Italian Journal of
Gynæcology & Obstetrics
December 2019 - Vol. 31 - N. 4 - Quarterly - ISSN 2385 - 0868

Treatment of women with genitourinary syndrome of the menopause with application of vaginal hyaluronic acid cream

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ABSTRACT

The onset of genitourinary syndrome of menopause (GSM) is related to the drop of estrogen occurring in women during menopause and it is characterized by the involution of the mucous membranes and tissues of the vulva and vagina. GSM is associated with a significant deterioration of quality of life (QoL) and sexual function and sexual implications may affect >50% of postmenopausal women. Hyaluronic acid (HA) is a natural polysaccharide representing an important part of the extra-cellular matrix of the skin and cartilage. This single centre, retrospective cohort study evaluated the application of HA vaginal cream for 12 months in 51 postmenopausal women with GSM. After the end of the treatment, the large majority of patients treated were satisfied. All GSM-related symptoms and QoL scores significantly improved at the same time-point. Moreover, sexual function as measured with female sexual function index (FSFI) as well as overall satisfaction with sexual life were significantly ameliorated by HA treatment among who reported sexual activity at baseline. Overall, this study demonstrated the efficacy of long-treatment with HA vaginal cream for improving disease-related symptoms, sexual function and QoL in a population of postmenopausal women with GSM.

Keywords: genitourinary syndrome of menopause; hyaluronic acid, hyaluronic acid vaginal cream, sexual function, menopause, quality of life, estrogen depletion, vaginal dryness, vaginal burning, vaginal atrophy.

SOMMARIO

L'insorgenza della sindrome genito-urinaria della menopausa (SGM) è correlato alla deplezione di estrogeni che si verifica nelle donne durante la menopausa ed è caratterizzato dall'involuzione delle mucose e dei tessuti della vulva e della vagina. LA SGM è associata a un significativo deterioramento della qualità della vita (QoL) e della funzione sessuale e le implicazioni sessuali possono interessare > 50% delle donne affette in post menopausa. L'acido ialuronico (HA) è un polisaccaride naturale rappresentante un costituente fondamentale della matrice extracellulare della cute e della cartilagine. Questo studio monocentrico retrospettivo di coorte ha valutato l'applicazione di una crema vaginale a base di HA per 12 mesi in 51 donne in post menopausa affette dalla SGM. Dopo la fine del trattamento, la grande maggioranza delle pazienti trattate era soddisfatta. Tutti i sintomi correlati alla SGM e i punteggi QoL sono notevolmente migliorati alle visite durante il trattamento. Inoltre, la funzione sessuale misurata tramite il questionario standardizzato "Indice della Funzione Sessuale Femminile" (FSFI) e la soddisfazione generale per l'attività sessuale delle pazienti sono state significativamente migliorate durante il trattamento tra coloro che hanno riportato un'attività sessuale prima dell'inizio dello studio. In conclusione, questo studio ha dimostrato l'efficacia del trattamento a lungo termine con una crema vaginale a base di HA per migliorare i sintomi, la funzione sessuale e la qualità della vita in una popolazione di donne in post menopausa con SGM.

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DOI: 10.14660/2385-0868-134

INTRODUCTION

Vulvovaginal atrophy (VVA) is due to the drop of estrogen that occurs in women during menopause and it is characterized by the involution of the mucous membranes and tissues of the vulva and vagina[1–3]. The decrease of estrogen after menopause causes histological involution both in the vulva and in the vagina[2], such as thinning, reduced vascularization and elasticity, decreased engorgement and lubrication. Recently, the new terminology, genitourinary syndrome of menopause (GSM) has been proposed instead of VVA, to describe more accurately the constellation of symptoms and signs associated with menopause[4]. The syndrome includes genital symptoms such as dryness, burning, and irritation; sexual symptoms such as lack of lubrication, discomfort, and pain; and urinary symptoms such as urgency, dysuria, and recurrent urinary tract infections. Furthermore, GSM is associated with a significant deterioration of quality of life (QoL) and sexual function and sexual implications may affect >50% of postmenopausal women[5-7].

Current management of GSM is influenced by the type of signs and symptoms, by their severity but also by patients' clinical history, preferences and expectations[8,9]. Treatment of GSM is mainly distinguished in non-hormonal and hormonal therapies. The latter are usually indicated to treat patients reporting moderate-severe symptoms. However, non-hormonal therapies are popular since patients may be contraindicated to use hormones (mainly women with breast cancer or other estrogen-dependent gynecological malignancies) or refuse systemic/local hormones for personal reasons. In the last years, a fold of non-hormonal therapies has been suggested, and lubricants and moisturizers are the most commonly prescribed medications in clinical practice.

Hyaluronic acid (HA) is a natural polysaccharide representing an important part of the extra-cellular matrix of the skin and cartilage. A recent study conducted in the rat model demonstrated that HA gel was effective in the reversal of vaginal atrophy and is beneficial for improving vaginal microecosystem in the postmenopausal rat model. The HA vaginal gel can also improve the repair capacity of the vaginal epithelium[10]. Furthermore, different human studies have shown the efficacy and safety of different formulations (i.e. suppositories, gel, tablets) of HA for the treatment of GSM[11-15].

Here, we report our experience on the use of vaginal HA gel for the treatment of patients with GSM. The primary outcome of the study was to evaluate the proportion of satisfied patients with HA gel treatment at 12-month follow up. Secondary outcomes of the study were to assess the modifications in GSM-related symptoms, in the Vaginal Health Index (VHI) scores, QoL, sexual function and overall satisfaction with sexual life before and after treatment with HA gel.

MATERIAL AND METHODS

This was a single centre, retrospective cohort study conducted at the IRCCS Ospedale Policlinico San Martino of Genoa (Italy). The study included women referred to our clinic because of reporting GSM-related symptoms. It was conducted according to the Declaration of Helsinky revised in 1983. The participation of the women to the study was subjected to the acquisition of the written consent.

Inclusion criteria for this study were: symptoms of GSM; age >50 years; absence of menstruation for ≥12 months. Exclusion criteria were: use of any hormone replacement therapies (either systemic or local) within the 6 months prior to inclusion in the study; use of vaginal moisturizers, lubricants or any other local preparation within the 30 days prior to inclusion in the study; acute or recurrent urinary tract infections (UTIs); active genital infections (e.g., herpes genitalis, candida); prolapse stage ≥ II according to the pelvic organ prolapse quantification (POP-Q) system; (16) previous reconstructive pelvic surgery; any serious disease or chronic condition that could interfere with study compliance; psychiatric disorders precluding informed consent.

The primary outcome of the study was to assess the proportion of satisfied patients at 12-week follow up. Secondary outcomes were 1) effects of HA treatment on GSM-related symptoms; 2) changes VHI score before and after treatment; 3) changes in overall QoL; 4) changes in sexual function and overall satisfaction with sexual life.

Patients accepting to participate in the study were submitted to the following treatment: vaginal HA cream three times a week (Lubrigyn™, Uniderm Farmaceutici Srl, Rome, Italy). The duration of treatment was 12 months.

Sociodemographic characteristics of the study sample were collected at baseline and inclusion/exclusion criteria will be verified before starting the study protocol.

At baseline (T1), at 12-week follow-up (T2) and 12-month follow-up (T3), women were evaluated by using the VHI which consists of five measures:

elasticity, fluid volume, pH, epithelial integrity and moisture[17].

The intensity of GSM-related symptoms (vaginal dryness, vaginal burning, vaginal itching, dyspareunia and dysuria) was measured using a 10 cm visual analogue scale (VAS), where the left extreme of the scale indicates "absence of symptom" and the right indicated "symptom as bad as it could be", as previously reported in VVA. The intensity of GSM-related symptoms was evaluated before starting the treatment (T1), at T2 and at T3. At T3, the women rated the overall degree of satisfaction with the treatment by answering the following question: "Taking into consideration the variations in VVA symptoms, in overall well-being and quality of life, as well as the adverse effects experienced, if any, how would you define the level of satisfaction with HA gel treatment?". Answers were scored on a five-point Likert scale (very satisfied, satisfied, uncertain, dissatisfied, very dissatisfied). Satisfaction with the treatment was defined as "very satisfied" or "satisfied" answers.

At T1 and T3 women included in the study will fill-in the following anonymous questionnaires:

the Italian version of the female sexual function index (FSFI), a 19-item questionnaire developed as a brief, multidimensional, self-reported instrument for assessing the key dimensions of sexual function in women 18 (administered only to women who had sexual intercourses at baseline);

a 10-cm VAS to measure the overall satisfaction with sexual life, where the left extreme of the scale indicated "the worst level of satisfaction" and the right indicated "the best level of satisfaction" (administered only to women who had sexual intercourses at baseline);

the Short Form 12 (SF-12) to assess physical (PCS12) and mental (MCS12) component summary scores of QoL, as previously reported. 19

The normal distribution of continuous variable data was evaluated with the Kolmogorov-Smirnov test. Categorical variables were analysed using the Chi-square test. Continuous variables, before and after treatment, were analysed by using the paired t-test and the Wilcoxon Rank Sum Test accordingly to data distribution. Data are presented as mean ± standard deviation (SD), median and range. Data were analysed using the SPSS software version 20.0 (SPSS Science, Chicago, IL, USA). $P < 0.05$ was considered statistically significant.

RESULTS

Out of 51 patients invited to participate in the present study, 45 women (88.2%) finally accepted and were recruited. All patients included in the study completed the 12-month follow-up. The main characteristics of the study population are reported in tab. 1.

At T3, 18 (40.0%) women were very satisfied, 24 (53.3%) were satisfied, one (2.2%) was uncertain and two (4.4%) was unsatisfied with HA gel treatment **(Figure 1)**.

At baseline all the patients included in the study reported more than one GSM-related symptom. Vaginal dryness was reported by 45/45 women (100%), vaginal hitching by 37/45 women (82.2%), vaginal burning 39/45 (86.7%) women and dysuria by 27/45 (60.0%). A total of 33 women (73.3%) had sexual intercourses and, among these patients, dyspareunia was experienced by 28 women (84.8%).

Tab. 2 describes the changes in the severity of GSM-related symptoms during the study period. As far as QoL measured by SF-12 was concerned, at T3 the PCS12 was significantly improved ($p=0.007$) (50.8 ± 6.0) in comparison with baseline (47.8 ± 6.6). At the same follow-up time, a significant improvement was reported also for the MCS12 (46.4 ± 7.2) in comparison with baseline values (42.9 ± 8.5, $p=0.001$).

Fig. 2 shows the FSFI total and domain scores at baseline and at T3. A significant amelioration ($p<0.001$) of FSFI total score was observed among

Table 1. *Main characteristics of the study population*

Age (mean ± standard deviation)	60.4 ± 6.
Body mass Index (BMI (mean ± standard deviation))	24.2 ± 2.6
Smokers (n, %)	15 (33.3)
Level of education (n, %): Primary Secondary University	 3 (6.7) 27 (60.0) 15 (33.3)
Patients with previous live births (n, %)	42 (93.3)
Parity (median, range) Sexually active women (n, %)	1 (1-4) 33 (73.3)
Previous systemic hormone replacement therapy (HRT) (n, %)	12 (26.7)
Duration of previous HRT (months; median, range)	18 (2-60)

Figure 1. *Overall satisfaction after 12 months of treatment*

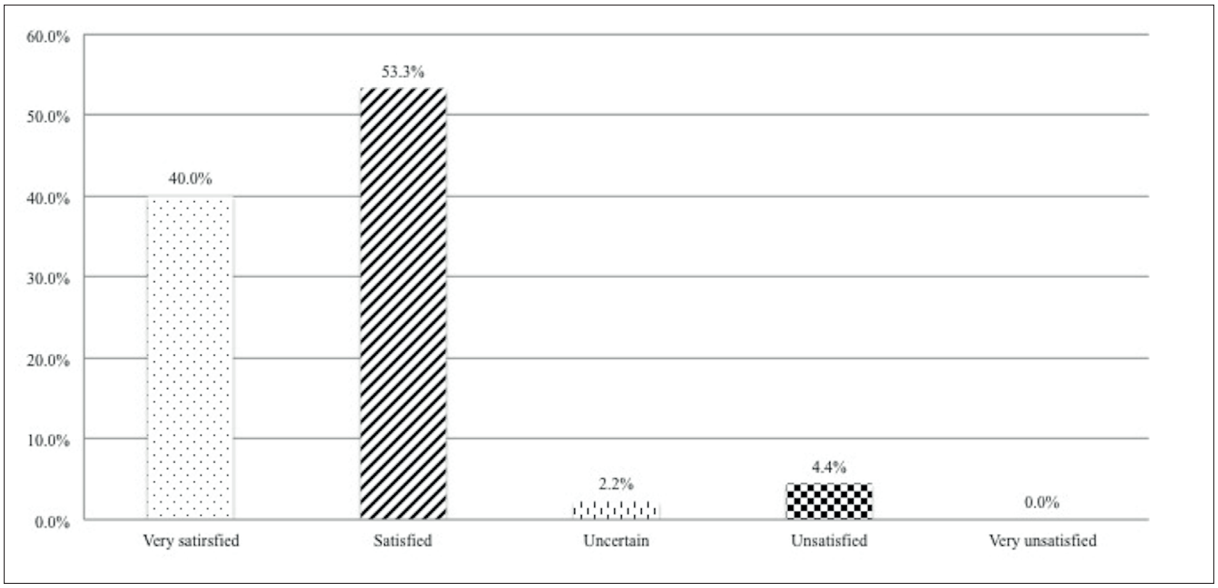


Table 2. *Presence and the severity of GSM-related symptoms in the study population.*

	Patients reporting GSM-related symptoms (n, %)	Baseline (T1)	12-week follow-up (T2)	12-month follow-up (T3)	p (T1 vs T2)	p (T1 vs T3)	p (T2 vs T3)
Vaginal dryness	45/45 (100)	8.4 ± 2.0	5.8 ± 2.0	2.7 ± 1.9	< 0.001	< 0.001	< 0.001
Vaginal hitching	37/45 (82.2)	6.7 ± 2.5	4.7 ± 1.5	2.3 ± 2.1	0.005	< 0.001	< 0.001
Vaginal burning	39/45 (86.7)	6.9 ± 2.2	4.9 ± 1.9	2.0 ± 2.8	0.001	< 0.001	0.001
Dysuria	27/45 (60.0)	5.9 ± 2.4	4.0 ± 1.6	2.3 ± 1.5	0.030	< 0.001	< 0.001
Dyspareunia*	28/33 (73.3)	8.1 ± 2.4	6.2 ± 2.9	3.2 ± 2.1	< 0.001	< 0.001	< 0.001

Severity of symptoms was measured using a 10-cm visual analogue scale. Data are presented as mean ± standard deviation

** Evaluated only among patients who had sexual intercourses at baseline*

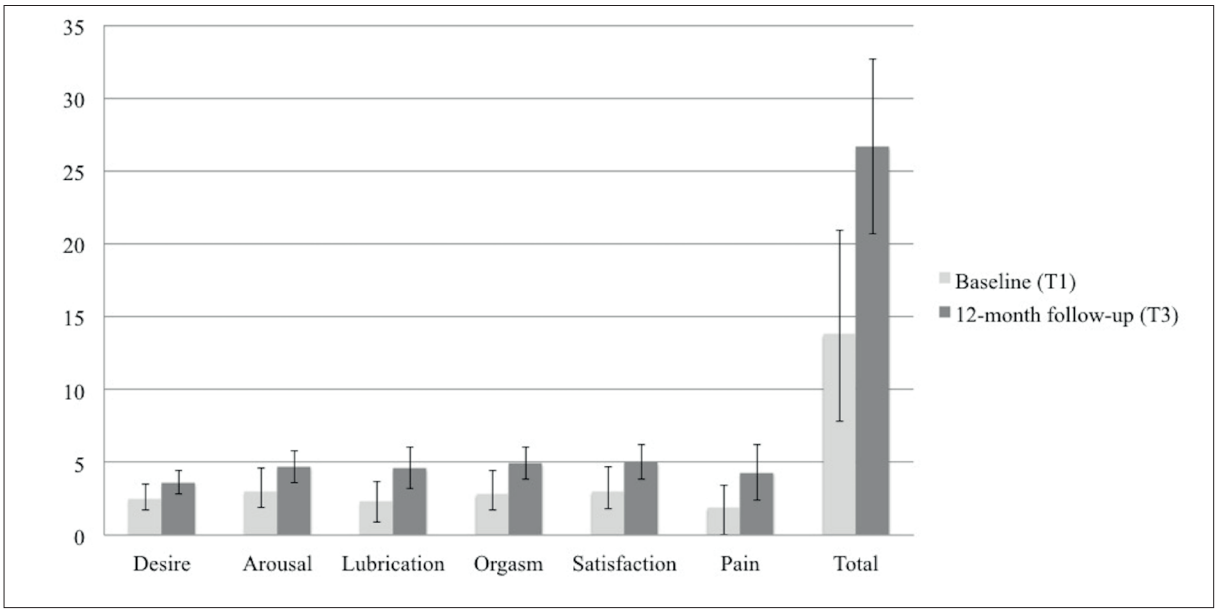
sexually active women at T3 (26.7 ± 6.0) in respect to baseline (13.8 ± 7.1). Similarly, each individual FSFI domain score was ameliorated after HA gel treatment (p<0.001, all) **(Figure 2)**. When compared with baseline (4.5 ± 1.5), the overall satisfaction with sexual life was significantly improved at the T3 (7.9 ± 1.7; p<0.001).

DISCUSSION

An involution of the mucous membranes and tissues of the vulva and vagina caused by the physiological drop of estrogen occur among women during menopausal age[1-3]. The vagina becomes narrower and shorter and the introitus can constrict[20]. Other common modifications occurring during the menopause are the progressive loss of elasticity and of rugal folds of the vaginal lining which becomes thinner and may show petechiae. Sebaceous glands decrease the production of secretions and consequently, lubrication is reduced and delayed, particularly during sexual intercourses[21,22]. For these reasons, postmenopausal women frequently experience GSM-related symptoms including vaginal dryness, burning and itching, but also dysuria and dyspareunia.

GSM is the new term for VVA and it is a

***Figure 2**. Changes in sexual function and overall satisfaction with sexual life after 12 months of treatment*



chronic and progressive syndrome. GSM may affect approximately 15% of premenopausal women and 40-54% of postmenopausal women, having a detrimental impact on quality of life, social activities and sexual relationships[8,9]. It is estimated that since women have a longer life expectancy than men, and about >17% of the population will be age >65 years by 2030, the consequences of declined endogenous estrogen levels in menopausal women should be of great interest to clinicians[25]. GSM is commonly underdiagnosed and undertreated due to sexual embarrassment or general disregard due to associating it as a liability of natural aging[26]. Current management of GSM is mainly based on the severity of symptoms, but also on patients' clinical history, preferences and expectations[8,9]. Available therapies are distinguished in hormonal and non-hormonal medications. Among non-hormonal therapies HA has been demonstrated efficacious and safe for the treatment of GSM. HA is a natural polysaccharide able to storage significant amount of water molecules and owns a crucial role due to the properties of formation and conservation of extra-cellular inflation, skin moistening in the case of inflammation and preservation of water equilibrium. An animal study including 60 ovariectomized rats aimed to evaluate the role and mechanism of the HA vaginal gel in their vaginal epithelium. This study demonstrated that this treatment was effective in the reversal of vaginal atrophy and beneficial for improving vaginal microecosystem in the postmenopausal rat model. In addition, it improved the repair capacity of the vaginal epithelium[10]. Different HA formulations (i.e. cream, tablets, suppositories, ovules) are available for the treatment of women with GSM. (11-15) In 2016, an Italian observational study including 46 consecutive postmenopausal women aimed to evaluate the effectiveness of an 8-week treatment with topical vaginal preparation containing HA in controlling signs and symptoms correlated with postmenopausal VVA. All patients have been investigated by the use of the VHI and of a VAS of symptoms at baseline and one month after the end of the study. This study showed that both VHI and VAS of genital symptoms reported significant improvements at the end of the study protocol. Furthermore, patients' degree of satisfaction at the end of treatment was reported as high (95%)[15]. The efficacy of HA vaginal tablets for the treatment of patients with VVA has been also tested in a Turkish randomized controlled trial. This study aimed to compare vaginal tablets of hyaluronic acid with vaginal tablets of estradiol. A total of postmenopausal women with VVA symptoms were randomized to take vaginal tablets of 25 µg estradiol (n = 21) (group I) or 5 mg HA (n = 21) (group II) for 8 weeks. VVA symptoms were evaluated by a self-assessed 4-point scale of composite score and the degree of epithelial atrophy was determined as, none, mild, moderate and severe. Vaginal pH and maturation index were measured and compared in both the groups. Both treatments were associated with significant

relief of vaginal symptoms, improved epithelial atrophy, decreased vaginal pH, and increased maturation of the vaginal epithelium, and these improvements were greater in group I. Therefore, the Authors concluded that HA vaginal tablets could be particularly indicated for those patients with VVA who do not want to or cannot take local estrogen treatment[13].

The current study aimed to evaluate the proportion of satisfied patients with HA cream treatment at 12-month follow up. In addition, this research assessed the modifications in GSM-related symptoms, in the VHI scores, QoL, sexual function and overall satisfaction with sexual life before and after treatment with HA cream. The first finding of this study is that the large majority of patients were satisfied with treatment at 12-month follow-up. The second finding was that all GSM-related symptoms and QoL scores significantly improved at the same time-point. The third finding was that sexual function as measured with FSFI was significantly ameliorated by HA treatment among who reported sexual activity at baseline. In particular, FSFI total score and all domains were significantly improved at 12-month follow-up. Furthermore, overall satisfaction with sexual life was significantly higher after 12-month treatment with HA cream.

This study has some limitations. The first limitation is represented by the inherent biases of the retrospective, single centre study design. Secondly, the limited number of patients included in the study and the absence of a control group prevent to draw definitive conclusions about the efficacy of treatment with HA vaginal cream for patients with GSM.

However, the study has also different strengths. Firstly, this is the first study with a long-term follow-up showing the benefits of HA local treatment at 12-month follow-up. Secondly, not only VHI and the intensity of GSM-related symptoms were evaluated but also the impact of the therapy on overall QoL using a validated questionnaire. Thirdly, this is the first study evaluating also the impact of HA treatment on sexual life of patients. In this study, women's sexual function was validated by using a standardized specific questionnaire to measure, in a statistically significant manner, multiple dimensions of their sexual response; moreover, it was also added a subjective assessment based on patients' perception of satisfaction with sexual experience after HA treatment.

In conclusion, this study demonstrated the efficacy of 12-month HA cream treatment to improve GSM-related symptoms, VHI, QoL, sexual function and overall sexual life in a population of postmenopausal women with GSM.

ACKNOWLEDGEMENTS

None

The authors declare that they have no conflict of interest.

This paper was not funded.

The study was conducted according to the Declaration of Helsinky revised in 1983. Informed consent was obtained from all individual participants included in the study.

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