PROGRESOS DE
Obstetricia y Ginecología
Revista Oficial de la Sociedad Española de Ginecología y Obstetricia

Prog Obstet Ginecol 2019;62(3):230-236

Trabajo Original

Effectiveness of nonhormonal products for the treatment of women with vaginal atrophy

Efectividad de productos no hormonales para el tratamiento de las mujeres con atrofia vaginal

Ignacio Cristóbal García[1], Lidia Lorite Aguilera[2], Esperanza Álvarez Martinez[2], Verónica Piedrabuena[3]

[1]Servicio Obstetricia y Ginecología. Hospital Universitario Sanitas la Zarzuela. Madrid. Universidad Francisco de Vitoria, Madrid. [2]Servicio Obstetricia y Ginecología. Hospital Universitario Sanitas la Zarzuela. Madrid. [3]Asesora Médica Laboratorios Casen Recordati. Pozuelo de Alarcón. Madrid

Resumen

Objetivo: describir la evolución clínica de mujeres con atrofia vaginal que reciben un tratamiento no hormonal.

Material y métodos: estudio descriptivo observacional retrospectivo longitudinal unicéntrico en mujeres posmenopáusicas de 45 a 60 años con síntomas de atrofia vaginal que hubieran requerido tratamiento no hormonal.

Resultados: se incluyeron 98 mujeres con una edad media de 54,6 ± 3,2 años y un tiempo medio sin menstruación de 5,6 ± 3,0 años. El 63,3% de las mujeres eran tratadas con ácido hialurónico y lisado celular de centella asiática y el 36,7% con glicerol y policarbofil. El índice de maduración vaginal fue significativamente mejor tras tres meses de tratamiento con ácido hialurónico y lisado de centella asiática: descienden las células parabasales (-8,4%, IC95% (-10,6 – -6,2), p=0,001) y aumentan las intermedias (3,6%, IC95% (2,0 – 5,3), p=0,001) y las superficiales (4,8%, IC95% (3,8 – 5,7), p=0,001). Además, se redujeron todos los síntomas y signos de atrofia vaginal tras 3 meses con el tratamiento con ácido hialurónico y lisado de centella asiática. No se encontraron cambios tras tres meses de tratamiento con glicerol y policarbofil en el índice de maduración vaginal y de los síntomas y signos.

Conclusiones: El tratamiento no hormonal con ácido hialurónico y lisado de centella asiática mejora significativamente el índice de maduración vaginal y los síntomas y signos de atrofia vaginal tras tres meses de tratamiento.

Key words:

Vaginal atrophy. Treatment. Menopause. Hyaluronic acid. Vaginal maduration index.

Abstract

Objective: To describe the clinical progress of women with vaginal atrophy who receive nonhormonal treatment.

Material and methods: Single-center retrospective longitudinal observational descriptive study in postmenopausal women aged 45-60 years with symptoms of vaginal atrophy who required nonhormonal treatment.

Results: We included 98 women with a mean (SD) age of 54.6 (3.2) years and a mean time of 5.6 (3.0) years without menstrual periods. Of these, 63.3% were treated with hyaluronic acid and Centella asiatica cell lysate and the other 36.7% with glycerin and polycarbophil. The vaginal maturation index improved significantly after 3 months of treatment with hyaluronic acid and Centella asiatica: the parabasal cell count declined (-8.4%; 95%CI, –10.6 to –6.2; p=0.001) and the intermediate cell count increased (3.6%; 95%CI, 2.0-5.3; p=0.001), as did that of superficial cells (4.8%; 95%CI, 3.8-5.7; p=0.001). In addition, all symptoms and signs of vaginal atrophy improved after 3 months with treatment with hyaluronic acid and Centella asiatica lysate. There was no significant change in the vaginal maturation index or in symptoms and signs after 3 months of treatment with glycerin and polycarbophil.

Conclusions: Three months of nonhormonal treatment with hyaluronic acid and Centella asiatica lysate significantly improved the vaginal maturation index.

Palabras clave:

Atrofia vaginal. Tratamiento. Menopausia. Ácido hialurónico. Índice de maduración vaginal.

Recibido: 20/09/2018
Aceptado: 22/01/2019

Cristóbal García I, Lorite Aguilera L, Álvarez Martinez E, Piedrabuena V. Effectiveness of nonhormonal products for the treatment of women with vaginal atrophy. Prog Obstet Ginecol 2019;62(3):230-236. DOI: 10.20960/j.pog.00196

Correspondencia:
Verónica Piedrabuena
Asesora médica
Laboratorios Casen Recordati
Vía de las Dos Castillas, 33
28224 Pozuelo de Alarcón. Madrid
e-mail: vpiedrabuena@casenrecordati.com

INTRODUCTION

Vulvovaginal atrophy (VVA) is a chronic, progressive disease caused by reduced estrogen levels. It can appear at any time during a woman's lifetime, although it is more common after the menopause, coinciding with estrogen deficiency (1). It affects almost 50% of peri- and postmenopausal women, thus worsening their quality of life (2), and may be more common in specific subgroups of women such as survivors of breast cancer, where its prevalence exceeds 60% (1,3).

Changes in circulating estrogens are reflected in the physiology of the vagina and in the onset of symptoms at the level of the epithelium, which goes from being moist and thick with rugae to being smooth and thin as a result of the menopause and estrogen deficiency (1). The main changes that affect the vagina as a consequence of estrogen deficiency (4) are altered epithelial maturation with reduced superficial cells, reduced vaginal lactobacilli, increased pH with the subsequent risk of infections and inflammation, and reduced blood flow. These changes can affect the patient's sexual health.

VVA is responsible for the onset of symptoms that a affect a woman's quality of life (5). These symptoms include dryness, irritation, itching, dyspareunia, frequent urination, urgency, and urge incontinence. Dyspareunia secondary to vaginal atrophy plays a key role in female sexual dysfunction. In addition to the impact on sexuality and sexual relationships, vaginal atrophy affects urinary function and may impact activities of daily living (6). This wide range of effects has been reported to have a significant emotional impact and diminish the quality of life of postmenopausal women. Therefore, VVA is associated with comorbid conditions such as depression and anxiety (7).

Despite evidence that around 50% of middle-aged postmenopausal women experience vaginal discomfort caused by VVA, vaginal health in middle-aged women is underestimated for many reasons (8), mostly because of ignorance about the extent to which VVA can affect sexual health and the quality of life of women and their partners.

The objective of treatment of VVA is to relieve symptoms, especially vaginal dryness. Currently available options include nonpharmacological approaches, especially changes in lifestyle, and pharmacological options (hormonal and nonhormonal products).

Available nonhormonal treatments include lubricants for dyspareunia and vaginal moisturizers for symptoms of VVA (1). Nonhormonal options are indicated mainly in women who wish to avoid hormone therapy or high-risk women with a history of hormone-sensitive malignant neoplasm, such as breast or endometrial cancer (4).

Lubricants consist mainly of a combination of protective and thickening agents in a water-soluble base. They are used principally for relief of vaginal dryness and discomfort during intercourse, thus providing relief in the short term (3). Their use is not expected to change the histologic characteristics of vaginal tissue, but to reduce the irritation caused by friction of tissue during sexual intercourse, that is, there will be no effect on maturation of the vaginal epithelium; therefore, use of lubricants does not reverse the atrophy-induced changes associated with estrogen deficiency.

Vaginal moisturizers rehydrate dry mucosal tissue, hydrate collagen, are absorbed by the epithelium, and adhere to the vaginal lining, thus mimicking natural vaginal secretions, with improved vaginal moisture, elasticity, and pH. Vaginal moisturizers are indicated for the relief of vaginal dryness/atrophic vaginitis/vaginal atrophy. They are applied regularly (2-3 times per week). Their frequency of use is directly proportional to the severity of atrophy (ie, the worse the atrophy, the more frequent their use), and their effects last longer than lubricants (2-3 days) (3).

Although lubricants and moisturizers have proven effective, they differ in terms of composition. Therefore, it is important to choose the most appropriate lubricant or moisturizer and that which best adapts to the needs and specific situation of the patient (3).

Expert committees are showing increasing scientific interest in studying VVA, its determinants, and its impact on the quality of life and sex life of postmenopausal women. Therefore, the aim of the present study was to address this relevant question by attempting to describe the microbiological and clinical progress of a group of women with vaginal atrophy receiving treatment with nonhormonal products.

MATERIAL AND METHODS

We performed a single-center, descriptive, longitudinal, retrospective study of postmenopausal women aged 45 to 60 years with symptoms of vaginal atrophy seen at the Gynecology Clinic of Hospital Universitario Sanitas la Zarzuela, Madrid, Spain between September 2016 and October 2017. The women had been using nonhormonal treatment for the previous year or less. We excluded all women who had received hormonal treatment or who had gynecological tumors, genital bleeding, pelvic organ prolapse grade >1, or active vaginal infection.

The study was presented to the Research Ethics Committee of Hospital Puerta de Hierro on April 8, 2016 and approved on July 26, 2016. All patients were managed according to standard clinical practice at the participating center. As this was an anonymous retrospective observational study, patient informed consent was not considered necessary, although where possible, every attempt was made to obtain it. We followed the ethical principles of the World Medical Association Declaration of Helsinki.

Patients were included consecutively. The data collected from the clinical history at the center were demographic

characteristics (age, end of menstruation, profession), anthropometric data (weight, height, and body mass index), social habits (smoking, alcohol, sexual relations), disease history (prolapse, human papillomavirus [HPV], endocrine diseases [thyroid symptoms], and concomitant medication [antidepressants, antihistamines]). In addition, before beginning treatment and at 3 months after initiation, we used an intensity scale (none, mild, moderate, intense, very intense) to record symptoms of vaginal atrophy (burning sensation, itching, dyspareunia, dryness) and signs (epithelial thinning, redness, inflammation, loss of rugae, stiffness, and fissures) and took a vaginal smear (superficial, intermediate, and parabasal cell count). Finally, the patient was questioned about her satisfaction with the nonhormonal treatment received (comfort, hygiene, ease of use, and degree of recommendation) using a Likert-type scale (very much against, against, neutral, in favor, very much in favor).

The sample size was calculated based on changes in cytology (superficial, intermediate, and parabasal cells) at 3 months after initiation of therapy (9). We calculated that it would be necessary to recruit 106 women to estimate the change in the vaginal maturation index (VMI) with an accuracy of 2.1 units, a 95% confidence interval, a power of 80%, and a dropout rate of 10%.

We used the VMI as an objective measure of vaginal atrophy. The VMI indicates the degree of maturity reached by the vaginal epithelium based on the type of exfoliated cells. Since it represents the percentage of parabasal, intermediate, and superficial cells, a shift to the left indicates the presence of more immature cells on the surface (atrophy), whereas a shift to the right indicates the presence of more mature epithelia.

Variables were analyzed for the total sample, and some of the characteristics were analyzed according to the nonhormonal treatment received. Categorical variables were expressed as absolute and relative frequencies and quantitative variables as mean (SD). In order to compare progress after 3 months of treatment, the estimation of the change was shown with its 95%CI. We applied a paired-samples *t* test or the Wilcoxon signed rank test in the case of a non-normal distribution. Statistical significance was set at $p<0.05$. The analyses were performed using SAS© 9.4.

RESULTS

We included data from 98 women with vaginal atrophy who had started nonhormonal treatment. Since all of the patients fulfilled the selection criteria and completed the 3-month follow-up, they were all included in the analysis. Mean (SD) age was 54.6 (3.2) years, and mean time without menstruation was 5.6 (3.0) years. More than half (59.2%) worked outside the home. Nonsmokers accounted for 67.3%, and 75.5% did not consume alcohol. The patients had sexual relations a mean of 1.32 (0.6) times per week. As for concomitant conditions, 12.2% had grade I prolapse, 8.2% had HPV infection, and 28.6% had a thyroid condition; 8.2% were taking antidepressants and 1.0% antihistaminics.

The participants were divided into 2 groups: 63.3% took nonhormonal treatment based on hyaluronic acid and *Centella asiatica* cell lysate and 36.7% used treatment based on glycerin and polycarbophil. Baseline data for the whole sample and according to treatment are shown in Table I.

As for symptoms, before treatment, 75.5% of women felt a mild-moderate burning sensation, 45.9% mild itching, 78.6% moderate-intense dyspareunia, and 69.4% moderate-intense dryness. As for the signs, 74.5% presented moderate-intense thinning of the vaginal epithelium, 51.1% mild-moderate redness, 24.5% mild inflammation, 81.6% moderate-intense loss of rugae, 81.6% moderate-intense rigidity, and 23.5% mild fissures or erosions.

All of the signs and symptoms of vaginal atrophy improved after 3 months of nonhormonal treatment (Table II).

The VMI (parabasal/intermediate/superficial cells) in the total sample of 98 women was 90.4/7.4/2.2% at baseline. After 3 months of treatment it was 85.0/9.5/5.5%. Therefore, the VMI was significantly better after 3 months of nonhormonal treatment (Table II), that is, parabasal cell values fell significantly (-5.4%; 95%CI, -7.1 to -3,7; p=0.001), and intermediate cell values increased significantly (2.1%; 95%CI, 0.9-3.4; p=0.001), as did those of superficial cells (3.3%; 95%CI, 2.4-4.1; p=0.001).

Comparison of the treatments showed that the VMI at baseline was 90.8/7.4/1.8% in women who used hyaluronic acid and *Centella asiatica*; at 3 months, these values were 82.4/11.0/6.6%. Therefore, the VMI was significantly improved after 3 months of treatment with hyaluronic acid and *Centella asiatica*, since values fell significantly for parabasal cells (-8.4%; 95%CI, -10.6 to -6.2; p=0.001) and increased for intermediate cells (3.6%; 95%CI, 2.0-5.3; p=0.001) and superficial cells (4.8%; 95%CI, 3.8-5.7; p=0.001).

In the group of patients who used glycerin and polycarbophil, the VMI did not vary significantly after 3 months of treatment. Values for parabasal cells decreased 0.25% (95%CI, -2.0 to 1.5), as did those of intermediate cells 0.42% (95%CI -2.0 to 1.2), whereas superficial cells increased 0.67% (95%CI, -0.3 to 1.6).

After 3 months of treatment, signs and symptoms improved significantly for almost all of the variables analyzed, albeit with some differences in favor of the group that took hyaluronic acid and *Centella asiatica*. All signs and symptoms of vaginal atrophy improved after 3 months of treatment with hyaluronic acid and *Centella asiatica* (Table II), whereas with glycerin and polycarbophil, only

Table I.
Characteristics of the sample. Comparison between treatments used

	Total	Hyaluronic acid and *Centella asiatica* cell lysate	Glycerin and polycarbophil
Total patients, n (%)	98	62 (63.3)	36 (36.7)
Sociodemographic data, mean (SD)			
Age, y	54.6 (3.2)	54.7 (3.1)	54.4 (3.4)
Age at end of menstruation, y	49.0 (2.7)	49.2 (2.9)	48.6 (2.3)
Time without menstruation, y	5.6 (3.0)	5.6 (3.0)	5.7 (3.1)
Sexual relations, times per week	1.3 (0.6)	1.3 (0.6)	1.4 (0.54)
Anthropometric data, mean (SD)			
Weight, kg	68.8 (8.1)	67.6 (8.3)	71.5 (7.3)
Height, cm	165.7 (5.1)	165.2 (5.2)	166.5 (4.9)
Body mass index, kg/m2	25.1 (2.7)	24.8 (2.8)	25.8 (2.2)
Social habits, n (%)			
Actively working outside the home	58 (59.2)	38 (61.3)	20 (55.6)
Consumption of alcohol	24 (24.5)	19 (30.6)	5 (13.9)
Smoking			
Never smoked	66 (67.3)	41 (66.1)	25 (69.4)
Exsmoker	23 (23.5)	18 (29.0)	5 (13.9)
Active smoker	9 (9.2)	3 (4.8)	6 (16.7)
History of vulvovaginal atrophy, n (%)			
Grade I prolapse	12 (12.2)	6 (9.7)	6 (16.7)
Human papillomavirus	8 (8.2)	4 (6.5)	4 (11.1)
Concomitant endocrine diseases, n (%)			
Thyroid symptoms	28 (28.6)	15 (24.2)	13 (36.1)
Concomitant medication, n (%)			
Antidepressants	8 (8.2)	3 (4.8)	5 (13.9)
Antihistamines	1 (1.0)	1 (1.6)	0 (0.0)

SD: Standard deviation.

dyspareunia and vaginal dryness improved. In the case of signs, no significant changes were observed after 3 months of treatment with glycerin and polycarbophil, except for the loss of vaginal rugae and loss of vaginal elasticity, which were reduced.

The satisfaction assessment indicated that more than 90% of women were happy or very happy with hyaluronic acid and *Centella asiatica* for each of the items considered (comfort, hygiene, ease of use, and recommendation). Between 40% and 45% of women were satisfied or very satisfied with respect to comfort and hygiene with glycerin and polycarbophil, whereas 58.3% considered it easy or very easy to use. Among the women who used glycerin and polycarbophil, 2.8% would recommend it and 30.6% would not.

DISCUSSION

Our study analyzes the clinical progress of women with VVA after 3 months of treatment with a nonhormonal product. The signs and symptoms recorded in our sample are consistent with those published in other studies on VVA (10). While many studies have demonstrated the efficacy of hormonal treatments for VVA and compare these with nonhormonal treatments, few have compared non-

Table II.
Clinical progress after 3 months of treatment. Comparison between the treatments used

Change after 3 months of treatment, mean (95%CI)	Total n=98	Hyaluronic acid and Centella asiatica lysate n=62	Glycerin and polycarbophil n=36
Vaginal maturation index (%)			
Parabasal cells	-5.40 (-7.1 to 3.7)[a]	-8.39 (-10.6 to 6.2)[a]	-0.25 (-2.0 to 1.5)
Intermediate cells	2.14 (0.9-3.4)[a]	3.63 (2.0-5.3)[a]	-0.42 (-2.0 to 1.2)
Superficial cells	3.26 (2.4-4.1)[a]	4.76 (3.8-5.7)[a]	0.67 (-0.3 to 1.6)
Symptoms[1]			
Burning/stinging	-0.31 (-0.4 to 0.2)[a]	-0.45 (-0.6 to 0.3)[a]	-0.05 (-0.3 to 0.2)
Vaginal itching	-0.30 (-0.5 to 0.1)[a]	-0.40 (-0.6 to 0.2)[a]	-0.11 (-0.4 to 0.2)
Dyspareunia	-0.94 (-1.1 to 0.7)[a]	-1.21 (-1.5 to 0.9)[a]	-0.47 (-0.7 to 0.2) [a]
Vaginal dryness	-0.86 (-1.0 to 0.7)[a]	-1.08 (-1.3 to 0.9)[a]	-0.47 (-0.7 to 0.2)[a]
Signs[1]			
Epithelial thinning	-0.48 (-0.6 – -0.3) [a]	-0.66 (-0.8 – -0.5) [a]	-0.17 (-0.4 – 0.1)
Vaginal redness	-0.24 (-0.4 – -0.1) [a]	-0.44 (-0.6 – -0.3) [a]	0.08 (-0.1 – 0.3)
Vaginal inflammation	-0.15 (-0.3 – -0.1) [a]	-0.24 (-0.4 – -0.1) [a]	0.00 (-0.2 – 0.2)
Loss of vaginal rugae	-0.52 (-0.6 – -0.4) [a]	-0.67 (-0.8 – -0.5) [a]	-0.25 (-0.5 – -0.0) [a]
Loss of vaginal elasticity	-0.70 (-0.9 – -0.5) [a]	-0.97 (-1.2 – -0.8) [a]	-0.25 (-0.5 – -0.1) [a]
Vaginal erosions or fissures	-0.28 (-0.4 – -0.1) [a]	-0.35 (-0.5 – -0.2) [a]	-0.14 (-0.4 – 0.1)
Satisfaction[2]			
Comfort	2.86 (2.7 – 3.0)	3.13 (2.9 – 3.3)	2.39 (2.2 – 2.6)
Hygiene	3.00 (2.8 – 3.2)	3.35 (3.1 – 3.5)	2.39 (2.2 – 2.6)
Ease of use	3.26 (3.1 – 3.4)	3.60 (3.4 – 3.8)	2.67 (2.5 – 3.0)
Recommendation for treatment	2.62 (2.4 – 2.8)	3.15 (2.9 – 3.3)	1.72 (1.5 – 1.9)

[1] Scale for symptoms and signs: 0, nonexistent; 1, mild; 2, moderate; 3, intense; 4, very intense.
[2] Scale for satisfaction: 0, very much against; 1, against; 2, neutral; 3, in favor; 4, very much in favor.
[a] p<0.05: Vaginal maturation index (paired-samples t test), symptoms, and signs (Wilcoxon). 95% confidence interval.

hormonal treatments, and none have included Centella asiatica (3).

Many guidelines now recommend nonhormonal products as first-line treatments for VVA. The Spanish Society of Gynecology and Obstetrics recommends vaginal moisturizers supplemented with lubricants during intercourse as the first choice for mild-moderate symptoms of VVA (11). The North American Menopause Society considers nonhormonal products the first choice for relief of symptoms of VVA and to facilitate regular sexual relations (12).

The ideal nonhormonal treatment would be characterized by a moisturizing effect and have a maturational effect on the urogenital epithelium. The most widely used options are pectin- or polycarbophil polymer–based gels and compounds containing hyaluronic acid (2). In the present study, we compared 2 nonhormonal products by measuring changes in the symptoms of VVA, change in the VMI, and patient satisfaction (assessed using a subjective questionnaire).

Our study clearly shows an improvement in the symptoms associated with VVA resulting from treatment with a nonhormonal treatment based on hyaluronic acid and Centella asiatica. The results point to a significant improvement in symptoms and signs of VVA after 3 months of treatment and, more specifically, to changes in the VMI, an objective measure of vaginal atrophy.

Hyaluronic acid–based products have a double lubricating and moisturizing effect and have proven clinically successful in published studies (13). Moreover, hyaluronic acid is broadly effective in the treatment of skin diseases owing to the fact that it preserves tissue consistency, thus facilitating cell migration in cases of inflammation and the

process of improvement and regeneration of damaged tissues (2).

Other authors had already reported improvements in symptoms after treatment with hyaluronic acid (14), although the inclusion of Centella asiatica in this approach seems to have boosted the beneficial effects, as we show here. In vitro, the triterpenes of Centella have been proven to stimulate activation of fibroblasts and production of collagen I and III, which are key for wound healing owing to their re-epithelization effect (13).

A cytomorphometric analysis of vaginal smears from 38 postmenopausal women treated with a polycarbophil vaginal moisturizer revealed an increase in the mean cell area, thus indicating a positive effect on the maturation of vaginal epithelium. However, there was no effect on the overall maturation index/value, thus revealing a lack of effect on vaginal morphology (15). Our results are consistent with this, since the VMI remained unchanged in patients who were treated with glycerin and polycarbophil. Products containing only glycerin and polycarbophil did not lead to changes in vaginal cell populations; therefore, the only improvements observed were in symptoms such as dyspareunia and vaginal dryness. However, a significant improvement in the index was noted in patients treated with hyaluronic acid and Centella asiatica, thus highlighting the fundamental difference between the treatments. Therefore, these products have a more beneficial effect, since they act on the basis of the problem, thus leading to an improvement in the symptoms and signs of VVA (perceived by patients as significant), that translates into very high patient satisfaction.

Our results are consistent with those published in the literature to date, with data from other studies being very similar to ours. Most are open-label trials, one trial is double-blind, and another has a cross-over design. The studies generally last 6, 8, and 12 weeks, and sample size range from 15 to 200 participants (16).

The main limitation of the present study is its observational and retrospective design. Consequently, there is no placebo-controlled group, and this may limit our results. However, we performed an objective analysis of the signs of VVA and a vaginal smear study. In addition, as this was not a population-based study, we cannot guarantee that the study sample was representative of patients seen at gynecology clinics throughout Spain. However, we recruited a large number of patients in order to overcome this limitation. This information can be used in subsequent studies to construct models for the management of Spanish women with VVA.

In conclusion, the objectives of the present study were fulfilled, since we describe the clinical progress of women receiving nonhormonal treatment for VVA. Our results enable us to recommend products based on hyaluronic acid and Centella asiatica cell lysate.

CONCLUSIONS

A significant clinical improvement is observed after 3 months of treatment with hyaluronic acid and *Centella asiatica* lysate. Therefore, this combination can be considered an effective and safe nonhormonal approach for the treatment of VVA.

ETHICS

Protection of human subjects

The authors declare that no experiments were performed on human beings for this investigation.

Data confidentiality

The authors declare that they followed their institutional protocols on the publication of patient data. Data collection was completely anonymous.

Conflicts of interest

The authors declare that they have no conflicts of interest.
This study was funded by Laboratorios Casen-Recordati.

REFERENCES

1. Mac Bride MB, Rhodes DJ, Shuster LT. Vulvovaginal atrophy. Mayo Clin Proc 2010 Jan;85(1):87-94.
2. Origoni M, et al. Postmenopausal vulvovaginal atrophy (VVA) is positively improved by topical hyaluronic acid application. A prospective, observational study. Eur Rev Med Pharmacol Sci 2016;20(20): 4190-5.
3. Edwards D, Panay N. Treating vulvovaginal atrophy/genitourinary syndrome of menopause: How important is vaginal lubricant and moisturizer composition? Climacteric 2016;19(2):151-61.
4. Sturdee DW, Panay N; International Menopause Society Writing Group. Recommendations for the management of postmenopausal vaginal atrophy. Climacteric 2010;13(6):509-22.
5. Nappi RE, Palacios S. Impact of vulvovaginal athrophy on sexual health and quality of life at postmenopause. Climacteric 2014;17(1):3-9.
6. Huang AJ, Gregorich SE, Kuppermann M, et al. Day-to-day impact of vaginal aging questionnaire: A multidimensional measure of the impact of vaginal symptoms on functioning and well-being in postmenopausal women. Menopause 2015;22(2):144-54.
7. Monterrosa A, et al. Manejo de la atrofia vulvovaginal posmenopáusica. Rev Chil Obstet Ginecol 2014;79(6):489-501.
8. Nappi RE, Kokot-Kierepa M. Vaginal Health: Insights, Views & Attitudes (VIVA). Results from an international survey. Climacteric 2012; 15:36-44.
9. Karaosmanoglu O, Cogendez E, Sozen H, Asoglu MR, Akdemir Y, Eren S. Hyaluronic acid in the treatment of postmenopausal women with atrophic vaginitis. Int J Gynaecol Obstet 2011;113(2):156-7.
10. Palma F, Xholli A, Cagnacci A. Management of vaginal atrophy: A real mess. Results from the AGATA study. Gynecol Endocrinol 2017;33 (9):702-7.

11. Palacios S, Cancelo MJ, Castelo-Branco C, González S, Olalla MA. Recomendaciones de la Sociedad Española de Ginecología y Obstetricia sobre la prevención y el tratamiento de la atrofia vaginal. Prog Obst Ginec 2012;55(8):408-15.
12. Management of symptomatic vulvovaginal atrophy: 2013 position statement of The North American Menopause Society. Menopause 2013;20(9):888-902; quiz 903-4.
13. Baquedano Mainar L, Beltrán Montalbán E, Duran Jordà M. Menoguía. Asociación española para el estudio de la Menopausia. Marzo 2014.
14. Tersigni C, Di Simone N, Tempestilli E, Cianfrini F, Russo R, Moruzzi MC, et al. Non-hormonal treatment of vulvovaginal atrophy-related symptoms in post-menopausal women. J Obstet Gynaecol 2015;35(8): 835-8.
15. Van der Laak J, et al. The effect of replens on vaginal cytology in the treatment of postmenopausal atrophy: Cytomorphology versus computerized cytometry. J Clin Pathol 2002;55(6):446-51.
16. Stute P, May TW, Masur C, Schmidts-Winkler IM. Efficacy and safety of non-hormonal remedies for vaginal dryness: Open, prospective, randomized trial. Climacteric 2015;18(4):582-89.