CI)[a]	*P*
VVA score (before intervention)	10.91 (1.5)	10.52 (1.9)	–	0.348[b]
VVA score (after intervention)	3.30 (3.8)	3.91 (3.2)	0.63 (– 1.03–2.28)	0.449[c]
VHI score (before intervention)	10.1 (4.5)	9.8 (2.6)	–	0.728[b]
VHI score (after intervention)	13.2 (0.28)	13.8 (0.28)	0.64 (– 0.13–1.42)	0.101[c]
OABSS (before intervention)	10.3 (3.0)	8.6 (1.9)	–	0.006[b]
OABSS (after intervention)	4.701 (0.50)	4.962 (0.55)	0.261 (– 1.278–1.799)	0.736[c]

The Acquired range is 0–15 for the VVA score and 5–25 for the VHI score and 0–15 for the OABSS

OABS, overactive bladder syndrome; *OABSS*, overactive bladder syndrome score; *SD*, standard deviation; *VHI*, vaginal health index; *VVA*, vulvovaginal atrophy

[a] Adjusted mean difference (95% confidence interval)

[b] Independent t-test

[c] ANCOVA test with adjusted the baseline score

Table 3 Frequency of the severity of OABS and pH in the study groups

Variable	Study groups		P^a	OR (95%CI)
OABSS	**Intervention *n* = 36 (%)**	**Control *n* = 36 (%)**		
Before intervention				
Mild (3–5)	4 (11.1)	2 (5.6)	0.001	0.82 (0.78–1.3)
Moderate(6–11)	17 (47.2)	33 (91.7)		
Severe(12 ≤)	15 (41.7)	1 (2.8)		
After intervention				
None(0–3)	9 (25.0)	12 (33.3)	0.147	
Mild (3–5)	11 (30.6)	14 (38.9)		
Moderate(6–11)	12 (33.3)	10 (27.8)		
Severe(12 ≤)	4 (11.1)	0 (0.0)		
pH				
Before intervention				
6.1	13 (36.1)	19 (52.8)	0.142	0.73 (0.65–1.1)
5.6–6	18 (50.0)	16 (44.4)		
5.1–5.5	5 (13.9)	1 (2.8)		
After intervention				
6.1	3 (8.3)	4 (11.1)	0.270	
5.6–6	24 (66.7)	21 (58.3)		
5.1–5.5	9 (25.0)	11 (30.6)		

[a] Mantel–Haenszel test with adjusting baseline value of

OABS, overactive bladder syndrome; *OR*, Odd Rati; *CI*, Confidence Interval

taking 100 mg of vitamin E daily for more than one year are likely to develop hypervitaminosis E, which manifests as decreased platelet aggregation and interference with vitamin K metabolism, resulting in the risk of bleeding. Theoretically, a high systemic dose can cause nausea, diarrhea, stomach cramps, fatigue, weakness, headache, blurred vision, skin rash, bruising, and bleeding. However, topical use of vitamin E can rarely cause contact dermatitis, erythema multiforme, and xanthomatous reaction [29].

Considering the low dose of vitamin E in the present study and its topical use, no serious systemic complications were observed among vitamin E users. However, two cases of itching and burning were observed immediately after using vitamin E, which is probably due to a slight sensitivity to vitamin E. Furthermore, abdominal pain was reported in three other cases, which was not observed in previous similar studies.

Natural estrogen and synthetic estrogen may cause some common side effects, such as breast tenderness, nausea, vomiting, bloating, stomach cramps, headache, weight gain, skin pigmentation, hair loss, vaginal itching, abnormal uterine bleeding, and anaphylaxis [30].

In a study conducted by Mitchell et al. [31] on the effectiveness of vaginal estradiol tablets or vaginal moisturizers versus placebo for the treatment of vulvovaginal symptoms after menopause, one case of burning, two cases of itching, and four cases of gastrointestinal symptoms were observed.

Considering that in the present study, eight women reported abdominal pain in the first ten days of use, this complication may be due to the systemic absorption of vaginal estrogen. Further, three cases of itching were observed among the patients**.**

4.1 Limitation

This study has a few limitation, since little study has been done on the effects of vitamin E, especially on the genitourinary system, we had to use the studies done on other vitamins and drugs in order to compare the present study with previous studies. Due to time constrains, we could not measure the long-term effects of the intervention on atrophic vaginitis and irritable bladder syndrome due to time constraints. Moreover, we could not measure the maturity index of vaginal cells and pap smear due to financial limitation.

5 Conclusion

The present study demonstrated that the use of vitamin E vaginal cream was effective in improving the symptoms of VVA and OABS, and there was no significant difference between the group receiving vitamin E vaginal cream and the group using estrogen vaginal cream. Further, vitamin E was safe in appropriate doses and has

no side effects. Accordingly, this vitamin can be considered as an appropriate substitute for conjugated estrogen, which can be recommended to patients.

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Author contributions
Research conception and design were contributed by SH, EM, and YJ. Data acquisition was contributed by NA. Statistical analysis was contributed by SH and NA. Data analysis and interpretation were contributed by SH and NA. Drafting of the manuscript was contributed by NA and SH. Critical revision of the manuscript was contributed by EM and YJ. Obtaining funding was contributed by EM and SH. Administrative, technical, or material support was contributed by YJ. Supervision was contributed by SH. Approval of the final manuscript was contributed by NA, EM, YJ, and SH.

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Availability of data and materials
The datasets used in the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate
Recruitment started after obtaining ethical approval from Ethics Committee of Tabriz University of Medical Sciences (ethics code: IR.TBZMED.REC.1400.098) and Iranian Registry of Clinical Trials (IRCT20150424021917N12). Participants completed questionnaires before and after the intervention and written consent was obtained.

Consent for publication
Not applicable.

Competing interests
The authors have no conflicts of interest relevant to this article.

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