

Comparison of Vaginal Estrogen, Hyaluronic Acid, and Oral Probiotics for the Treatment of Genitourinary Syndrome of Menopause

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Submitted: 06.07.2025
Revised: 31.07.2025
Accepted: 05.08.2025

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Keywords: Hyaluronic acid; estrogens; menopause; probiotics; vaginal atrophy.



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ABSTRACT

Objective: The objective of this study was to compare the efficacy of a non-hormonal alternatives, vaginal hyaluronic acid, oral probiotics, to a standard of care therapy, vaginal estradiol, for the treatment of genitourinary syndrome of menopause (GSM).

Methods: This prospective study was conducted in the Obstetrics and Gynecology Clinic of the Education and Research Hospital between June and September 2024. Women with GSM were assigned to hyaluronic acid vaginal ovules, estradiol vaginal tablets or oral probiotics for 8 wk. The primary outcome was the change in the Vaginal Health Index (VHI) score. Secondary outcomes included changes in the Female Sexual Distress Scale-Revised (FSDS-R) and the Menopause Rating Scale (MRS).

Results: Sixty participants (vaginal estrogen=20, vaginal HA=20, oral probiotic=20) provided data at week 8. All three treatment groups showed statistically significant improvements in VHI scores and significant reductions in FSDS-R and MRS scores from baseline to week 8 ($p<0.001$) for within-group comparisons). Changes in FSDS-R scores were similar across all three groups ($p=0.176$). No treatment-related serious adverse events occurred.

Conclusion: This study found that vaginal estradiol, vaginal hyaluronic acid, and oral probiotics led to significant improvements in vaginal health, reductions in sexual distress, and alleviation of menopausal symptoms in women with GSM. In addition, oral probiotics and vaginal hyaluronic acid may represent promising non-hormonal alternatives for the management of GSM, particularly for women who prefer to avoid hormone therapy.

INTRODUCTION

Genitourinary syndrome of menopause (GSM), is a prevalent condition affecting a substantial proportion of postmenopausal women due to the decline in estrogen levels.^[1] This estrogen deficiency leads to a cascade of changes in the vulvovaginal tissues, resulting in thinning of the vaginal epithelium, decreased vascularity, and reduced lubrication. Consequently, women experience a wide range of symptoms, such as vaginal dryness, pruritus, dyspareunia, and urinary discomfort, all of which can significantly impair their quality of life and sexual function.^[2] Despite its high prevalence and substantial impact, GSM remains underdiagnosed and undertreated in many women, highlighting the need for effective and acceptable treatment options.

Vaginal estrogen therapy is considered a well-established and highly effective first-line treatment for GSM.^[3] By directly addressing the estrogen deficiency in the vaginal tissue, topical estrogens, available in various formulations

such as creams, tablets, and rings,^[4] can effectively alleviate symptoms and improve vaginal health. However, some women may have concerns about potential systemic absorption and the long-term safety associated with hormone therapy, leading to a desire for non-hormonal alternatives.

Hyaluronic acid has emerged as a non-hormonal option for managing GSM symptoms.^[5] As a natural polysaccharide with significant water-binding capacity, hyaluronic acid can provide lubrication and hydration to the vaginal mucosa, potentially alleviating dryness and other vulvovaginal atrophy-related discomforts.^[6] While some systematic reviews suggest that hyaluronic acid has comparable efficacy to vaginal estrogens in improving certain aspects of GSM,^[7-9] others indicate that estrogen may be superior in relieving vaginal symptoms and improving objective markers of vaginal health.^[10,11] These inconsistencies highlight the need for further comparative research.

Another less conventional approach under investigation for managing GSM symptoms is the use of oral probiotics. The rationale behind this approach lies in the gut-vagina axis, suggesting that the composition of the gut microbiome can influence the vaginal microbiome.^[12] Specific strains of probiotics, particularly *Lactobacillus* species, are known to play an important role in sustaining a healthy vaginal microenvironment by producing lactic acid, which aids to lower vaginal pH and inhibit the growth of pathogenic microorganisms.^[13] While research on the efficacy of oral probiotics for GSM is still emerging, and many studies focus on vaginal probiotics for conditions like bacterial vaginosis,^[14,15] the potential for oral probiotics to positively impact the vaginal microbiome and alleviate GSM symptoms warrants further investigation.

Given the need for more comparative evidence to guide treatment decisions for postmenopausal women with GSM, this study aimed to compare the efficacy of vaginal estradiol, hyaluronic acid, and oral probiotics on vaginal health, sexual distress, and menopausal symptoms. The primary objective was to assess and compare the changes in the Vaginal Health Index (VHI) among the three treatment groups. Secondary objectives included comparing the effects on sexual distress, as measured by the Female Sexual Distress Scale-Revised (FSDS-R), and overall menopausal symptoms, as assessed by the Menopause Rating Scale (MRS).

MATERIALS AND METHODS

Study Design, Setting, and Ethical Approval

This prospective study was conducted in the Obstetrics and Gynecology Clinic of the Education and Research Hospital. Before starting the research, ethical permission was obtained from the Ethics Committee of the hospital (Approval No: 2023/514/256/23, Date: 28 August 2023). The study adheres to the tenets of Declaration of Helsinki. Patient recruitment and data collection took place between June 1 and September 1, 2024.

Participant Recruitment and Informed Consent

Postmenopausal women who visited the gynecology outpatient clinic reporting symptoms of vaginal dryness, itching, burning, or dyspareunia were invited to participate in the study. A female healthcare provider thoroughly explained the study's purpose, methodology, potential risks, and benefits in a private consultation room. Each participant had ample opportunity to ask questions and discuss any concerns before providing written informed consent. We emphasized that participation was entirely voluntary and assured confidentiality, clarifying that all collected data would be anonymized and used exclusively for research purposes.

Inclusion and Exclusion Criteria

Inclusion criteria for participation were: Being sexually

active, having serum estradiol levels <20 pg/mL, follicle-stimulating hormone levels >40 IU/L, a negative Pap smear result within the past year, no pathological findings suggestive of malignancy on bilateral mammography, no family history of breast or endometrial cancer, absence of neurological disorders requiring treatment, no contraindications to hormone therapy (such as acute thromboembolism or a history of myocardial infarction), age between 45 and 65 years, at least 12 months of amenorrhea, and the presence of bothersome vaginal symptoms including dryness, itching, burning, and/or dyspareunia.

Exclusion criteria were: A history of breast cancer or any other type of cancer, unexplained genital bleeding, active thrombophlebitis or a history of estrogen-dependent thromboembolism, use of any form of hormone therapy within the 12 months prior to study enrollment, and the presence of an active vaginal infection.

Interventions

Eligible participants were non-randomly assigned to one of three treatment groups based on clinical assessment and patient preference. The three intervention groups were: (1) Vaginal estradiol group (n=20) received estradiol vaginal tablets (Vagifem 25 mg, Novo Nordisk). The treatment regimen consisted of one vaginal tablet administered daily for the first two weeks, followed by a maintenance dose of one tablet administered twice weekly for the remaining six weeks. (2) Hyaluronic acid group (n=20) received hyaluronic acid vaginal ovules (Cicatridina, Farma-Derma). Participants were instructed to insert one vaginal ovule daily for the entire duration of the 8-week treatment period. (3) Oral probiotic group (n=20) received one oral probiotic capsule daily (Evo probiyotik kapsül, Evopharm). Each capsule contained a blend of *Lactobacillus acidophilus* (1x10⁹ CFU), *Bifidobacterium longum* (1x10⁹ CFU), *Streptococcus thermophilus* (1x10⁹ CFU), *Lactobacillus bulgaricus* (1x10⁹ CFU), *Lactobacillus rhamnosus* (1x10⁹ CFU), and 50 mg of inulin. This specific combination of probiotic strains was chosen based on evidence suggesting their potential to positively influence the vaginal microbiome by promoting the growth of beneficial *Lactobacillus* species and contributing to a lower vaginal pH, which inhibits the proliferation of pathogens.^[12] Inulin was included as a prebiotic to further support the growth and activity of the probiotic bacteria.

Participants were provided with detailed instructions on how to use their assigned treatment and were encouraged to adhere to the prescribed regimen for the entire 8-week study period. They were also instructed not to use any other vaginal treatments or hormone therapies during the study.

Outcomes

The primary endpoint of this study was the difference in VHI scores between baseline and the 8-week follow-up assessment after treatment initiation. The VHI is a clinical assessment tool used to evaluate vaginal wellness based

on five parameters: Mucosal thickness, moisture, pH level, elasticity, and epithelial integrity. Each parameter is graded on a scale from 1 (worst condition) to 5 (best condition), resulting in a total score ranging from 5 to 25. A total VHI score of 15 or less is generally considered indicative of vaginal atrophy.^[15] The VHI was assessed through clinical inspection by the same experienced gynecologist at both baseline and week 8.

Secondary endpoints included changes in sexual distress and menopausal symptoms, evaluated using two validated instruments: We assessed sexual distress using the Turkish version of the FSDS-R, a 13-item questionnaire measuring distress related to sexual dysfunction. Participants rated each item on a 5-point Likert scale (0="never" to 4="always"), with total scores ranging from 0-52. A cut-off score of ≥ 11 indicated clinically significant sexual distress.^[16] Participants completed the FSDS-R at baseline and week 8. Menopausal symptom severity was evaluated using the MRS questionnaire, which comprises 11 items across three domains: Somatic (hot flushes, heart discomfort, sleep problems), psychological (depressive mood, irritability, anxiety), and urogenital (sexual problems, bladder problems, vaginal dryness). Each item is scored from 0 (asymptomatic) to 4 (extremely severe), yielding a total score range of 0-44, where higher scores reflect greater symptom burden.^[17] Participants completed the MRS at baseline and week 8.

Endometrial thickness was assessed using transvaginal ul-

trasonography with a 6.5 MHz vaginal endoprobe (Voluson PRO 730, General Electrics®, USA) at baseline and week 8.

Demographic and clinical characteristics, including age, gravidity, parity, body mass index (BMI), age at menopause, duration of menopause, history of surgical menopause, comorbidities, were recorded at the baseline visit through patient interviews and review of medical records.

Data Collection Procedures

Data were collected at two time points: At the initial visit (baseline) before the start of the treatment and after eight weeks of treatment. At both visits, a thorough gynecological examination and the assessment of the endometrial thickness via transvaginal ultrasound were performed. Then, participants were asked to complete the VHI, FSDS-R and MRS questionnaires.

Sample size

Sample size of the study was determined using the G Power 3.1 based on established literature.^[18] A 90% statistical power ($1-\beta$) was considered at the 0.05 (α) significance level, and the two-way ANOVA was used for medium effect size. The required sample size was computed to be 45 subjects, with 15 patients per group. However, to account for potential attrition during the follow-up period, 20 patients were recruited for each group, yielding a total of 60 participants.

Table 1. Baseline characteristics

Characteristic	Hyaluronic Acid (n=20)	Probiotic (n=20)	Estradiol (n=20)	p-value
Age (years), Mean $\pm$ SD	54.8 $\pm$ 6.6	54.6 $\pm$ 6.5	53.4 $\pm$ 4.4	0.724
BMI (kg/m ²), Mean $\pm$ SD	27.7 $\pm$ 5.1	28.7 $\pm$ 4.4	31.8 $\pm$ 4.3	0.019
Parity (median, IQR)	3 (1-6)	3 (1-5)	3 (1-6)	0.658
Mode of Delivery (CS delivery, n (%))	2 (10.0)	2 (10.0)	1 (5.0)	0.804
Married, n (%)	19 (95.0)	19 (95.0)	20 (100.0)	0.596
Education Level (n (%))			0.857	
Primary	6 (30.0)	4 (20.0)	3 (15.0)	
Secondary	5 (25.0)	6 (30.0)	6 (30.0)	
High School	1 (5.0)	1 (5.0)	9 (45.0)	
University	6 (30.0)	9 (45.0)	2 (10.0)	
Place of Residence, n (%)			0.733	
Village	3 (15.0)	4 (20.0)	4 (20.0)	
Town	2 (10.0)	1 (5.0)	2 (10.0)	
District	6 (30.0)	2 (10.0)	6 (30.0)	
City	9 (45.0)	12 (60.0)	7 (35.0)	
Abroad	0 (0.0)	1 (5.0)	1 (5.0)	
Menopause Age (years), Mean $\pm$ SD	48.1 $\pm$ 2.9	48.8 $\pm$ 3.0	47.6 $\pm$ 3.4	0.465
Menopause Duration (years), Mean $\pm$ SD	6.7 $\pm$ 5.1	5.9 $\pm$ 5.1	5.8 $\pm$ 3.5	0.789
Surgical Menopause (n (%))	1 (5.0)	1 (5.0)	1 (5.0)	0.596
Endometrial Thickness (mm), Mean $\pm$ SD	4.8 $\pm$ 0.9	4.8 $\pm$ 0.8	5.0 $\pm$ 0.7	0.813

* p<0.05 considered statistically significant.

Table 1. Demographic and characteristic features of the patients

Scale	Time	Hyaluronic Acid (n=20) Mean±SD	Probiotic (n=20) Mean±SD	Estradiol (n=20) Mean±SD	p-value [*]
VHI	Baseline	11.40±3.45	12.10±3.06	12.10±2.44	0.700
	Week 8	15.20±3.62	18.25±2.82	19.80±1.12	0.001
	Change	3.80±1.11	6.15±1.56	7.70±1.38	0.001
p-value ^o		0.001	0.001	0.001	
FSDS-R	Baseline	54.45±9.54	56.30±8.46	52.95±9.18	0.508
	Week 8	44.45±7.92	43.70±7.12	41.70±7.40	0.491
	Change	-10.00±4.03	-12.60±4.83	-11.25±4.40	0.176
p-value ^o		0.001	0.001	0.001	
MRS	Baseline	34.60±6.32	39.45±4.67	40.15±4.25	0.002
	Week 8	25.15±5.63	24.85±4.67	26.55±4.50	0.516
	Change	-9.45±1.82	-14.60±2.60	-13.60±2.39	0.001
p-value ^o		0.001	0.001	0.001	

VHI: Vaginal Health Index; FSDS-R: Female Sexual Distress Scale-R; MRS: Menopause Rating Scale. ^{*}: comparison between groups, ^o: comparison within groups. *p<0.05 considered statistically significant.

Statistical Analysis

Analyses were performed using SPSS version 22.0 (IBM Corp., Armonk, NY, USA). Continuous variables are reported as mean±SD; categorical variables as n (%). Normality was assessed via Shapiro-Wilk tests with Q-Q plot verification. Baseline characteristics were compared using ANOVA (continuous) or χ^2 tests (categorical). Within-group changes (baseline to week 8) were evaluated with paired t-tests (normal) or Wilcoxon signed-rank tests (non-normal). Between-group differences at week 8 were analyzed using ANOVA or Kruskal-Wallis tests, with Bonferroni-corrected post hoc tests for significant findings. The level of statistical significance was set at p<0.05.

RESULTS

Demographic Characteristics

Table 1 shows the sociodemographic and baseline clinical characteristics of the participants in the three treatment groups. No statistically significant differences were found between the groups regarding age, parity, mode of delivery, marital status, education level, place of residence, age at menopause, duration of menopause, history of surgical menopause, or baseline endometrial thickness. However, a significant difference was found in baseline body mass index (p=0.019), with the vaginal estradiol group having a significantly higher mean weight and BMI compared to the vaginal hyaluronic acid and oral probiotic.

Comparison of Scale Scores

As presented in Table 2, all three treatment groups showed clinically and statistically significant improvements in vaginal health, as measured by VHI scores, from baseline to the 8-week follow-up (p<0.001 for each within-

group comparison). The complete descriptive statistics and comparative results for VHI, FSDS-R, and MRS scores at both assessment points are detailed for each treatment arm. The magnitude of this increase was significantly different between the groups (p<0.001 for between-group comparison of change scores). Post-hoc analysis revealed that the improvement in VHI was significantly lower in the hyaluronic acid group (mean change=3.80±1.11) compared to both the probiotic group (mean change=6.15±1.56, p=0.001) and the estradiol group (mean change=7.70±1.38, p<0.001).

All three groups showed a statistically significant decrease in FSDS-R scores from baseline to week 8 (p<0.001 for all within-group comparisons), indicating a reduction in sexual distress. No statistically significant difference was observed in the magnitude of this reduction between the three groups (p=0.176 for between-group comparison of change scores).

All three groups also exhibited a statistically significant decrease in MRS scores from baseline to week 8 (p<0.001 for all within-group comparisons), indicating an improvement in overall menopausal symptoms. The magnitude of this reduction significantly differed between the groups (p<0.001 for between-group comparison of change scores). Post-hoc analysis showed that the reduction in MRS scores was significantly smaller in the hyaluronic acid group (mean change=-9.45±1.82) compared to both the probiotic group (mean change=-14.60±2.60, p<0.001) and the estradiol group (mean change=-13.60±2.39, p<0.001).

DISCUSSION

This prospective study investigated the comparative effectiveness of vaginal estradiol, hyaluronic acid vaginal ovules,

and oral probiotics in treating postmenopausal women with symptoms of GSM. The findings of this study indicate that all three interventions resulted in significant improvements in vaginal health, as measured by the VHI, and significant reductions in both sexual distress, assessed by the FSDS-R, and overall menopausal symptoms, evaluated by the MRS.

A key finding of this study was the significantly lower improvement in VHI scores observed in the hyaluronic acid group compared to the vaginal estradiol group. This suggests that while hyaluronic acid provided some benefit in improving objective markers of vaginal health, its efficacy in this regard may be less pronounced than that of topical estrogen used in this study. This finding contrasts with some systematic reviews that have reported comparable efficacy between hyaluronic acid and vaginal estrogens for treating GSM.^[19-21] However, other reviews have indicated the superiority of estrogen in relieving vaginal symptoms and improving objective measures.^[22,23] The discrepancy in findings might be attributed to variations in the specific formulations and dosages of hyaluronic acid used across different studies, as well as the characteristics of the study populations.

Interestingly, the oral probiotic group demonstrated comparable efficacy to the topical estradiol group in improving VHI scores and reducing FSDS-R and MRS scores. This is a novel and potentially significant finding, as the use of oral probiotics for managing GSM symptoms is a less established approach compared to topical hormone therapy. While much of the research on probiotics in vaginal health has focused on the use of vaginal probiotics for conditions like bacterial vaginosis,^[24] the comparable efficacy observed in this study suggests that specific strains of oral probiotics may exert a positive influence on the vaginal environment, possibly through the gut-vagina axis.^[25] The *Lactobacillus* species included in the probiotic formulation are known to contribute to a healthy vaginal microbiome by producing lactic acid, which lowers vaginal pH and inhibits the growth of pathogens.^[26] Further research is needed to elucidate the specific mechanisms by which oral probiotics may alleviate GSM symptoms and to identify the most effective strains and dosages.

The clinical implications of these findings are noteworthy. Vaginal estradiol, as standard-of-care therapy, effectively improved VHI scores and reduced menopausal symptoms and sexual distress, which is consistent with the well-established efficacy of topical estrogen therapy for GSM.^[27] The comparable efficacy of oral probiotics to topical estradiol in improving VHI and reducing menopausal symptoms suggests that oral probiotics may represent a viable non-hormonal alternative for managing GSM, particularly for women who prefer to avoid hormone therapy or have contraindications to its use.^[20] As hyaluronic acid has shown benefit in improving VHI, it may also be an effective option to improve the objective signs of vaginal atrophy in this specific population.^[28]

This study has several strengths, including its prospective

design, the use of validated outcome measures to assess multiple relevant domains (vaginal health, sexual distress, and menopausal symptoms), the direct comparison of three relevant treatment modalities, and the comprehensive data collection at baseline and after the intervention period. However, the study also has some limitations that should be considered when interpreting the findings. The relatively small sample size may limit the generalizability of the results. The short duration of the intervention (8 weeks) may not be sufficient to fully capture the long-term effects of these treatments. The single-center design also restricts the generalizability of the findings to other populations and settings. The baseline difference in BMI between the estradiol group and the other two groups could potentially have influenced the results, although correlation analysis did not reveal a significant relationship between BMI and treatment response. The lack of randomization and blinding of participants and investigators to the treatment assignments could also introduce bias in the subjective outcome measures. Furthermore, the specific strains and dosage of the oral probiotic used in this study may not be representative of all available probiotic formulations, and the findings may not be generalizable to other probiotic products.

This study highlights several important avenues for subsequent investigation. First, methodological enhancements should include larger-scale randomized controlled trials with adequate statistical power, extended follow-up periods to evaluate treatment durability, and multi-center designs to enhance generalizability.

Conclusion

In conclusion, this study found that vaginal estradiol, vaginal hyaluronic acid, and oral probiotics led to significant improvements in vaginal health, reductions in sexual distress, and alleviation of menopausal symptoms in postmenopausal women experiencing GSM. These findings suggest that oral probiotics and vaginal hyaluronic acid may represent promising non-hormonal alternatives for the management of GSM, particularly for women who prefer to avoid hormone therapy.

Ethics Committee Approval

The study was approved by the Kartal City Hospital Ethics Committee (Date: 28.08.2023, Decision No: 2023/514/256/23).

Peer-review

Externally peer-reviewed.

Authorship Contributions

Concept: E.M., İ.B., E.K.; Design: E.M., İ.B.; Supervision: E.M., E.K.; Fundings: E.M., İ.B., E.K.; Materials: E.M., İ.B., E.K.; Data collection &/or processing: İ.B., E.K.; Analysis and/or interpretation: E.M., İ.B., E.K.; Literature search: E.M., E.K.; Writing: E.M., İ.B., E.K.; Critical review: İ.B., E.K.

Conflict of Interest

None declared.

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Menopozal Genitoüriner Sendrom Tedavisinde Vajinal Östrojen, Hiyalüronik Asit ve Oral Probiyotiklerin Karşılaştırılması

Amaç: Bu çalışmanın amacı, menopozal genitoüriner sendromun (GÜSM) tedavisinde standart tedavi yöntemi olan vajinal östradiol ile hormonal olmayan alternatifler olan vajinal hiyalüronik asit ve oral probiyotiklerin etkinliğini karşılaştırmaktır.

Gereç ve Yöntem: Bu prospektif çalışma, Haziran-Eylül 2024 tarihleri arasında Kartal Dr. Lütfi Kırdar Şehir Hastanesi'nde yürütüldü. GÜSM tanısı konulan kadınlar, sekiz hafta süreyle vajinal hiyalüronik asit ovülleri, vajinal östradiol tabletleri veya oral probiyotik tedavisine randomize edildi. Birincil sonuç ölçütü, Vajinal Sağlık İndeksi (Vaginal Health Index, VHI) skorundaki değişimdi. İkincil sonuç ölçütleri arasında Kadın Cinsel Sıkıntı Ölçeği-Gözden Geçirilmiş (Female Sexual Distress Scale-Revised, FSDS-R) ve Menopoz Değerlendirme Ölçeği (Menopause Rating Scale, MRS) skorlarındaki değişiklikler yer aldı.

Bulgular: Çalışmaya toplam 60 katılımcı (vajinal östrojen=20, vajinal hiyalüronik asit=20, oral probiyotik=20) sekizinci haftada veri sağladı. Üç tedavi grubunun tamamında VHI skorlarında anlamlı iyileşmeler ve FSDS-R ile MRS skorlarında başlangıça kıyasla anlamlı azalmalar gözlemlendi (grup içi karşılaştırmalarda $p<0.001$). FSDS-R skorlarındaki değişim açısından gruplar arasında anlamlı fark saptanmadı ($p=0.176$). Tedaviye bağlı ciddi advers olay bildirilmedi.

Sonuç: Bu çalışma, vajinal östradiol, vajinal hiyalüronik asit ve oral probiyotiklerin GÜSM'li kadınlarda vajinal sağlıkta belirgin iyileşme, cinsel sıkıntıda azalma ve menopozal semptomların hafiflemesinde etkili olduğunu göstermiştir. Ayrıca, oral probiyotikler ve vajinal hiyalüronik asit, özellikle hormon tedavisinden kaçınmak isteyen kadınlar için umut vaat eden hormonal olmayan tedavi seçenekleri olabilir.

Anahtar Sözcükler: Hiyalüronik asit; menopoz; östrojenler; probiyotikler; vajinal atrofi.