Real-world performance and safety of vaginal ovules in reducing the vaginal symptoms associated with vulvovaginal atrophy and postmenopausal sexual dysfunction

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Abstract. Decreasing estrogen levels during the postmenopausal period results in tissue atrophy and physiological changes, such as thinning of the vaginal epithelium, prolapse and decreased pelvic floor strength and control. Sexual dysfunction associated with vaginal dryness occurs in postmenopausal patients. The present study (trial no. NCT05654610) was designed as an observational, multicenter, real-world clinical investigation to evaluate the performance and safety of the medical device Halova® ovules in decreasing vaginal symptoms associated with vulvovaginal atrophy and sexual dysfunction. A total of 249 female participants were treated with Halova ovules, both in monotherapy and in combination with vaginal lubricants. The primary objective was to evaluate the tolerability of Halova ovules in the management of symptoms associated with perimenopause or genitourinary syndrome of menopause. The evolution of clinical manifestations such as vaginal dryness, dysuria, dyspareunia and endometrial thickness was defined a secondary objective. Halova ovules were rated with 'excellent' clinical performance by 92.74% of participants as a standalone treatment and 95.71% of the study participants when used in association with vaginal lubricants. Sexual dysfunction-associated parameters, such as vaginal dryness and dyspareunia, were reduced by similar percentages in each arm, 82% (monotherapy) and 80% (polytherapy) for vaginal dryness and 72% in monotherapy vs. 48% polytherapy in reducing dyspareunia. No adverse reactions associated with treatment with Halova were reported. The medical device demonstrated anti-atrophic activity in the genitourinary tract, resulting in significantly improved symptoms associated with normal sexual functioning.

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Introduction

Vaginal dryness can be a sign of vulvovaginal atrophy, also known as the genitourinary syndrome of menopause. Vulvovaginal atrophy has key medical and psychological consequences, such as vulvovaginal pain, dyspareunia, urinary incontinence, less sexual desire and satisfaction, more difficulty reaching orgasm, as well as depression and anxiety, and is the most common symptom during menopause. Unlike hot flashes and night sweats, which resolve spontaneously, symptoms of vaginal dryness affecting the lower urinary tract develop over time. The prevalence of vaginal dryness increases in the years following menopause and causes symptoms such as itching, burning and pain during intercourse. Furthermore, it is estimated that ~17% of female patients between the ages of 17 and 50 years experience vaginal dryness and pain during sexual contact, which leads to anxiety and decreased libido (1). Its prevalence ranges from 36 to almost 84% and it is often underdiagnosed and undertreated (2,3). The condition may also occur earlier in perimenopausal women who take antiestrogenic medications or who have decreased levels of estrogen (4).

Currently, estrogen therapy, which is approved for the treatment of vaginal atrophy, is often associated with adverse effects and multiple contraindications in menopausal patients. Among these, metabolic imbalance, mood swings, bloating and risk of developing ovarian cancer are the most common (5,6). Furthermore, long-term use of estrogen therapy

may lead to breast cancer and should therefore be limited (7). During the reproductive age, ovaries produce a large number of circulating estrogens (3,6). Normally, vaginal walls are lubricated by cervical-vaginal fluid produced by the cervix at the top of the vagina. Lower levels of estrogen during the post-menopausal period decrease sexual desire and may affect all layers of the vagina, leading to narrowing of the vagina, loss of rugae, keratinization of the surface and thinning of the vaginal epithelium. A thin vaginal epithelium leads to increased susceptibility to trauma, with clinical signs such as bleeding, petechiae and ulceration with any type of pressure, including sexual activity or a simple gynecological maneuver (3,7).

In addition to the onset of menopause, estrogen levels decrease significantly due to other causes such as birth or breastfeeding, cancer treatment, surgical removal of the ovaries and anti-estrogen drugs used to treat uterine fibroids and endometriosis. Other causes of vulvovaginal atrophy include Sjogren's syndrome, allergies, cold medicines, antidepressants, vaginal washings, anxiety and stress overload (6,8).

The main symptoms of vulvovaginal atrophy include vaginal dryness and reduced lubrication during sexual activity, urge incontinence, inflammation, itching, discomfort, atypical vaginal discharge and dyspareunia, which affect the quality of life (9). In addition, recurrent urinary tract infections have frequently been reported (5,10).

Urinary complaints in postmenopausal patients should be managed following physical examination and laboratory diagnostic testing, including serum estrogen levels and Papanicolaou smear. Differential diagnosis should be considered to eliminate vaginal infection (candidiasis, trichomoniasis or bacterial vaginosis) or other conditions that cause chronic vaginal and vulvar itching, discharge or pain such as irritants and vulvovaginal dermatoses (11). Irritants that can cause chronic vaginal itching include perfumes, locally applied lubricants or cosmetic soaps. Vulvovaginal dermatoses that may cause similar symptoms include lichen sclerosus, planus and simplex chronicus.

The principal therapeutic target in the management of vaginal atrophy is the relief of its symptoms, particularly vaginal dryness. Treatment strategies are primarily based on the use of moisturizers and lubricants, including physical therapy, low-dose vaginal estrogen therapy, vaginal dehydroepiandrosterone and oral ospemifene, with a more modern approach including the use of vaginal lasers (12,13). Patients who experience problems with natural vaginal lubrication due to hormonal changes often benefit from estrogen therapy. In addition to estrogen treatment, or in case of side effects, preparations with moisturizing agents that help introduce and maintain water in the vaginal mucosa are recommended.

Non-hormonal treatments include vaginal/topical moisturizers and lubricants, such as a combination of *Hippophaë rhamnoides* oil, hyaluronic acid, glycogen, collagen, isoflavones and vitamins (14,15). Lubricants provide short-term relief and are typically used for vaginal dryness during intercourse, whereas moisturizers have long-lasting effects and may be used every 2-3 days (16).

Hormonal replacement therapy may be systemic (oral estrogen replacement) or localized (intravaginal/topical estrogen, intravaginal releasing rings and vaginal dehydroepiandrosterone). Estrogenic therapy is considered the most effective treatment for vaginal atrophy, dryness and dyspareunia in patients with estrogen deficiency. On the other hand, estrogen therapy is known for increased risk of stroke and thromboembolism. In addition, estrogen therapy should be administered with caution in patients who survive hormone-sensitive cancer as the systemic absorption of estrogen can stimulate the proliferation of breast cancer cells. Although systemic estrogen therapy improves symptoms of vaginal atrophy, systemic doses are higher than those used for topical application and should be administered only if other menopausal symptoms requiring treatment are present (3,7,17).

Post-marketing studies are primarily used to determine whether medical devices are effective and safe in a non-controlled, real-life setting. Halova is a medical device in the form of ovules with local action, intended for use as an adjuvant in the healing, re-epithelialization or calming of wounded, atrophic or irritated vaginal mucosa. The primary objective of this study was to observe the tolerability of Halova ovules in treating vaginal dryness and restoring the natural lubrication of the vaginal mucosa. The secondary objective was to evaluate the performance of the medical device by clinical examination in decreasing the symptoms of vulvovaginal atrophy, evaluation of endometrium thickness and vaginal pH. Additionally, the degree of patient satisfaction was assessed using a 5-point Likert Scale (18). There is need for insights on alternative therapeutic strategies for symptoms, sexual function and quality of life of patients with vulvovaginal atrophy and postmenopausal sexual dysfunction.

Materials and methods

Study design. The present study was designed as part of a medical device post-marketing clinical follow-up, involving routine care from a number of clinical practices. The study had an open-label, multicenter, non-randomized, real-world evidence study design. The data were collected between March and July 2022. The clinical sites and locations are listed in Table I.

Participants. The participant population included female patients aged 18-70 years of Caucasian ethnicity with clinical manifestations associated with the following conditions: Dryness in the vaginal region, perimenopause, vulvovaginal atrophy, menopausal disorder or vaginal prolapse. A total of 249 patients were evaluated; 179 patients received Halova ovules as monotherapy, while 70 used Halova ovules in association with vaginal lubricants (polytherapy). Subjects with psoriasis, vitiligo, plantar ulcers, lipoid necrobiosis, granuloma annulare and vulvar or cervical cancer were excluded. The sample size initially included a total of 249 subjects, with baseline characteristics shown in Table II.

The study involved 18 Romanian specialist physicians as investigators, each with 4-20 patients undergoing treatment with Halova ovules. Endometrial evaluation was performed by transvaginal ultrasonography. The total duration of the study was 30 days. The medical device was applied once daily, during days 1-10.

Prospective data were collected, including the initial diagnosis, transvaginal ultrasonography, vaginal pH value,

Table I. Clinical practices and locations.

Practice	City
Societatea comerciala Pan Medical SRL	Sibiu
Gynecological Office of Dr Ispasoiu Corina	Sibiu
Natisan Medical Center	Pitesti
Gynecological Office of Dr Rădulescu G Mihaela Elena	Ramnicu Valceea
Medical Office of Dr Saleh K Majed	Craiova
Hospital MedLife Humanitas Cluj-Napoca	Cluj-Napoca
Gynecological Office of Dr. Ioana Trotea Targu Jiu	Targu Jiu
Medical Office of Dr Surpanelu Oana	Iasi
Medsan	Cluj
Medical Clinic of Dr Cioata Ionel Trifon	Timisoara
Clinical Hospital 'Dr. Ion Cantacuzino' Bucharest	Bucharest
Tulcea County Emergency Hospital	Tulcea
Clinical Hospital 'Dr. Ion Cantacuzino' Bucharest	Bucharest
Clinical iMed Sibiu Oftalmologie, Obstetrica-Ginecologie	Sibiu
Medical Office of Obstetrics and Gynecology of Dr Popescu Dragos SRL	Sibiu
Gynecological Office of Dr Iliescu Irina	Iasi
Medical office of Obstetrics and Gynecology of Dr Sterie Ionut SRL	Tulcea
Medical Office of Dr Todorut Florina	Timisoara

All practices are located in Romania.

Table II. Baseline demographic data for sample population.

Baseline characteristic	n	%
Age, years		
<50	77	32.08
≥50	163	67.91
Female	240	100.00
Caucasian	240	100.00
Menopausal status		
Premenopausal	42	17.92
Perimenopausal	35	14.58
Menopausal	162	67.50
Physical activity		
Yes	49	20.42
No	191	79.58
Sexual activity		
Yes	141	58.75
No	99	41.25

vaginal symptoms and adverse events. Endometrial thickness on transvaginal ultrasound were as follows: >5 mm, absent; 4.1-5 mm, mild thickness; 3.1-4.0 mm, moderate thickness; 2.1-3 mm for serious thickness; and ≤2, mm severe. To assess pH, a piece of litmus paper was placed on the lateral vaginal wall until moist. A pH ≥4.6 indicated vulvovaginal atrophy, assuming the patient did not have bacterial vaginosis (if tests and wet mount were performed to exclude infection with *Gardnerella vaginalis*). Primary and secondary outcomes were collected at baseline and after 30 days.

Medical device. Halova is a medical device manufactured by Perfect Care Manufacturing S.R.L (European Medical Device Regulation device identification no. 5944754000754). Intravaginal administration is intended to promote and accelerate hydration, healing, epithelialization and/or soothing of injured, atrophic or irritated vaginal mucosa. Halova vaginal ovules are composed of sodium hyaluronate (5 mg), marigold extract (60 mg), vitamin E (10 mg), aloe vera oil (60 mg), semi-synthetic glycerides (1,587 mg), lanolin (50 mg), silicon dioxide (25 mg) and xylitol (3 mg).

The ovules melt evenly in the vaginal mucosa, forming a cream that contributes to restoring normal lubrication of the vaginal mucosa and helps preserve normal pH and vaginal flora. Halova ovules are intended for use in adult patients (including those in menopause) and are indicated for vaginal dryness caused by age, various pathologies or other drug treatments, relief of pain and discomfort during sexual intercourse, balancing of vaginal flora and vaginal pH preservation. Halova ovules contain ingredients that promote or accelerate hydration, healing, re-epithelialization and/or soothing of injured, atrophic or irritated vaginal mucosa.

Hyaluronic acid is an alternative to non-hormonal treatment for signs of vaginal atrophy and dyspareunia. Sodium hyaluronate retains a large amount of water, provides moisture to the vaginal tissue and is an effective treatment for vulvovaginal discomfort (19). Hyaluronic acid is contained in Halova at a concentration of 5 mg/ovule and is used to promote hydration of dry vaginal mucosa and re-epithelialization of damaged tissue. The mechanism of action of hyaluronic acid

with a high molecular mass at the level of the vaginal mucosa is realized by formation of an extracellular matrix with water trapped in the structure (20).

Calendula officinalis extract (3.3%) is used to prevent contamination with exogenous bacteria during handling of the medical device and to prevent microbiological contamination of the fat base with gram-negative bacteria and fungi.

Xylitol serves as a nutritional substrate. The ovule base is composed of a mixture of fatty base, lanolin and oily extract of aloe vera. Vitamin E prevents oxidative degradation of the fatty base (21).

The medical device is in the form of ovules of 1.8 g each, ovoid in shape, white or pale yellow, with a smooth appearance, without spots of color or areas with agglomerated powders. In the longitudinal section, the ovules have a homogeneous appearance, without agglomeration of particles and air bubbles. The medical device was administered for 10 days to patients meeting the eligibility criteria.

Ethical and regulatory considerations. Written consent for participation in the study was obtained from all patients. Owing to legal considerations (General Data Protection Regulation Directive effective from May 21, 2018, in all European Union countries), patients or their legal representatives have an absolute right to request that their data be removed from the study database. A notified Body (ENTE CERTIFICATIONE MACCHINE SRL) reviewed the post-marketing clinical follow-up plan, including ethical considerations. As the present study was a post-marketing clinical follow-up study, ethics approval was not required.

The study was conducted according to the Guide to Medical Devices: 'Post-market clinical follow-up studies and International Society for Pharmacoepidemiology (2015) Guidelines for 'Good Pharmacoepidemiology Practices (GPP)'.

The data collection and study procedures were conducted following the ethical principles of the Declaration of Helsinki (2013. Data were stored according to Annex E of ISO 14155:2020, Good Clinical Practice in Clinical investigation of medical devices for human subjects (22-25). The study and its details are registered at clinicaltrials.gov (ID no. NCT05654610).

Primary objectives. The primary objective was to evaluate the tolerability of Halova ovules in treating vaginal dryness and restoring natural lubrication of the vaginal mucosa.

Secondary objectives. The secondary objectives were to investigate the performance of the medical device by clinical examination, along with the degree of patient satisfaction (5-point Likert scale).

Statistical analysis. All statistical analyses were performed using Microsoft Excel Analysis ToolPak version 16.69.1, Excel Windows 10. $P<0.05$ was considered to indicate a statistically significant difference. The quality and completeness of data were preliminarily assessed. To examine treatment effect over time, Fisher's exact test was performed for categorical variables and the Mann-Whitney U test was used for non-normally distributed variables.

Results

Clinical performance. CONSORT diagram is shown in Fig. 1. In the monotherapy group, the treatment was rated by the majority of patients as 'excellent' (84.35%); in the polytherapy group, the treatment was rated as 'excellent' or 'highly effective' for the majority of patients (95.71%; Fig. 2).

Vaginal pH evaluation. The vaginal pH levels of the patients were evaluated after 30 days (Fig. 3). Normal vaginal pH was noted in 75% of patients treated with monotherapy and in 84% of patients receiving polytherapy.

Dyspareunia symptoms. Dyspareunia symptoms were evaluated using a 5-point scale, from 'absent' to 'severe' (Fig. 3). In patients using Halova ovules as monotherapy, 72% reported absent dyspareunia; in patients receiving polytherapy, 48% reported absent and 52% mild dyspareunia.

Endometrial thickness evaluation. Ultrasound was performed to determine endometrial thickness (Fig. 3). A notable proportion (76% in the monotherapy and 78% from the polytherapy group) of patients exhibited an endometrial thickness rating of 'absent'. 'Mild' and 'moderate' endometrial thickness accounted for 20 and 4%, respectively, of the study participants in the monotherapy group. In polytherapy, the percentages were similar, with 78% of patients with a rating of absent, 20% with a rating of mild and 2% with a rating of moderate.

Dysuria symptoms. A total of 64% of patients receiving monotherapy reported absent dysuria (Fig. 4). When Halova was administered as polytherapy, 78% of the study participants reported absent dysuria.

Vaginal dryness symptoms. Halova decreased vaginal dryness, with no vaginal dryness reported at in 82% in the monotherapy group and 80% of the patients from the polytherapy group respectively (Fig. 5).

Patient satisfaction. A total of 94.38% of patients treated with Halova monotherapy rated the treatment as 'excellent' (Fig. 6).

Discussion

Vulvovaginal atrophy and its primary symptoms (vaginal dryness and dyspareunia) are closely associated with female sexuality. Vaginal dryness can be severe and distressing enough to affect daily activity, sexual desire, and normal sexual intercourse (26). A total of ~40% of the women with vaginal atrophy report dyspareunia (27). Dyspareunia is defined as the recurrent pain that occurs during sexual intercourse. This has negative effects on sexuality and sexual function. Studies report that dyspareunia and postmenopausal vaginal health are taboo topics for a substantial number of patients (28,29). Both healthcare professionals and patients may find it difficult to approach the subject of sexual problems associated with menopause and vulvovaginal atrophy (29).

With the administration of Halova ovules, the symptoms of dyspareunia were decreased, thus favoring normal sexual function in affected patients. The beneficial effects of decreasing

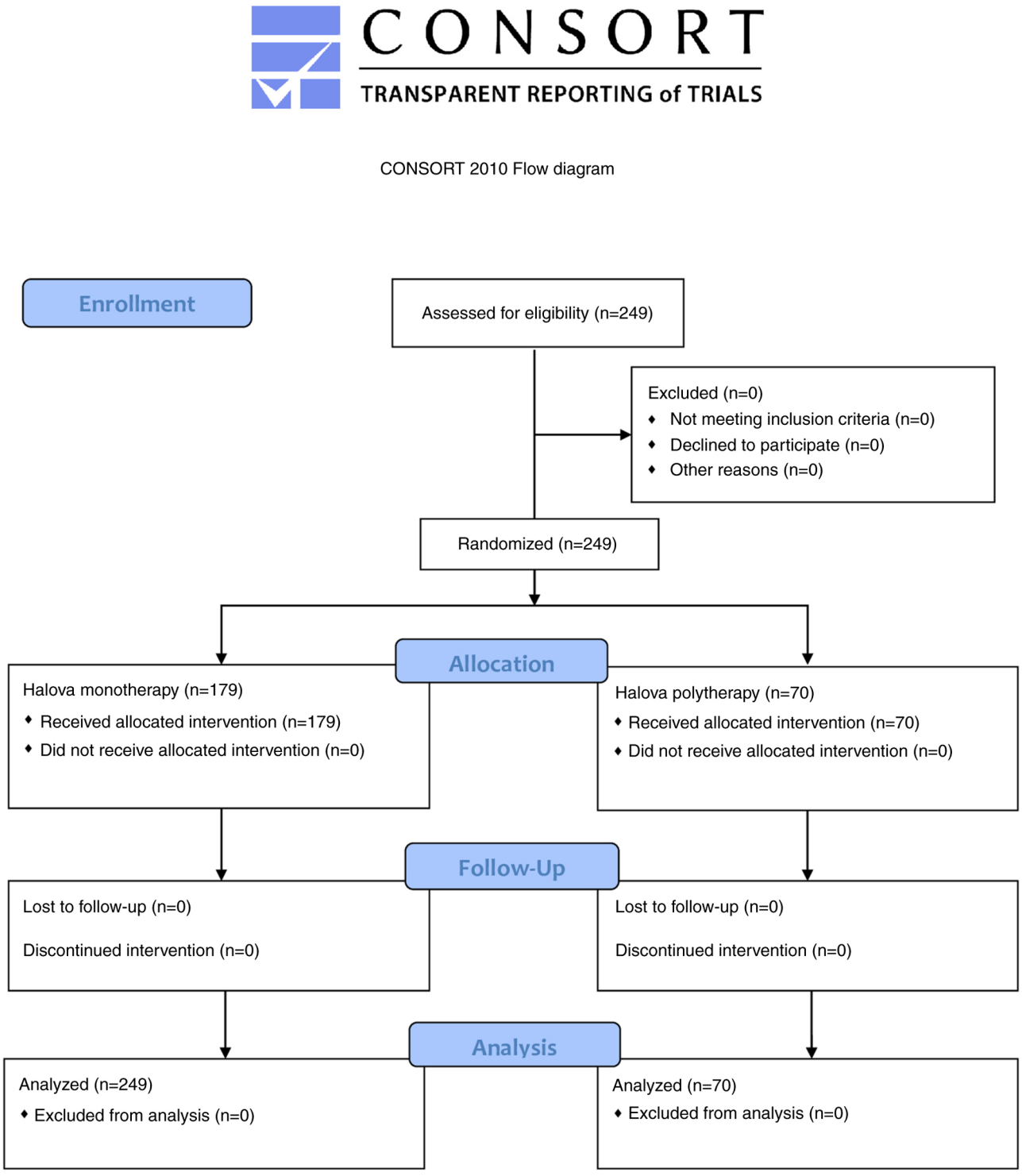

Figure 1. CONSORT diagram.

vaginal dryness can be explained by the local action of sodium hyaluronate. Multiple studies have confirmed the advantages of using topical sodium hyaluronate to treat vaginal dryness since it is a modern, safe and well-tolerated product (30,31). Owing to its highly anionic properties, sodium hyaluronate can attract water to swell, create volume, and provide structural support, thereby acting as a topical lubricant (32). Sodium hyaluronate is the salt form of hyaluronic acid, with a smaller molecular structure that increases stability and resistance to oxidation. Water solubility is associated with better skin and mucosal penetration, leading to better hydration. The mechanical protection of the vaginal endothelium is ensured by its high viscosity (33). Sodium hyaluronate has been used since 1980 for the treatment of various other diseases, such as dry eye, joint diseases, cystitis, atopic dermatitis, cataract extraction and osteoarthritis and as a filler for skin wrinkles (34,35). It provides a high safety profile that has been previously studied in postmenopausal patients (30).

During menopause, there is a decrease in the number of epithelial cells and glycogen production, which translates to

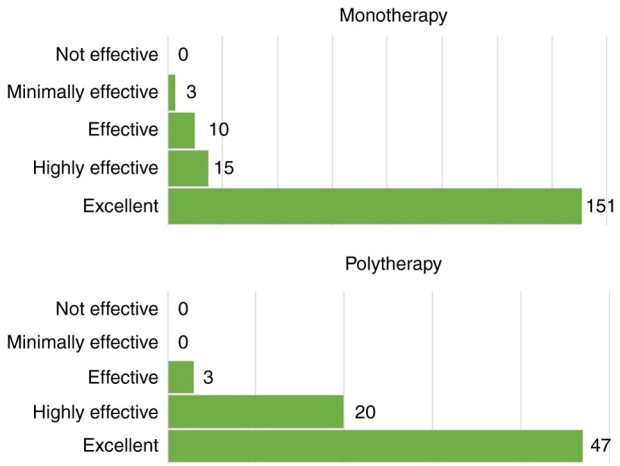

Figure 2. Clinical performance rated by investigators.

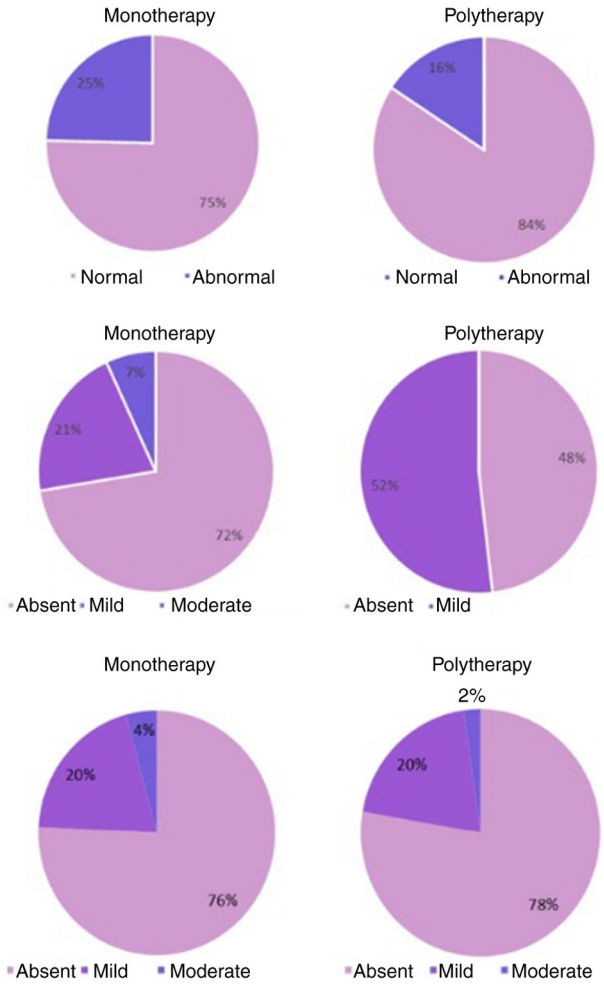

Figure 3. Measurement of vaginal pH, endometrium thickness and dyspareunia.

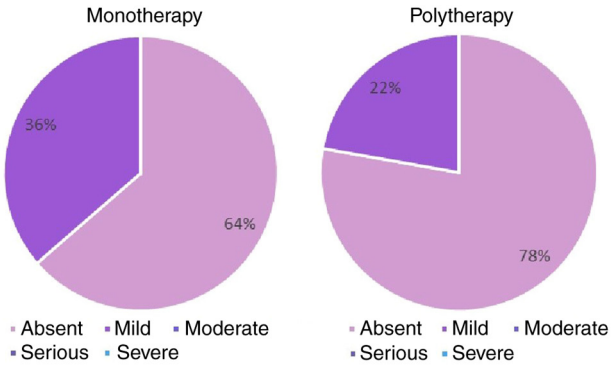

Figure 4. Dysuria symptoms at 30 days.

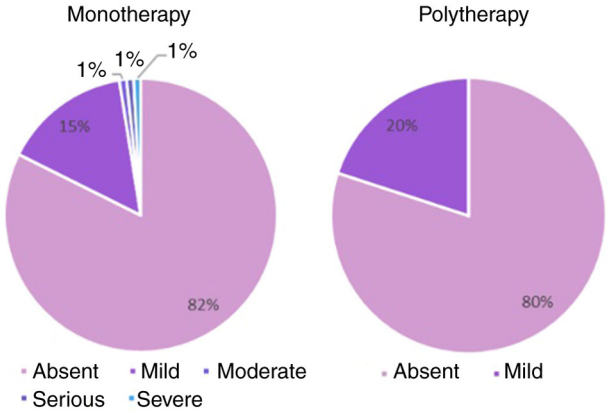

Figure 5. Vaginal dryness symptoms at 30 days.

less glucose converted to lactic acid. Lactic acid is important for maintaining a highly acidic pH and sustaining the activity of lactobacilli. The increase in vaginal pH in the absence of the lactic acid leads to alteration of the vaginal microflora, allowing the onset of urinary tract infections and vaginitis (36,37). A pH ≥5 is associated with vaginal atrophy and typical signs and symptoms, such as labial thinning, pale and dry vaginal mucosa and vulvovaginal erythema with or without bleeding (25). Poor sleep, cardiometabolic symptoms, muscle and joint pain and mood changes affect ~80% of women during diminishing estrogenic activity (26).

Halova is efficient in maintaining a healthy vaginal pH. The normal vaginal pH (3.8-4.5) is key for its protective role in blocking yeast and bacterial multiplication. Thus, the supportive role of the medical device in preventing vaginal infection was demonstrated based on its effective role in correction of unbalanced vaginal pH, with 88.79% of patients in the mono- and 95.35% in the polytherapy arm reporting normal vaginal pH.

The therapeutic indications of the device are linked to the treatment of both postmenopausal and non-menopausal vaginal dryness, relief of pain and discomfort during sexual intercourse, balance of vaginal flora, treatment of vaginal pH disturbances and boosting vaginal lubrication (38). Vitamin E, due to its rich composition of phytoestrogens, is a key element in stabilizing estrogen levels and can improve menopausal symptoms including hot flashes, irritability, insomnia, dizziness, palpitations, shortness of breath, and vaginal dryness. When applied locally, it favors healing and re-epithelialization through its nourishing and moisturizing effects. A recent review by Porterfield *et al* (27) summarized evidence for vaginal vitamin E efficacy in reducing patient-reported genitourinary symptoms in healthy

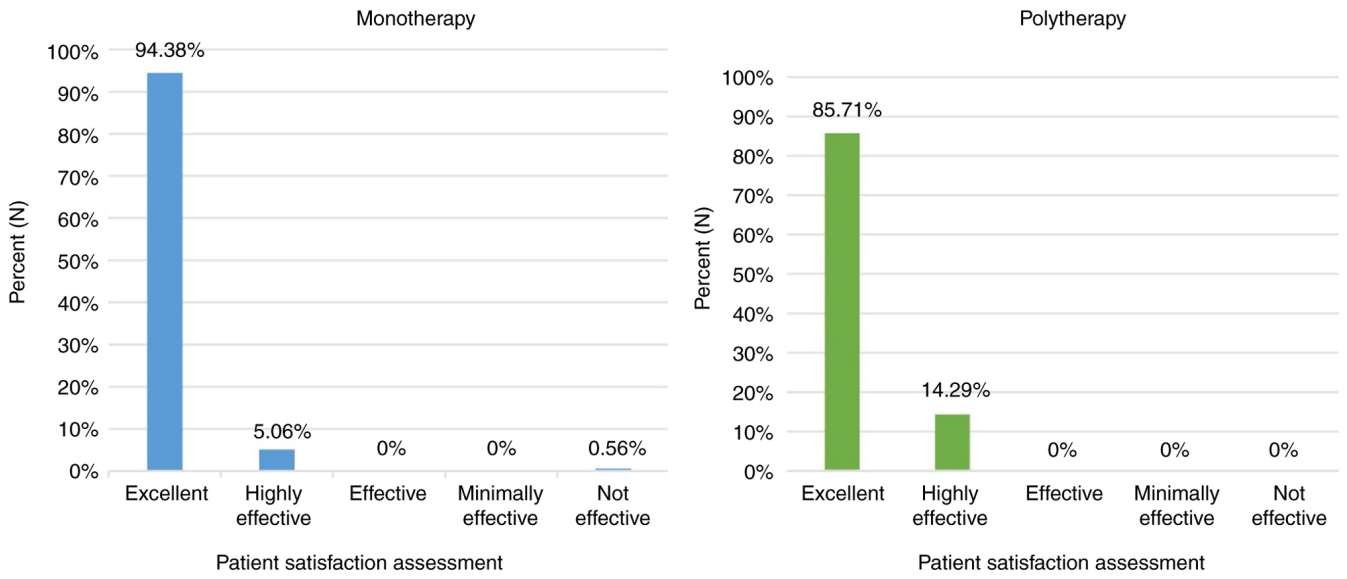

Figure 6. Patient satisfaction after using Halova ovules.

postmenopausal patients compared with placebo or vaginal estrogen. A review by Feduniw *et al* (28) concluded that vitamin E might be an option for standard hormone therapy and may be an option to treat symptomatic patients with contraindications to estrogen.

Fractional CO_2 laser has been proposed as alternative treatment in patients with vaginal atrophy with significant success rates and short-term adverse effects but a possible disadvantage is discomfort related to probe introduction, extraction and laser impulse transmission (39). Also, Schiavi *et al* (31) reported the efficacy of a medical device containing purified bovine colostrum in improving vulvo-vaginal atrophy, sexual function, urinary symptoms and quality of life in postmenopausal patients when applied topically.

There are concerns associated with the treatment of vaginal atrophy and its symptoms in patients with breast cancer. The increasing use of aromatase inhibitors has led to an increased incidence of vaginal atrophy, with an impact on the quality of life of patients with breast cancer (40). However, systemic or topical hormonal therapy is contraindicated in patients with breast cancer. Thus, Halova might be a therapeutic alternative in these patients and in patients in whom local estrogenic treatment is controversial, such as those with uterine cancer or a history of deep vein thrombosis or pulmonary embolism, stroke or myocardial infarction or blood clotting disorder (41). In the present study, recurrence of symptoms was not evaluated after the treatment period. An ancillary study should be designed to detect long-term performance.

A treatment consisting of 10 ovules of Halova was administered to 249 patients. Clinical endpoints were collected before and after the treatment. The results related to clinical performance, vaginal pH, vaginal symptoms indicate the device performance after 10 days of treatment.

Halova notably alleviated symptoms such as vaginal dryness, dyspareunia and dysuria while restoring the normal pH, thus harnessing the protective features of the vaginal microbiome. Halova applied intravaginally once per day for 10 days, may be a suitable treatment option for vulvovaginal atrophy and urogenital complaints in patients of reproductive age and postmenopausal status. The medical device was safe and effective in alleviating signs and symptoms of atrophic vaginitis in postmenopausal patients, such as dysuria, dyspareunia and vaginal dryness.

The medical device demonstrated anti-atrophic activity in the genitourinary tract, resulting in notably improved symptoms associated with normal sexual functioning. Future research is needed to confirm its long-term tolerability and performance long-term as well as during pregnancy. Limitations of the present study include the absence of a control group, short treatment follow-up, and heterogeneity of the sample population. Halova may be a promising treatment for conditions such as endometriosis or cystitis in treating symptoms such as dyspareunia, dysuria and pelvic pain; further studies are required to determine its efficacy in treating such conditions.

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Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Authors' contributions

IP, RP and DGI designed the study, and wrote the manuscript. IP and CT performed data collection and analysis. RP reviewed and edited the manuscript. IP, RAO and AAA interpreted data. All authors have read and approved the final manuscript. DGI and IP XX and XX confirm the authenticity of all the raw data.

Ethics approval and consent to participate

All participants provided written consent to the collection of their study data. The study was performed in accordance with the Declaration of Helsinki. Ethics approval was not required due to the nature of the study.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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