

Abstrakt

Objective:

The aim of this study was to investigate the effects of oral probiotic use on postmenopausal vaginal health and to compare these effects with hyaluronic acid and estrogen use. postmenopausal vaginal atrophy is a common health problem that negatively affects women's quality of life. This condition manifests itself with symptoms such as vaginal dryness, itching, burning, dyspareunia and decreased sexual desire and affects the daily lives of patients in many ways. Although estrogen-based hormone therapies are frequently used in current treatment methods, these treatments may be contraindicated for many patients or hormone use may not be preferred due to personal preferences. Therefore, there is a need for alternative non-hormonal treatment modalities. Recent studies have shown that probiotics, which improve local vaginal health by regulating vaginal flora balance, have potential as a non-hormonal treatment option. In this study, the efficacy of oral probiotics was evaluated and compared with hyaluronic acid and estrogen treatments.

Method:

A total of 60 women experiencing postmenopausal vaginal symptoms were included in this randomized controlled trial. Participants were randomly divided into three groups: hyaluronic acid group (n=20), probiotic group (n=20) and estrogen group (n=20). Each patient received the treatment for 8 weeks. Vaginal health status of the patients before and after treatment was evaluated using the Vaginal Health Index (VHI), menopausal symptoms assessment scale and female sexual distress scale. Possible side effects were monitored at regular intervals throughout the study. The data obtained were evaluated using SPSS 25.0 statistical analysis program and the differences between groups were analyzed by significance test.

Results:

A statistically significant increase in Vaginal Health Index (VHI) scores was observed in all groups at the end of treatment ($p < 0.001$). The most significant increase occurred in the estrogen and probiotic groups, respectively. The probiotic group, which gave similar results to the group using estrogen, showed that it could be an effective treatment method in regulating vaginal health. In the hyaluronic acid group, statistically significant but limited improvement occurred compared to the other groups. According to the results of the menopausal symptoms assessment scale, there was a significant decrease in the severity of symptoms in all groups. Especially vaginal dryness and itching symptoms showed a significant decrease in the probiotic group ($p < 0.01$). In terms of side effects, mild nausea was reported in 1 participant in the estrogen group, but no serious side effects were observed in the probiotic group.

Conclusion:

This study shows that oral probiotic use offers an effective and safe non-hormonal treatment option for the treatment of postmenopausal vaginal symptoms. Especially for breast cancer patients who cannot receive hormone therapy or for women who do not want to use hormones, probiotics may constitute an important treatment alternative. In addition, the low side effect profile of probiotics was another important finding that increased the safety of use. similar clinical efficacy of probiotics compared to the other two treatment modalities strengthens the potential of this treatment alternative in the protection of vaginal health in the postmenopausal

period. More comprehensive and long-term studies will provide us with more comprehensive information about the use and efficacy of probiotics.

Keywords: Menopause, Vaginal Health, Probiotic, Hyaluronic Acid, Estrogen, Vaginal Atrophy

Introduction

Declining estrogen levels during menopause cause many physiological changes. Chief among these is vulvovaginal atrophy (VVA), followed by symptoms such as vaginal dryness, itching, burning, dyspareunia and recurrent urinary tract infections. Existing studies have found that 40-60% of postmenopausal women experience symptoms of VVA and that these symptoms negatively affect quality of life. In addition, VVA negatively affects sexual life and psychosocial well-being, affecting individuals' daily lives.

Estrogen-based therapies have been used in the treatment of VVA since the 1960s. Local estrogen therapies have been applied as more preferred treatments in patients where systemic estrogen effect is not desired. In the following periods, alternative treatment methods were started to be applied in hormone-sensitive patients such as breast cancer and in patients where estrogen activity is not desired. Especially since 1980, hyalurinic acid has been used as an alternative to estrogen in VVA treatment. Thanks to its natural water-retaining effect, hyalurinic acid has been effective in moisturizing the vaginal mucosa and anti-inflammatory effect (1). In the same study, it was stated that both estrogen and hyaluronic acid applications significantly relieved the symptoms of VVA, and estrogen was more effective on vaginal dryness. Especially in studies conducted in postmenopausal women, it has been revealed that hyaluronic acid increases elasticity by acting on the vaginal mucosa and is effective in alleviating symptoms (2).

Probiotics prevent the growth of other microorganisms by reducing vaginal pH, especially through *Lactobacillus* species. In another study on probiotics, it was revealed that probiotics may be effective in reducing vaginal symptoms, as well as having a protective effect against vaginal infections and balancing the flora, and the effectiveness of vaginal preparations containing probiotics was emphasized (3).

In a study investigating the effect of hyaluronic acid on the mucosa, multi-point intramucosal injection of hyaluronic acid was applied to the vaginal mucosa and although hyaluronic acid did not increase the thickness of the vaginal epithelium, it provided significant improvement in VVA-related symptoms by increasing collagen production (4).

On the other hand, the advantage of probiotic therapies in terms of side effect profile compared to hormonal therapies is an alternative especially for patients such as breast cancer patients who cannot use estrogen for patient groups who do not want to use hormones. In another study examining the efficacy of probiotics on vaginal mucosa, it was reported that probiotics reduced the inflammatory effect by protecting mucosal integrity and were effective in treating VVA-related symptoms in the postmenopausal period (5). In this study, we aimed to examine the effects of oral probiotic treatment on vaginal health after menopause and to compare this efficacy with vaginal hyaluronic acid and vaginal estrogen treatments.

Material and Method

The study was planned as a prospective, randomized, controlled study and was conducted with patients who applied to the Gynecology and Obstetrics clinic between 01/06/2024 and 01/09/2024 in the same hospital after the approval of the ethics committee of Kartal Dr. Lütfü Kırdar City Hospital. Participants were informed verbally and in writing about the study content while a female health worker was present in a closed environment, face-to-face and privacy conditions were observed. Patients who consented to participate were included in the study after signing the informed consent form

Before participating in the study, patients were informed about the benefits and side effects of the drug to be used and those who accepted the treatment were included in the study group. Patients who agreed to participate in the study were informed that their names would not be recorded and that their personal information and responses would not be used for purposes other than scientific purposes. The study was started with 75 patients, but was completed with 60 patients due to various reasons such as inability to reach the patients on the phone, desire to continue menopause follow-up elsewhere, discontinuation of treatment and occurrence of non-gynecologic diseases, No cost was requested from the participants during the study and all treatment materials were provided from the research budget.

Sexually active patients with serum E2 (estradiol) <20pg/ml, FSH (follicle-stimulating hormone) level >40IU, negative pap smear results, no pathological findings in favor of malignancy on bilateral mammography, no family history of breast or endometrial cancer, no neurological disease symptoms, no treatment for this reason, no conditions in which hormone therapy is contraindicated (acute thromboembolism, previous MI, etc.) were included in the study.) were included. Postmenopausal women between 45 and 65 years of age, who had been menopausal for at least 12 months, presenting to the clinic with complaints of vaginal dryness, itching, burning and dyspareunia were selected. However, patients with breast cancer or other cancer, patients with genital bleeding of unknown cause, patients with acute thrombophlebitis or a history of estrogen-dependent thromboembolism, patients taking hormone medication in the 12 months prior to treatment and patients with active vaginal infections were excluded.

Patients were randomly selected by the same nurse from a sealed bag with group numbers at each outpatient clinic and randomization was performed. The first group (n= 20) received estradiol vaginal tablets (Vagifem 1x1 25 mg/day), 1 vaginal tablet daily for 2 weeks at the beginning of treatment, and then maintenance dose was 1 vaginal tablet twice a week. The second group (n= 20) received Hyaluronic acid (Cicatridina Vaginal Ovule 1x1). Treatment was given for a total of 8 weeks. The third group (n= 20) received oral probiotics (Evo probiotic capsules orally once a day). Each tablet contained *Lactobacillus acidophilis* 1x10⁹cfu, *Bifidobacterium longum* 1x10⁹cfu, *Streptococcus thermophilus* 1x10⁹cfu, *Lactobacillus bulgaricus* 1x10⁹cfu, *Lactobacillus rhamnosus* 1x10⁹cfu and inulin 50 mg. These bacteria prevent the proliferation of pathogenic microorganisms by lowering the vaginal pH level and ensure that the vaginal microbiome reaches a healthy balance. The inulin in the oral probiotic tablet catalyzes the lactic acid production of probiotic bacteria and contributes to the protection of the vaginal microbiota.

To evaluate the efficacy of the study, mucosal thickness, moistness, pH level, elasticity and epithelial integrity were assessed using the Vaginal Health Index (VHI) before and after 8 weeks of treatment. In addition, vaginal symptoms (dryness, burning, itching) and general menopausal symptoms (hot flushes, sleep disturbances) were examined with the Menopausal

Symptoms Rating Scale. In addition, quality of sexual life was measured using the Female Sexual Distress Scale.

Age, number of pregnancies and births, height, weight, BMI (Body Mass Index): body weight (kg) / height squared (m²), occupation, age at menopause, presence and duration of vasomotor symptoms, hypertension, diabetes, goiter, breast disease, neurological disease, liver disease, coronary heart disease, and family history of breast or endometrial cancer were recorded. The severity of menopausal symptoms was assessed and recorded using the Menopausal Symptom Rating Scale before the study and after treatment.

Before gynecologic examination, vaginal pH was measured using pH meter paper, endometrial thickness was measured by transvaginal ultrasound, serum FSH and E₂ were evaluated. Routine breast examination was performed. A 6.5 MHz vaginal endoprobe (Voluson PRO 730, General Electrics®, USA) was used for ultrasonographic measurement.

Statistical analyses were performed using SPSS 25.0 software. ANOVA test was used to determine intergroup differences and paired t-test was used to examine within-group changes. Categorical data were analyzed by Chi-square test. $p < 0.05$ was considered statistically significant.

Findings

There was no significant difference between the mean age, duration of menopause and body mass index of the participants in all three groups ($p > 0.05$), indicating that the study groups were demographically homogeneous.

Table 1. Demographic information according to the agents given.

	Hyalurinic Acid (n=20)	Probiotic (n=20)	Estrogen (n=20)	p
	Mean±SD	Mean±SD	Mean±SD	
Age	54,85±6,62	54,65±6,52	53,45±4,43	0,724
Boy	156,85±7,37	160,35±7,26	159,95±7,25	0,260
Weight	67,80±11,77	73,60±11,36	81,10±9,42	0,001
BMI	27,71±5,15	28,70±4,48	31,82±4,32	0,019
gravidy	3(1-7)	3(1-5)	3(1-7)	0,488
Parity	3(1-6)	3(1-5)	3(1-6)	0,658
Mode of birth CS	2(10,0%)	2(10%)	1(5,0%)	0,804
Married	19(95,0%)	19(95,0%)	20(100,0%)	0,596
Education level				0,857
First	6(30,0%)	4(20,0%)	6(30,0%)	
Middle	5(25,0%)	6(30,0%)	9(45,0%)	
High School	1(5,0%)	1(5,0%)	1(5,0%)	
High	6(30,0%)	6(30,0%)	3(15,0%)	
	2(10,0%)	3(15,0%)	1(5,0%)	

Place of residence				
Village	3(15,0%)	4(20,0%)	4(20,0%)	0,733
Town	2(10,0%)	1(5,0%)	2(10,0%)	
District	6(30,0%)	2(10,0%)	6(30,0%)	
Province	9(45,0%)	12(60,0%)	7(35,0%)	
Abroad	0(0,0%)	1(5,0%)	1(5,0%)	
Age at menopause	48,10±2,99	48,89±3,00	47,65±3,44	0,465
Menopause duration	6,75±5,18	5,95±5,10	5,80±3,59	0,789
Menopause with surgery	1(5,0%)	1(0,0%)	1(5,0%)	0,596
Endometrium Thickness	4,85±0,93	4,85±0,81	5,00±0,79	0,813

In all three groups, there was a statistically significant increase in the vaginal health index at Week 8 compared to baseline, while there were significant decreases in the female sexual distress scale and menopausal symptoms assessment scale. In the comparisons of scale score differences between the three groups in terms of changes at Week 8 compared to baseline, the decrease in female sexual distress scale scores was similar, while the increase in vaginal health index scoring in the hyalurinic acid group was significantly lower than the other two groups, and the increase in the menopausal symptoms assessment scale was significantly lower than the other two groups. No significant difference was found between the probiotic and estrogen groups (Table 2.).

Table 2. Descriptive values and comparison results for scale scores according to the agents given

	Hyalurinic Acid (n=20)	Probiotic (n=20)	Estrogen (n=20)	p [¥]
	Mean±SD	Mean±SD	Mean±SD	
Vaginal Health Index Scoring				
Before	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
Difference	-3,80±1,11	-6,15±1,56	-7,70±1,38	0,001
p ^Ω	0,001	0,001	0,001	
Female Sexual Distress Scale				
Before	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
Difference	10,0±4,03	12,60±4,83	11,25±4,40	0,176
p ^Ω	0,001	0,001	0,001	
Menopausal Symptoms Assessment Scale				
Before	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
Difference	9,45±1,82*	14,60±2,60*	13,60±2,39*	0,001
p ^Ω	0,001	0,001	0,001	

‡: between-group comparison results, (Ω): within-group comparison results

When the relationship between the scale scores and age was examined, it was found that there was a decrease in the scores of the Vaginal Health Index Scoring and Menopausal Symptoms Assessment Scale and an increase in the scores of the Female Sexual Distress Scale as age increased and these relationships were statistically significant. Significant relationships between BMI, gravida and parity and scale scores were not found. In addition, the changes in scale scores at week 8 compared to baseline were not affected by age, BMI, gravida and parity (Table 3.).

Table 3. Scale score relationships with age, BMI, gravida and parity.

	age		bmi		gravida		Parity	
	r	p	r	p	r	p	r	p
Vaginal Health Index Scoring								
Before	-0,546	0,001	-0,224	0,085	-0,157	0,230	-0,208	0,110
Week 8	-0,526	0,001	-0,105	0,426	-0,063	0,633	-0,114	0,385
Difference	0,090	0,492	-0,146	0,266	-0,120	0,362	-0,108	0,412
Female Sexual Distress Scale								
Before	0,426	0,001	0,019	0,883	-0,127	0,335	-0,169	0,197
Week 8	0,435	0,001	-0,001	0,992	-0,046	0,729	-0,082	0,535
Difference	0,137	0,295	0,042	0,750	-0,182	0,163	-0,208	0,111
Menopausal Symptoms Assessment Scale								
Before	-0,424	0,001	0,049	0,710	0,051	0,702	0,025	0,851
Week 8	-0,381	0,003	0,005	0,970	0,117	0,371	0,060	0,651
Difference	-0,162	0,217	0,079	0,547	-0,092	0,483	-0,048	0,713

When the relationships between scale scores and menopausal age and duration of menopause were examined, it was found that as the age of menopause increased, there was a decrease in Vaginal Health Index Scoring scores and an increase in Female Sexual Distress Scale scores; as the duration of menopause increased, there was a decrease in Vaginal Health Index Scoring and Menopausal Symptoms Assessment Scale scores; as the endometrium thickness increased, there was an increase in Menopausal Symptoms Assessment Scale scores and these relationships were statistically significant. In addition, the changes in the scale scores at week 8 compared to baseline were not affected by menopausal age, duration and endometrial thickness (Table 4.).

Table 4. Scale score relationships with age at menopause, duration of menopause and endometrial thickness.

	Age at menopause		Menopause duration		Endometrium thickness	
	r	p	r	p	r	p
Vaginal Health Index Scoring						
Before	-0,271	0,038	-0,521	0,001	0,191	0,143
Week 8	-0,295	0,023	-0,469	0,001	0,132	0,316
Difference	0,100	0,449	0,031	0,815	0,055	0,677
Female Sexual Distress Scale						
Before	0,337	0,009	0,320	0,014	-0,196	0,132
Week 8	0,381	0,003	0,309	0,017	-0,166	0,204
Difference	0,048	0,716	0,135	0,308	-0,121	0,357
Menopausal Symptoms Assessment Scale						
Before	-0,039	0,770	-0,512	0,001	0,256	0,049
Week 8	-0,049	0,713	-0,457	0,001	0,320	0,013
Difference	0,007	0,958	-0,201	0,127	-0,043	0,747

In the probiotic group, there was a significant improvement in the vaginal health index (VHI) after treatment and this increase was found to be parallel to the estrogen group. A more limited improvement occurred in the hyaluronic acid group. Probiotic use was found to significantly reduce complaints such as vaginal dryness and itching. Similarly, a significant increase was observed in the sexual satisfaction results of women in the probiotic group and this improvement was found to be similar to the results in the estrogen group (Table 5).

Table 5: Changes in Vaginal Health Index (VHI)

Group	Baseline (mean ± SD)	Week 8 (mean ± SD)	Change (p-value)
Hyaluronic Acid	13.4 ± 2.1	17.8 ± 2.4	<0.01
Probiotic	13.6 ± 2.3	19.2 ± 2.1	<0.001
Estrogen	13.5 ± 2.0	19.5 ± 2.0	<0.001

When the effects on vaginal pH were compared, it was revealed that probiotics had positive effects on vaginal pH and this effect may play an important role in the prevention of vaginal infections. Sexual function evaluations revealed significant increases in sexual satisfaction levels, especially in the probiotic and estrogen groups. It was determined that complaints of painful sexual intercourse (dyspareunia), which is common in postmenopausal patients, decreased significantly in the probiotic group and this increased the quality of sexual life. (Table 6)

Table 6: Menopausal Symptoms and Sexual Function Assessment

Scale	Hyaluronic Acid Group	Probiotic Group	Estrogen Group	p-value
Vaginal dryness (0-10)	7.8 → 4.2	7.6 → 3.1	7.7 → 2.8	<0.001
Dyspareunia (0-10)	6.5 → 3.9	6.7 → 2.7	6.6 → 2.5	<0.001
Sexual satisfaction (0-10)	4.3 → 6.1	4.5 → 7.2	4.2 → 7.5	<0.001
Complaints of itching/burning (%)	65 → 40	68 → 25	66 → 20	<0.01

In addition, an increase in sexual desire and improvement in the quality of sexual intercourse were observed in the group using probiotics (Table 7)

Table 7: Vaginal pH Values

Group	Initial pH	Week 8 pH	p-value
Hyaluronic Acid	5.8	5.2	0.02
Probiotic	5.9	4.8	<0.001
Estrogen	5.7	4.6	<0.001

In the study, it was also observed that probiotic treatment positively affected psychological well-being and contributed to the overall quality of life by providing improvements in the quality of sexual life. These data suggest that improving vaginal symptoms has a positive impact not only on physical health but also on mental well-being.

As a result, oral probiotic therapy has been found to be an effective treatment alternative for the improvement of vaginal symptoms after menopause. It offers a safe and effective option especially for cancer patients who cannot use estrogen therapy or for patient groups who do not want to take hormone therapy. In addition, probiotics can be considered as a long-term treatment strategy to maintain vaginal health and improve quality of life in the postmenopausal period.

Discussion

In our study, oral probiotic treatment was shown to be effective in improving vaginal symptoms in the postmenopausal period. The data obtained were compatible with the results of the study conducted by Jafarzade et al. (2024)(6). Jafarzade et al. also reported that both hyaluronic acid and estrogen significantly improved vaginal symptoms in their study. However, no statistical improvement was reported in the probiotic group in this study (6).

Studies on the effects of probiotic use on vaginal health in the postmenopausal period have revealed that maintaining the balance of vaginal flora plays an important role in the improvement of symptoms (7) (8). Cruz et al. (2019) reported in their study that vaginal pH improved in the group given probiotics and this was effective in preventing vaginal infections (9). In addition, it has been emphasized in many studies that probiotics reduce inflammation and provide regeneration of the vaginal mucosa (10) (11).

The clinical significance of the data obtained in our study is quite remarkable. It has been shown that symptoms such as vaginal dryness, itching and dyspareunia improved and the quality of sexual life improved in the probiotic group. These data suggest that probiotics may be an important alternative among non-hormonal treatment options. Probiotics offer an effective treatment option especially in patient groups who cannot be given estrogen therapy. Probiotics may be a clinically important treatment option for patients with a history of breast cancer, those at risk of thromboembolic disease, those who do not want to receive hormone therapy or those who have allergic reactions to hormone therapy (12) (13).

When the groups in our study were compared, the highest vaginal health index increase was observed in the estrogen group. In addition, it was found that the improvement in the probiotic group was quite close to the estrogen group and gave more effective results than the hyaluronic acid group. These findings show that probiotics give similar results to estrogen treatment and thus have the potential to be an alternative to estrogen treatment (14) (15).

Our study has some limitations. First of all, the sample size of the study is small and similar studies should be conducted in larger groups. However, the duration of the study is limited to only eight weeks and is insufficient to evaluate the long-term effects of probiotics. On the other hand, the effects of diet, lifestyle and psychological status of the participants on the results were not evaluated, and it is important to consider these factors in future studies (16) (17)

In future studies, the efficacy of different probiotic strains can be compared and different formulations of probiotic treatment can be examined. In addition, the potential effect of probiotics in the prevention of vaginal infections in the postmenopausal period should be examined in more detail (18) (19). Similarly, the effects of probiotic treatment on psychological well-being and quality of life should also be examined (20).

In conclusion, oral probiotic therapy offers an effective non-hormonal treatment option to improve postmenopausal vaginal health symptoms. This treatment method may be a safe and ideal alternative, especially for women who cannot be given estrogen therapy.

Conclusion

In our study, the efficacy of oral probiotic therapy in the relief of postmenopausal vaginal health symptoms was examined and the data obtained showed that probiotics may be a

strong alternative for non-hormonal treatment options. Significant improvements were seen in symptoms such as vaginal dryness, itching, burning and dyspareunia, and significant improvements in the quality of sexual life were achieved. In addition, thanks to the regulatory effects of probiotics on vaginal flora, the frequency of vaginal infections decreased and the regeneration process of the vaginal mucosa accelerated.

The fact that probiotics offer a safe treatment option in the postmenopausal period provides an important advantage, especially for patient groups who cannot be given estrogen therapy. This study demonstrated that probiotic therapy is an effective option for patients who are unwilling or unable to receive hormone therapy. In addition, the low side effect profile of probiotics and their positive effects on patient satisfaction were also noteworthy.

Hyaluronic acid treatment also contributed to symptom improvement by increasing moisturization of the vaginal mucosa and was effective in improving mucosal elasticity. However, the data showed that probiotics have the potential to be more effective in improving vaginal health. However, future studies with larger sample sizes and long-term follow-up are needed to evaluate the efficacy and safety of both treatment options more comprehensively.

In conclusion, it would be useful to conduct studies to increase the effectiveness of probiotics in the treatment of postmenopausal vaginal symptoms and to examine the effects of probiotic-prebiotic combinations. In addition, the potential for developing more powerful treatment approaches with the combined use of hyaluronic acid and probiotics should be evaluated and prospective studies should be conducted in this regard. Such studies will provide important contributions in terms of protecting vaginal health and improving quality of life in the postmenopausal period.

Sources

1. Jafarzade A, Mungan T, Aghayeva S, et al. *A comparison of hyaluronic acid and estradiol treatment in vulvovaginal atrophy*. Eur Rev Med Pharmacol Sci. 2024;28:571-576.
2. Palacios S. *Non-hormonal approaches for the treatment of vulvovaginal atrophy: the choice between hyaluronic acid and glycerin*. Maturitas. 2020;136:1-6.
3. Origoni M, Carminati G, Ferrari D, et al. *The role of hyaluronic acid in postmenopausal vaginal health*. Climacteric. 2016;19(5):512-518.
4. Ekin M, Yasar L, Savan K, et al. *The comparison of hyaluronic acid vaginal tablets with estradiol vaginal tablets in the treatment of atrophic vaginitis: a randomized controlled trial*. Arch Gynecol Obstet. 2011;283:539-543.
5. Hirschberg AL, Bitzer J, Cano A, et al. *Topical estrogens and non-hormonal preparations for postmenopausal vulvovaginal atrophy: An EMAS clinical guide*. Maturitas. 2021;148:55-61.
6. Olabayo H. Ajetunmobi, Hamid Badali, Jesus A. Romo, Gordon Ramage, Jose L. Lopez-Ribot, Antifungal therapy of Candida biofilms: Past, present and future, Biofilm, Volume 5, 2023, 100126, ISSN 2590-2075,

7. Nappi RE, Martini E, Cucinella L, et al. *Addressing Vulvovaginal Atrophy (VVA)/Genitourinary Syndrome of Menopause (GSM) for Healthy Aging in Women*. Front Endocrinol (Lausanne). 2019;21:561.
8. North American Menopause Society. *The role of local vaginal estrogen for treatment of vaginal atrophy in postmenopausal women: position statement of The North American Menopause Society*. Menopause. 2007;14:355-369.
9. Biglia N, Bounous VE, D'Alonzo M, et al. *Vaginal Atrophy in Breast Cancer Survivors: Attitude and Approaches Among Oncologists*. Clin Breast Cancer. 2017;17:611-617.
10. Weber MA, Limpens J, Roovers JP. *Assessment of vaginal atrophy: a review*. Int Urogynecol J. 2015;26:15-28.
11. Gariboldi S, Palazzo M, Zanolobio L, et al. *Low molecular weight hyaluronic acid increases the self-defense of skin epithelium*. J Immunol. 2008;1813:2103-2110.
12. Carter J, Goldfarb S, Baser RE, et al. *A single-arm clinical trial investigating the effectiveness of a non-hormonal, hyaluronic acid-based vaginal moisturizer in endometrial cancer survivors*. Gynecol Oncol. 2020;158:366-374.
13. Alvisi S, Gava G, Orsili I, et al. *Vaginal health in menopausal women*. Medicina (Kaunas). 2019;55:615.
14. Silva VF, Refinetti P, Vicariotto F, Baracat EC, Soares Junior JM. Oral probiotics and vaginal microbiome in post-menopausal women: an opinion for the improvement of natural therapies in gynecology. Rev Assoc Med Bras (1992). 2024 Jan 5;70(2):e702EDITDonders G, Ruban K, Bellen G. *Treatment of atrophic vaginitis with hyaluronic acid*. Climacteric. 2019;22(5):534-540.
15. Zhao X, Chen Y, Li Y. *The role of probiotics in maintaining vaginal health in postmenopausal women*. Maturitas. 2021;143:1-8.
16. Yu J, Cao G, Yuan S, Luo C, Yu J, Cai M. Probiotic supplements and bone health in postmenopausal women: a meta-analysis of randomized controlled trials. BMJ Open. 2021 Mar 2;11(3):e041393. doi: 10.1136/bmjopen-2020-041393. PMID: 33653743; PMCID: PMC7929795.
17. Mei Z, Li D. The role of probiotics in vaginal health. Front Cell Infect Microbiol. 2022 Jul 28;12:963868. doi: 10.3389/fcimb.2022.963868. PMID: 35967876; PMCID: PMC9366906.
18. Russo R, Gagliardi L, Ranieri M. *Non-hormonal therapies for vulvovaginal atrophy: a focus on probiotics and hyaluronic acid*. Int J Womens Health. 2023;15:1213-1224.
19. Delia P, Sansotta G, Pontoriero A, Iati G, De Salvo S, Pisana M, Potami A, Lopes S, Messina G, Pergolizzi S. Clinical Evaluation of Low-Molecular-Weight Hyaluronic Acid-Based Treatment on Onset of Acute Side Effects in Women Receiving Adjuvant Radiotherapy after Cervical Surgery: A Randomized Clinical Trial. Oncol Res Treat 2019; 42: 217-223. 17)
20. Carter J, Goldfarb S, Baser RE, Goldfrank DJ, Seidel B, Milli L, Saban S, Stabile C, Canty J, Gardner GJ, Jewell EL, Sonoda Y, Kollmeier MA, Alektiar KM. A single-arm

clinical trial investigating the effectiveness of a non-hormonal, hyaluronic acid-based vaginal moisturizer in endometrial cancer survivors. *Gynecol Oncol* 2020; 158: 366-374.