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Menopausal vaginal syndrome (MVS): a new-nonhormonal topical therapy

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ABSTRACT

Objective. The aim of this clinic retrospective study was to assess the regression of Menopausal Vaginal Syndrome following topical therapy with 2 g vaginal device *in ovuli* based on "DuoLact-EvoGold", whose active ingredients are: "A. Lactoferrin, *Lactobacillus casei* and *acidophilus*, FOS, and GOS and B. Natural vitamin E and Extravirgin Olive Oil".

Materials and Methods. The treatment consisted of one ovule 2 g "Duolact-Evogold" administered each evening for 10 consecutive days, followed by a 15day treatment suspension, and then a maintenance phase of 5 days. Symptom severity was evaluated using the Verbal Numerical Scale, while vaginoscopic findings and vaginal pH were assessed using the Visual Analogue Scale and Visual Colorimetric Scale. The "Grading classification" uses a score from 0 to 3. Sexual satisfaction was measured by the "Female Sexual Function Index".

Results. At baseline (T0), the most severe symptoms in patients with Menopausal Vaginal Syndrome were vaginal dryness and dyspareunia (each present in 47 patients; 78.3 %) and postcoital spotting (27 patients; 45%). Complete regression at T3 was observed for vaginal dryness and dyspareunia in 47 (78.3%) and 45 (75%) patients, respectively; complete absence of postcoital spotting was noted in 40 patients (66.7%). Spontaneous vaginal pain regressed completely.

Conclusions. Local therapy with "DuoLac-EvoGold" appears promising for the treatment of MVS, given its high rate of complete symptom regression.

INTRODUCTION

With menopause, the vagina undergoes both anatomical and physicochemical changes affecting the

mucosa, muscle tissue, and connective tissue. In menopause, estrogenic deficiency leads to mucosal thinning, leaving only basal and parabasal cells. In the stroma, collagen and lipofuscin deposition

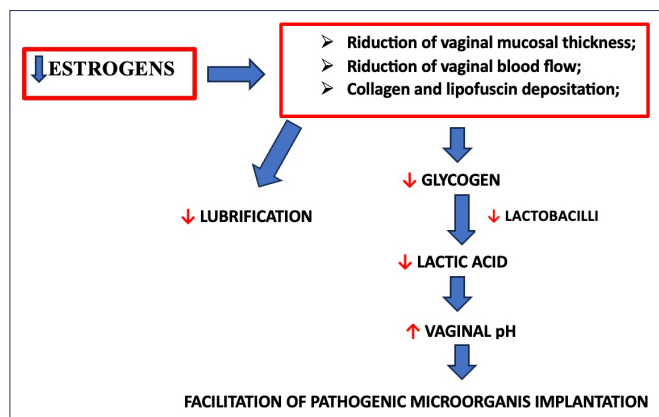


Figure 1. Vaginal physiopathology in menopause.

Table 1. Clinical examination of the menopausal vagina.

| |
|---|
| Atrophic, smooth vaginal mucosa with hyperkeratotic areas |
| Vaginal and/or urethral meatal stenosis |
| Ecchymotic and telangiectatic areas of the vaginal mucosa |

Table 2. Menopausal vagino urinary symptoms.

| | | |
|----------------------|---|-----------|
| Vaginal dryness | ➔ | Urgency |
| Dyspareunia | | Dysuria |
| Vaginal burning | | Frequency |
| Vaginal pain | | Burning |
| Itching | | |
| Post-coital spotting | | |
| Urinary symptoms | | |

Table 3. Genitourinary complications in menopause.

| |
|--------------|
| Vaginitis |
| Cystitis |
| Haematuria |
| Colporrhagia |

occur, and the stroma becomes infiltrated by lymphocytes and plasma cells. The connective tissue appears dense and fibrotic, the subepithelial elastic network is fragmented, and blood flow is reduced (Figure 1).

Clinically, the menopausal vagina presents an atrophic, smooth mucosa with hyperkeratotic areas, vaginal and/or urethral meatal stenosis, and often ecchymotic/telangiectatic areas (Table 1). Initially, symptoms may be confined to the vagina (Menopausal Vaginal Syndrome: MVS), whereas in advanced menopause, the urinary tract may also be involved, potentially leading to severe complications and the Genitourinary Syndrome of Menopause (GSM) (Tables 2 and 3). Physiologically, in reproductive age, vaginal pH is 4-4.5: lactobacilli metabolize glucose to lactic acid, lowering vaginal pH and forming a primary barrier against pathogens [1-3]; in menopause, alkalinization often raises

pH to ≥ 6.8 causing the onset of vaginal infections [1]. Estrogenic deficiency reduces cellular maturity, decreases glycogen production, lowers lactic acid formation, and thus alkalinizes the vaginal environment [1].

Acid pH ($\leq 4-4.5$) is important in the prevention of the infections [4, 5]. An important bioactive factor in the cervical-vaginal mucosa is lactoferrin with adjuvant function to lactobacilli [6].

In menopause, CST IV predominates (pH > 5), characterized by *Candidatus Lachnocurva vaginae*, *Gardnerella vaginalis*, *Atopobium vaginae*, *Prevotella*, *Streptococcus*, *Enterococcus*, *Bifidobacterium*, and *Staphylococcus*. A pH > 5 increases bacterial adhesion to the vaginal mucosa [1]. This predisposition leads to recurrent vaginal and genitourinary infections, affecting 28-40% of women in advanced menopause (Tables 2 and 3) [7].

Topical estrogenic therapy (suppositories or creams) has yielded the best results in menopause. Absorption depends on the degree of vaginal atrophy, receptor integrity, and vehicle used, being greatest at treatment onset and with severe atrophy [8]. Topical estrogen is contraindicated in a history of endometrial or breast carcinoma and atypical endometrial hyperplasia.

Recently, restoration of vaginal trophism with good patient compliance has been achieved using oral ospemifene tablets and intravaginal prasterone suppositories. Ospemifene, a selective estrogen receptor modulator (SERM), stimulates vaginal estrogen receptors, combating atrophic symptoms [9, 10]. Prasterone (dehydroepiandrosterone) is an inactive steroid precursor converted locally into estrogens and androgens with selective action on the vaginal mucosa [11, 12]. Literature remains cautious regarding both agents in patients with gynaecological oncologic history [10, 12].

Among nonhormonal topical therapies, polycarboxophil vaginal (PCV) gel, a highly adhesive polymer with strong buffering action, acidifies vaginal pH and rapidly alleviates symptoms of vaginal atrophy (dryness, pain, mucosal irritation) [13, 14].

Innovative physical therapies include fractional CO₂ laser and dynamic quadripolar radiofrequency, which alleviate GSM symptoms by promoting regeneration of epithelial and subepithelial vaginal tissues, improving vaginal trophism and MVS symptomatology [15].

Objective of the study

The purpose of the study is to evaluate the regression of MVS, after topical therapy with 2 g vaginal

suppositories based on “DuoLact-Evogold” whose active ingredients are: A. Lactoferrin, *Lactobacillus casei* and *acidophilus*, FOS (β FructoOligoSaccharides) and GOS (α GlucoOligoSaccharides); and B. Natural vitamin E and Extravirgin Olive Oil. The following parameters were considered:

- Attenuation or disappearance of symptomatology.
- Improvement of the clinical/structural vaginal picture.
- Satisfactory sexual life.
- Limitation of complications.

MATERIALS AND METHODS

The retrospective study took into consideration sixtythree patients with MVS attending the Lower Female Genital Tract Pathology Service at the Obstetrics and Gynaecology Unit of Città di Castello (PG) USL1 Umbria from January 1 to December 12, 2024. Inclusion criteria were patients affected by MVS with the following symptoms: vaginal itching, vaginal burning, vaginal pain, dyspareunia, vaginal dryness, post-coital spotting.

Patients with the following pathologies were excluded from the study: urinary tract and cervical-vaginal infections, neoplastic lesions, positive PAP smear and/or HPV Test, genito-urinary prolapse. Three patients were excluded from treatment: one with CIN 3, one with a urinary tract infection and genitourinary prolapse and one with Pap Test ASCH and positive HPV test.

The remaining 60 patients were treated with DuoLac-EvoGold 2 g suppositories.

The indications for topical treatment with 2 g “DuoLac-EvoGold” suppositories were as follows:

1. Vaginal menopausal symptomatology (vaginal dryness, dyspareunia, vaginal burning, vaginal itching, vaginal pain, postcoital spotting) (Table 2);
2. Severe dyspareunia and post-coital spotting: lubricating effect and adjuvant in the repair processes of the vaginal mucosa.
3. Restoration of vaginal trophism.
4. Vaginal atrophy in oncological patients undergoing chemotherapy and/or radiotherapy and/or oophorectomy with contraindications to the use of hormonal therapies.
5. Vaginal atrophy with contraindications to Hormone Replacement Therapy (HRT).

Patient age ranged from 50 to 80 years (mean 68.6 years). Obstetric history was as follows:

42 multiparous, 10 nulliparous, 8 with previous caesarean section. Gynaecological history included: three total laparohysterectomies with bilateral adnexectomy for uterine fibromatosis; three radical laparohysterectomies with bilateral adnexectomy plus chemo and radiotherapy (two for invasive endometrial carcinoma, one for invasive cervical carcinoma); one radical mastectomy with axillary lymphadenectomy plus chemo and radiotherapy for infiltrating mammary adenocarcinoma.

In the 53 patients without hysterectomy, colposcopy showed nonvisible SCJ T3, cervical mucosal atrophy, and normal transformation zone. All 60 underwent vaginoscopy to assess mucosal atrophy and ecchymotictelangiectatic areas. For colposcopy and vaginoscopy, performed at three time points with physiological solution, 3% acetic acid, and Lugol’s iodine, was used a Zeiss 150 FC colposcope. Vulvology exam was normal in all. No patient had received HRT.

The mechanism of action for topical vaginal therapy with 2 g “DuoLac-EvoGold” suppositories in MVS is shown in Table 4.

Table 4. The mechanism of action for topical vaginal therapy with 2 g “DuoLac-EvoGold” suppositories.

| DuoLact | |
|---|---|
| Lactoferrin | Bacteriostatic and bactericidal effects Interactions with lipoteichoic acid, LPS, and bacterial membranes Inhibition of bacterial adhesion to host tissue Promotion of biofilm formation Suppression of TNF α and IL 6 expression |
| <i>Lactobacillus casei</i> | Produces lactic acid, fostering beneficial vaginal bacteria Promotes growth of <i>Lactobacillus acidophilus</i> via amylase-media carbohydrate metabolism |
| <i>Lactobacillus acidophilus</i> | Adheres to vaginal epithelial cells, obstructing pathogen interaction Bactericidal activity against <i>G. vaginalis</i> , <i>E. coli</i> , <i>A. vaginae</i> , <i>S. aureus</i> Immunostimulatory effects |
| FOS (β fructooligosaccharides) & GOS (α gluco oligosaccharides) | Prebiotics that promote growth of lactobacilli and bifidobacteria, enhancing lactic acid synthesis in the vaginal microbiome |
| EvoGold | |
| Vitamin E | Antioxidant properties; protects cell membranes from oxidative damage and supports cellular renewal |
| Extra virgin olive oil | Protective effect on vaginal mucosa via phenolic derivatives (reducing oxidative mechanisms, enhancing cell vitality, decreasing histological alterations) Antitumoral and antibacterial effects Upregulates genes involved in cellular differentiation |

Table 5. Clinical, vaginoscopic, and vaginal pH grading.

| Score | Clinical grading VNS (Verbal Numerical Scale) | | | | | |
|-------|---|-------------|-----------------|------------------|---------|---------------------|
| | Dryness | Dyspareunia | Vaginal burning | Spontaneous pain | Itching | Postcoital spotting |
| | Absent | Absent | Absent | Absent | Absent | Absent |
| 0 | < 3 | < 3 | < 3 | < 3 | < 3 | < 3 |
| 1 | 3 – 7 | 3 – 7 | 3 – 7 | 3 – 7 | 3 – 7 | 3 – 7 |
| 2 | > 7 | > 7 | > 7 | > 7 | > 7 | > 7 |
| 3 | | | | | | |

| Score | Vaginoscopic grading VAS (Visual Analogue Scale) | | |
|-------|--|----------------------------------|----------------------------------|
| | Mucosal atrophy | Vaginal and/or urethral stenosis | Ecchymotic teleangiectatic areas |
| | Normal | Absent | Absent |
| 0 | ↓ 1/3 | ↓ 1/3 | 1/3 |
| 1 | ↓ 2/3 | ↓ 2/3 | 1/3 |
| 2 | ↓ >2/3 | ↓ >2/3 | >2/3 |
| 3 | | | |

| Score | Vaginal pH grading VCS (Visual Colorimetric Scale) |
|-------|--|
| 0 | 4-4.5 (Normal) |
| 1 | 4.6 – 5.6 (Mild Abnormality) |
| 2 | 5.7 – 6.7 (Moderate Abnormality) |
| 3 | > 6.8 (Severe Abnormality) |

Therapy

In the period from 1st January to 12th December 2024 the therapy involved the administration of one 2 g “DuoLact-EvoGold” suppository every evening to the 60 patients for 10 consecutive days; then a 15day suspension; then maintenance with one suppository every evening for 5 days. Evaluations at baseline (T0), after 10 days (T1°), and after 5 days of maintenance (T3°) included symptom assessment, vagin- oscopy, vaginal pH, and sexual grading test (FSFI).

- Time 0 (T0): after vaginal symptom assessment, vagin- oscopy, vaginal pH, FSFI begin with one suppository nightly for 10 nights.
- Time 1 (T1°): after 10 days, reevaluate vaginal pH, symptoms, vagin- oscopy, FSFI.
- Time 2 (T2°): after 15 days off therapy, patient applied one suppository nightly for 5 nights.
- Time 3 (T3°): after 5 days of treatment, reeva- luate vaginal pH, symptoms, vagin- oscopy, FSFI.

The clinical records of patients with MVS included a detailed recent and past obstetric and gynaecolog- ical history, menstrual history, vaginoscopic, vul- vological and colposcopic examinations and any previous use of hormonal therapies, vaginal symp- toms, vagin- oscopy with assessment of vaginal mu- cosal atrophy, vaginal and/or urethral stenosis and ecchymotic and teleangiectatic areas, vaginal pH and quality of sexual life were also notated.

The following tests were performed before the the- rapy: HPV test, Pap test, cervicalvaginal and urethral swabs, urine exam. The symptoms are “Graded” by Verbal Numerical Scale (VNS), vaginoscopic and pH

findings by Visual Analogue Scale (VAS) and Visual Colorimetric Scale (VCS). Grading is associated with a specific score (0-1-2-3) (Table 5).

Clinical grading was evaluated according to the in- tensity of the symptom (0; < 3; 3-7; > 7) (VNS: Verbal Numerical Scale) to which the respective score was given (0-1-2-3); the symptoms considered were the following: vaginal dryness, dyspareunia, vaginal burning, vaginal pain, postcoital spotting.

For vaginoscopic grading the following parameters have been taken into consideration by means of VAS:

1. degree of vaginal mucosal atrophy by histological evaluation: absent; reduction of 1/3; reduction of 2/3; reduction > 2/3;

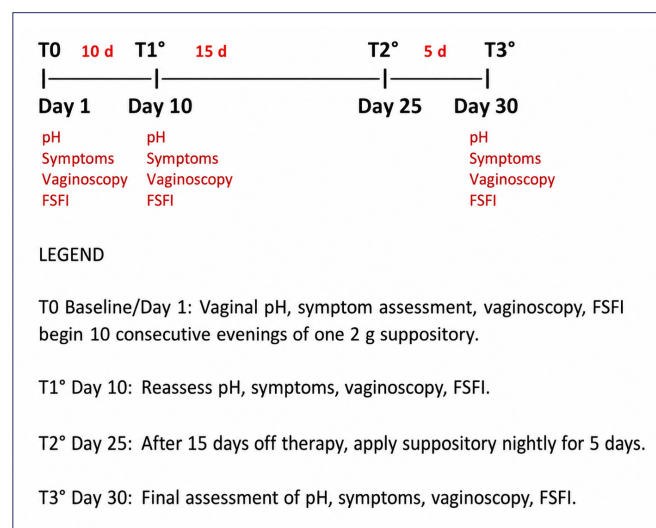


Figure 2. Protocol.

2. Vaginal and/or urethral meatus stenosis: absent; reduction of 1/3; reduction of 2/3; reduction > 2/3; vaginal stenosis: clinical evaluation; urethral stenosis: evaluation by cautious use of Hegar dilators - Ø 1-2-3 mm - for approximately 5 mm;
3. ecchymotic telangiectatic areas whose extension has been assessed (absent; 1/3, 2/3 and >2/3); visual assessment of the extension of the vaginal areas affected by menopausal ecchymosis/telangiectasia. Patients with uterus: examination of the ant-post-right/left side wall; Patients without uterus: examination of the ant-post-right/left side wall-vaginal dome divided into 4 quadrants.

For the vaginoscopic grading, the individual numerical evaluations were given a score of 0-1-2-3 in relation to the thickness of mucosal atrophy, diameter of vaginal stenosis and/or urethral meatus and the extent of ecchymotic-telangiectatic areas. For the vaginal pH grading, the following parameters were considered in range using VCS: pH 4-4.5 (normal); pH 4.6-5.6 (mild abnormality); pH 5.7-6.7 (moderate abnormality); pH \geq 6.8 (severe abnormality). For the Vaginal pH grading, the individual numerical evaluations were given a score (0-1-2-3). The degree of sexual satisfaction was expressed with the Female Sexual Function Index (FSFI). The score has been obtained from 19 questions that investigate multiple aspects of sexual life: desire, excitement, lubrication, reaching orgasm, the degree of satisfaction and pain during sexual intercourse. Each answer to each single question expressed a score, the sum of these scores provided a result that went from 2 to 36: severe sexual disorder < 10; moderate sexual disorder from 11 to 17; mild sexual disorder from 18 to 26; normality > 26. Follow-ups have been performed after 10 days of therapy (T1°) (symptomatology, vaginocopy, vaginal pH, quality of sexual life) and at 30 days (T3°) (symptomatology, vaginocopy, vaginal pH and quality of sexual life) after 5 days of therapy; 15 days of therapeutic suspension were planned from the 10th to the 25th day (**Figure 2**). At the end of the treatment, to evaluate the efficacy index of topical medical therapy, four parameters were considered (symptomatology, vaginoscopic examination, vaginal pH and quality of sexual life).

The retrospective study has also evaluated the complications that could arise during treatment.

The therapeutic efficacy index allowed to classify the VMS after therapy as “regressed”, “improved” or “persistent”.

RESULTS

The clinical, vaginoscopic, vaginal pH and FSFI parameters were evaluated at the 1st visit and start of therapy (T0), at 10 days of therapy (T1) and at 30 days (end of therapy) (T3) (**Tables 2 and 6**).

Table 6 summarizes in T0 (start of therapy – day 1) and T3° (end of therapy) the clinical grading expressed by VNS, the vaginoscopic grading by VAS and the vaginal pH grading by VCS.

For the evaluation of the “clinical grading”, the VNS was used with the corresponding score. The following symptomatic parameters were considered: vaginal dryness, dyspareunia, vaginal burning, spontaneous vaginal pain, vaginal itching and postcoital spotting (**Tables 2 and 6; Figure 3**).

The “vaginal dryness” at T0 (1st visit) was present in 47 patients (78.3%) with a score of 3 (severe symptomatology) and in 13 (21.7%) with a score of 2 (moderate symptomatology); at T3 (end of therapy) in 47 patients (78%) there was a complete absence of the symptom (score 0).

The “dyspareunia” at T0 (1st visit) was present in 47 patients (78.3%) with a score of 3 (severe symptomatology) and in 13 (21.7%) with a score of 2 (moderate symptomatology); at T3 (end of therapy) in 45 patients (75.0%) there was a complete regression of the symptom (score 0).

The “vaginal burning” at T0 (1st visit) was present in 34 patients (56.6%) with a score of 2 (moderate symptomatology), in 13 (21.7%) a scores of 1 (mild symptomatology) and in 13 (21.7%) a score of 0 (absence of symptom) while at T3 47 patients (78.3%) had a score of 0 (complete absence of the symptom).

The “spontaneous vaginal pain” at T0 (1st visit) was present in 20 patients (33.3%) with a score of 2 (moderate symptomatology), in 7 (11.7%) a score of 1 (mild symptomatology), in 33 (55.0%) a score of 0 (absence of symptoms), while at T3 (end of therapy) 60 patients (100%) presented a score of 0 (complete absence of the symptom).

The “vaginal itching” at T0 (1st visit) was present in 27 patients (45.0%) with a score of 2 (moderate symptomatology), in 6 (10%) with a score of 1 (mild symptomatology), in 27 (45%) with a score of 0 (complete absence of the symptom) while at T3 (end of therapy), 40 patients (66.7%) had a score of 0 (complete absence of the symptom).

For “postcoital spotting” at T0 (1st visit) 27 patients (45%) presented a score of 3 (severe symptomatology), 13 (21.7%) a scores of 1 (mild symptomatology), 20 (33.3%) a scores of 0 (absence of symptoms)

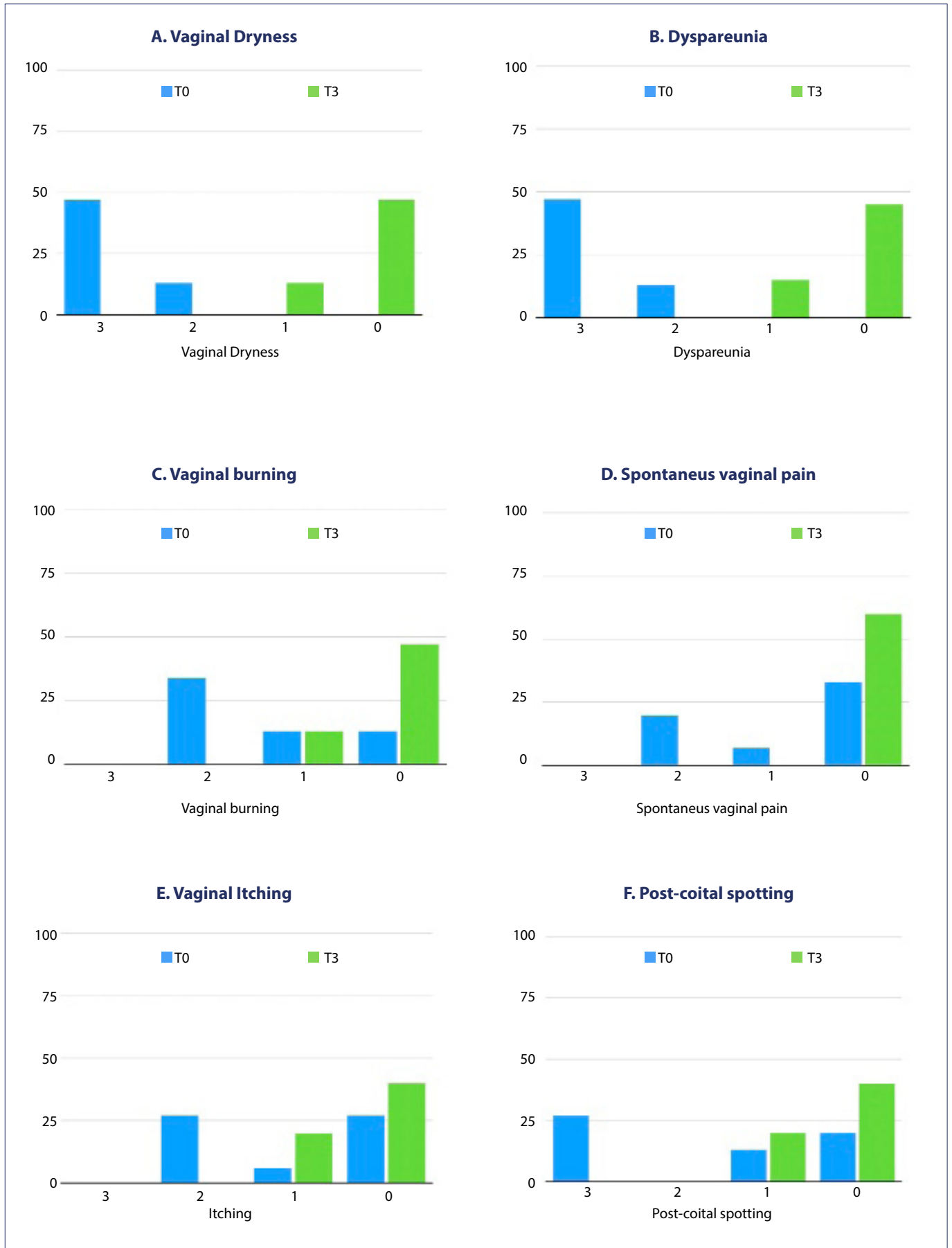


Figure 3. Clinical grading (T0-T3).

T0: Baseline; T3: end of the therapy

Table 6. Clinical, vaginoscopic and vaginal pH grading, (T0 - T3°).

| Score | Clinical grading VNS (Verbal Numerical Scale) | | | | | |
|-------|---|------------|-------------|------------|-----------------|------------|
| | Vaginal dryness | | Dyspareunia | | Vaginal burning | |
| | T0 | T3° | T0 | T3° | T0 | T3° |
| 0 | -- | 47 (78%) | -- | 45 (75.0%) | 13 (21.7%) | 47 (78.3%) |
| 1 | -- | 13 (21.7%) | -- | 15 (25.0%) | 13 (21.7%) | 13 (21.7%) |
| 2 | 13 (21.7%) | -- | 13 (21.7%) | -- | 34 (56.6%) | -- |
| 3 | 47 (78.3%) | -- | 47 (78.3%) | -- | -- | -- |

| Score | Clinical grading VNS (Verbal Numerical Scale) | | | | | |
|-------|---|-----------|-----------------|------------|----------------------|------------|
| | Spontaneous vaginal pain | | Vaginal itching | | Post-coital spotting | |
| | T0 | T3° | T0 | T3° | T0 | T3° |
| 0 | 33 (55.0%) | 60 (100%) | 27 (45.0%) | 40 (66.7%) | 20 (33.3%) | 40 (66.7%) |
| 1 | 7 (11.7%) | -- | 6 (10.0%) | -- | 13 (21.7%) | 20 (33.3%) |
| 2 | 20 (33.3%) | -- | 27 (45.0%) | -- | -- | -- |
| 3 | -- | -- | -- | -- | 27 (45%) | -- |

| Score | Vaginoscopic grading VAS (Visual Analogue Scale) | | | | | |
|-------|--|------------|----------------------------------|------------|---------------------------------|------------|
| | Mucosal atrophy | | Vaginal and/or urethral stenosis | | Ecchymotic telangiectatic areas | |
| | T0 | T3° | T0 | T3° | T0 | T3° |
| 0 | -- | -- | 7 (11.7%) | 7 (11.7%) | 3 (5.0%) | 20 (33.3%) |
| 1 | 13 (21.7%) | 40 (66.7%) | 20 (33.3%) | 40 (66.7%) | 7 (11.7%) | 33 (55.0%) |
| 2 | 27 (45.0%) | 20 (33.3%) | 20 (33.3%) | 13 (21.6%) | 7 (11.7%) | 7 (11.7%) |
| 3 | 20 (33.3%) | -- | 13 (21.7%) | -- | 43 (71.6%) | -- |

| Score | Vaginal pH grading VCS (Visual Colorimetric Scale) | | |
|-------|--|------------|------------|
| | pH | T0 | T3° |
| 0 | 4 - 4.5 (Normal) | | 53 (88.3%) |
| 1 | 4.6 - 5.6 (Mild) | 7 (11.7%) | 7 (11.7%) |
| 2 | 5.7 - 6.7 (Moderate) | 6 (10.0%) | -- |
| 3 | ≥ 6.8 (Severe) | 47 (78.3%) | -- |

T0: Baseline (Start of therapy - Day 1); T3°: Day 30 (End of the therapy) – See Figure 2.

while at T3 (end of therapy) 40 patients (66.7%) presented a score of 0 (complete absence of the symptom).

For the evaluation of the “vaginoscopic grading” the VAS was used with the corresponding score. The following parameters were considered: thickness of vaginal mucosal atrophy; diameter of vaginal and/or urethral stenosis; ecchymotic and/or telangiectatic areas whose extension was evaluated (Table 6, Figure 4).

The “vaginal mucosal atrophy” at T0 (first visit) was present in 20 patients (33.3%) with mucosal reduction > 2/3 (score 3) (severe atrophy), in 27 (45.0%) with mucosal reduction of 2/3 (score 2) (moderate atrophy), in 13 (21.7%) with mucosal reduction of 1/3 (score 1) (mild atrophy); no patients had normal mucosal trophism (score 0); at the end of therapy at T3 no complete absence of atrophy (score 0) nor persistence of severe atrophy (score 3) was observed at T3.

The “vaginal and/or urethral stenosis” at T0 (first visit) was present in 13 patients (21.7%) with score 3 (severe stenosis), in 20 (33.3%) with score 2 (moderate stenosis), in 20 (33.3%) with score 1 (mild stenosis) and in 7 (11.7%) with score 0 (absent stenosis); at T3 only in 7 patients (11.7%) the stenosis was regressed (score 0).

The “ecchymotic and/or telangiectatic areas” at T0 were present in 43 patients (71.6%) (area > 2/3) with score 3 (severe vaginopathy), in 7 (11.7%) (area ≈ 2/3) with score 2 (moderate vaginopathy), in 7 (11.7%) (area ≈ 1/3) with score 1 (mild vaginopathy), in 3 (5%) (absence of ecchymotic and/or telangiectatic areas) with score 0; at T3 20 patients (33.3%) had score 0 (complete absence of ecchymotic and/or telangiectatic areas).

The “vaginal pH grading” was evaluated with VCS. At T0 (1st visit) 47 patients (78.3%) presented score 3 (severe pH abnormality), 6 (10%) score 2 (moderate pH abnormality), 7 (11.7%) score 1 (mild



Figure 4. Vaginoscopic grading – vaginal pH grading – FSFI (T0-T3)

T0: Baseline; T3: end of the therapy.

pH abnormality); no patients had normal pH; at T3 (end of therapy) 53 patients (88.3%) presented normal pH (score 0) (Table 6, Figure 4).

In Table 7, all clinical, vaginoscopic and vaginal pH parameters were evaluated at T0 (baseline visit), T1 (after 10 days of treatment) and T3 (day 30, after 5 days of retreatment).

The parameters related to sexual function were evaluated with the FSFI. From the graph, on the abscissa all patients treated with “DuoLact-Evo-Gold” are indicated while on the ordinate at T0 is shown the FSFI score obtained before therapy and at T3 the score at the end of therapy. A substantial improvement in the score is demonstrated in all patients. In some patients the “sexual satisfaction” index exceeds 26. A general increase in FSFI values from T0 (1st visit) to T3 (end of therapy) is observed, in-

dicating an overall improvement in sexual function in the patients included in the study (Figure 4).

DISCUSSION

In menopause, with the progressive cessation of hormone production, the vaginal mucosa becomes atrophic, glycogenproducing epithelial cells disappear, lactobacilli are markedly reduced, and the vaginal environment presents a pH > 6.8. The vaginal microbiota is thus composed predominantly of a mixed bacterial flora of faecal origin that is potentially pathogenic, which increases the risk of genitourinary disorders [7].

The therapy for MVS includes a wide range of therapeutic options (Table 8).

Table 7. Clinical, vaginoscopic and vaginal pH grading (T0 - T1° - T3°).

| Score | Clinical grading VNS (Verbal Numerical Scale) | | | | | | | | |
|-------|---|-----------|-----------|-------------|-----------|-----------|-----------------|-----------|-----------|
| | Vaginal dryness | | | Dyspareunia | | | Vaginal burning | | |
| | T0 | T1° | T3° | T0 | T1° | T3° | T0 | T1° | T3° |
| 0 | -- | -- | 47(78%) | -- | -- | 45(75.0%) | 13(21.7%) | 20(33.3%) | 47(78.3%) |
| 1 | -- | 13(21.7%) | 13(21.7%) | -- | 13(21.7%) | 15(25.0%) | 13(21.7%) | 20(33.3%) | 13(21.7%) |
| 2 | 13(21.7%) | 47(78.3%) | -- | 13(21.7%) | 47(78.3%) | - | 34(56.6%) | 20(33.3%) | -- |
| 3 | 47(78.3%) | -- | -- | 47(78.3%) | -- | -- | -- | -- | -- |

| Score | Clinical grading VNS (Verbal Numerical Scale) | | | | | | | | |
|-------|---|-----------|----------|-----------------------|------------------------|-----------|----------------------|------------------------|-----------|
| | Spontaneous pain | | | Itching | | | Post-coital spotting | | |
| | T0 | T1° | T3° | T0 | T1° | T3° | T0 | T1° | T3° |
| 0 | 33(55.0%) | 40(66.7%) | 60(100%) | 27(45.0%) | 27(45.0%) | 40(66.7%) | 20(33.3%) | 20(33.3%) 27(45.0%) | 40(66.7%) |
| 1 | 7(11.7%) | 13(21.7%) | -- | 6(10.0%) 27(45.0%) | 20(33.3%) 13(21.7%) | -- | 13(21.7%) | 13(21.7%) | 20(33.3%) |
| 2 | 20(33.3%) | 7(11.6%) | -- | -- | -- | -- | -- | -- | -- |
| 3 | -- | -- | -- | -- | -- | -- | 27 (45%) | -- | -- |

| Score | Vaginoscopic grading VAS (Visual Analogue Scale) | | | | | | | | |
|-------|--|------------|-----------|------------------------------------|-----------------------|-----------------------|---------------------------------|------------------------|------------------------|
| | Mucosal atrophy | | | Vaginal and/or urethral stenosis | | | Ecchymotic telangiectatic areas | | |
| | T0 | T1° | T3° | T0 | T1° | T3° | T0 | T1° | T3° |
| 0 | -- | -- | -- | 7(11.7%) 20(33.3%) 20(33.3%) | 7(11.7%) 40(66.7%) | 7(11.7%) 40(66.7%) | 3(5.0%) 7(11.7%) | 6 (10.0%) 27 45.0%) | 20(33.3%) 33(55.0%) |
| 1 | 13(21.7%) | 40(66.7%) | 40(66.7%) | 13(21.7%) | 13(21.6%) | 13(21.6%) | 7(11.7%) | 27(45.0%) | 7(11.7%) |
| 2 | 27(45.0%) | 20 (33.3%) | 20(33.3%) | -- | -- | -- | 43(71.6%) | -- | -- |
| 3 | 20(33.3%) | -- | -- | -- | -- | -- | -- | -- | -- |

| Score | Vaginal pH grading VCS (Visual Colorimetric Scale) | | | |
|-------|--|-----------|------------|-----------|
| | pH | T0 | T1° | T3° |
| 0 | 4 - 4.5 (Normal) | -- | 20(33.3%) | 53(88,3%) |
| 1 | 4.6 - 5.6 (Mild) | 7 (11.7%) | 33 (55.0%) | 7(11.7%) |
| 2 | 5.7 - 6.7 (Moderate) | 6(10.0%) | 7(11.7%) | -- |
| 3 | ≥ 6.8 (Severe) | 47(78.3%) | -- | -- |

T0: baseline (Day 1); T1°: Day 10; T2°: Day 25; T3°: Day 30 (End of the therapy) – See Figure 2.

Table 8. Treatment options for menopausal vaginal syndrome (MVS).

| |
|---|
| Hormonal therapy |
| Systemic hormone replacement (if indicated for other reasons): estrogens, estrogen-progestin, tibolone, TSEC |
| Vaginal estrogen therapy |
| Vaginal progesterone |
| SERMs |
| Ospemifene |
| Non-hormonal therapy |
| Non-hormonal lubricants, moisturizers, and emollients (e.g., hyaluronic acid with lactic acid, calendula) |
| Topical hyaluronic acid |
| Hyaluronic acid with autologous platelet-rich plasma |
| Hyaluronic acid with high-concentration norm baric oxygen |
| Local bovine colostrum |
| Colostrum with visnadine and prenyl-flavonoids |
| Isoflavones |
| Polycarbophil vaginal gel (PCV) |
| Physical therapies |
| Radiofrequency |
| Fractional CO ₂ laser |

It has been repeatedly demonstrated that topical hormonal treatments (estradiol, estriol, prasterone) are significantly superior to placebo for the improvement of GSM (genitourinary syndrome of menopause) and are nevertheless considered the “Gold Standard” for this syndrome [16, 17]. However, Scientific Society Guidelines indicate that nonhormonal, hydrating and lubricating products should be regarded as firstline treatment for GSM.

From a literature review of 136 studies meeting the search criteria, several medical and physical therapies were considered (vaginal dehydroepiandrosterone, ospemifene, polycarbophilbased moisturizing cream, tibolone, vaginal hyaluronic acid, testosterone, and CO₂ laser therapy). All therapies improved the subjective and objective signs of atrophy. Except for hyaluronic acid, all therapies improved sexual function. The authors concluded that most nonestrogenic therapies are effective treatments for the various symptoms of menopausal vaginal syndrome (MVS) [18]. Estrogenic topical vaginal therapies achieve results in MVS comparable to nonhormonal ones (hyaluronic acid, polycarbophil gel, CO₂ laser, etc.); hormonal therapies are contraindicated in patients with a positive oncological history of breast or endometrial cancer [19].

Vaginal hormonal therapies (estrogens – dehydroepiandrosterone) are safe and effective and improve

the symptoms of MVS. Systemic hormonal therapy is less effective on vaginal atrophy symptomatology [8, 20].

Twentyfive primary studies on the treatment of MVS with ospemifene demonstrated a high clinical response to symptoms (vaginal dryness and dyspareunia), with a favourable safety profile and very few adverse events [10, 21-23].

Over the years, many nonhormonal treatments have been used in cases of menopausal vaginal syndrome associated with mucosal atrophy. The most frequently used “lubricating/emollient substances” consist of a combination of several active ingredients (hyaluronic acid for hydrating action, lactic acid to restore physiological vaginal pH, calendula for hydrating and emollient properties, a complex of naturalorigin functional substances with soothing and antiinflammatory properties such as *Betula alba*, *Scrophularia nodosa*, *Aloe barbadensis*).

In recent years, alternative physical and nonhormonal topical vaginal therapies have been proposed. Among the “physical therapies”, fractional CO₂ laser [24-26], radiofrequency, and lipofilling have seen predominant use, with initially encouraging results. However, the pain associated with these physical procedures, their high costs, and the need for repeat interventions for recurrences are their major drawbacks. Recently, warnings from some American Scientific Societies regarding the risk of facilitating the progression of preneoplastic lesions have led to reduced use of CO₂ laser in cases of vaginal atrophy [27].

The use of “nonhormonal topical vaginal therapies” refers to the following substances: local hyaluronic acid; hyaluronic acid combined with autologous plateletrich plasma; hyaluronic acid combined with highconcentration norm baric oxygen; local colostrum; colostrum combined with visnadine and prenylflavonoids; isoflavones and PCV.

Hyaluronic acid is a natural polysaccharide present in large quantities in the extracellular matrix of the skin, cartilage, and submucosal connective structures. At the vaginal level it draws water by osmosis, ensuring adequate mucosal hydration.

In vitro studies on platelet cultures (PRP: Platelet Rich Plasma) or platelets with hyaluronic acid (PRPHA: Platelet Rich Plasma – Hyaluronic Acid) in autologous plasma on vaginal mucosa taken from surgical interventions for genital prolapse in postmenopausal women have shown an increase in the S and G2M phases of the cell cycle, confirming im-

proved cell proliferation, increased fibroblasts and collagen, and prevention of cellular senescence [28]. The use of hyaluronic acid combined with high-concentration norm baric oxygen in MVS has shown significant improvement in both patient-reported subjective symptoms and the clinical picture of the vagina (elasticity and mucosal trophism). The greatest benefit concerns the reduction of vaginal dryness and the disappearance of dyspareunia. Oxygenation of the vaginal mucosa promotes mucosal regenerative activity [29, 30].

Numerous studies have been conducted on the topical vaginal use of bovine colostrum, considering various indices related to the clinical and morphological aspects of the vaginal mucosa: total and single Verbal Rating Scale (VRS), Maturation Index (MI), FSFI and Vaginal Health Index (VHI). Improvement was noted in all indices. However, in the presence of mucosal atrophy, colostrum predominantly reduces vaginal dryness, promotes trophism, and reduces dyspareunia. This effect persists for about one month and is supported by improvement of the vaginal environment [31, 32]. The efficacy of colostrum cream combined with visnadine and prenylflavonoids was also evaluated, showing significant improvements in various MVS parameters. Visnadine has a vasodilatory effect, ensuring improved vaginal blood flow and thus better hydration and lubrication. Prenylation of flavonoids may increase their bioactivity but decrease their bioavailability [33].

Retrospective literature surveys on the use and efficacy of isoflavones in MVS over three time periods (1996-2013 Medline, 1990-2013 Scopus, 2013-Cochrane Central Register) selected 7 studies on cellular maturation and 2 on vaginal dryness. Soy isoflavones appeared to improve vaginal symptoms *versus* control but were more effective in quantitative analysis, albeit not statistically significant. While soy isoflavones can improve menopausal vaginal symptoms, studies remain inconclusive due to vast heterogeneity [34].

The effects of phytoestrogens on urogenital menopausal symptoms were evaluated by a systematic review from 2000 to 2020 (PubMed, Embase, Web of Science, Cochrane Library, Scopus, ProQuest), selecting 33 articles. Various phytoestrogens were used: *Pueraria mirifica*, fennel, hops (*Humulus lupulus* L.), *Glycine max* (L.) Merr, soy, red clover, *Cimicifuga racemosa*, genistein, daidzein, glycitein, and isoflavones in various forms (oral capsules and tablets, dietary supplements, creams, gels, and va-

ginal suppositories). A nonsignificant symptomatic urogenital improvement was demonstrated, greater with vaginal use. The study's limitation is heterogeneity of active ingredients and modes of use [35]. A significant increase in blood vessels in the vaginal mucosa of postmenopausal women was observed after topical treatment with 4% *Glycine max* (L.) Merr isoflavone gel, ensuring good vaginal lubrication and improved dyspareunia [36].

Use of PCV gel in perimenopausal and postmenopausal women, administered twice weekly for 30 and 180 days, resulted in a reduction of VAS scores for vaginal dryness, irritation, and dyspareunia, improvement in VHI and reduction in GSS (Global Symptom Score). No side effects were reported. PCV administration for 30 days rapidly improves atrophy symptoms, and extending to 6 months further increases efficacy. No contraindications were reported [13]. A randomized prospective study in MVS compared moisturizing polycarbophil gel *versus* hyaluronic acid with overlapping results for vaginal dryness [37].

From the retrospective survey on the use of "Duo-Lac-EvoGold" suppositories, the most severe symptoms (score 3) at the first examination (T0) in women with MVS were vaginal dryness and dyspareunia in 47/60 (78.3%) and postcoital spotting in 27/60 (45%) (Table 7); at T3 complete absence of the symptom (score 0) was observed in 47/60 (78.3%), 45/60 (75.0%), and 40/60 (66.7%) respectively.

Vaginal burning, spontaneous pain, and itching were not severe at T0 but mild to moderate; at T3 absence of these symptoms was seen in 47/60 (78.3%), 60/60 (100%), and 40/60 (66.7%) respectively.

Vaginal mucosal atrophy, vaginal/urethral stenosis, and ecchymotictelangiectatic areas were severe (score 3) at T0 in 20/60 (33.3%), 13/60 (21.7%), and 43/60 (71.6%) respectively. At T3 no patient had severe ecchymotictelangiectatic areas and 20/60 (33.3%) had no altered vaginal areas (score 0); vaginal atrophy at T3 was moderate in 20/60 (33.3%) and mild in 40/60 (66.7%), with no severe or absent atrophy. Vaginal/urethral stenosis at T3 was mild-moderate in 53/60 (88.3%), unchanged without atrophy (score 0) and no patients with severe stenosis.

Vaginal pH at T0 was severely abnormal (pH > 6.8, score 3) in 47/60 (78.3%) and regressed to normal (4.0-4.5, score 0) in 53/60 (88.3%) at T3.

In the FSFI, the wide variability of individual scores visible in the graph may reflect different individual responses. Most T3 scores are higher than T0, suggesting the therapeutic path contributed positively

to multiple aspects of sexual function (desire, arousal, lubrication, orgasm, etc.). This improvement is attributable to reduction of menopausal physical discomforts (vaginal dryness, dyspareunia, vaginal burning) (Figure 4).

Of the 60 patients treated with “DuoLac-EvoGold”, 36 (59.8%) showed complete clinical resolution of MVS, while 24 (40.2%) had mild–moderate persistence (improved MVS). No patients had severe persistence.

Normalization of vaginal pH is determined by *Lactobacillus casei* and *Lactobacillus acidophilus* reducing vaginal dryness and dyspareunia [38]. *L. casei* promotes growth of *L. acidophilus*, whose adhesion to vaginal epithelial cells hinders pathogen interaction with the mucosa. Lactoferrin also inhibits bacterial adhesion and has bactericidal effect [39]. Besides regression of MVS with reduction of its two main symptoms – vaginal dryness and dyspareunia – lactoferrin and lactobacilli *casei* and *acidophilus* reduce the risk of vaginal infections [1, 40]. In the Omicron Factor are Vitamin E and extravirgin olive oil. Vitamin E, besides antioxidant properties, protects cell membranes from oxidative damage and promotes renewal of vaginal mucosal cells. Extravirgin olive oil exerts a protective effect on vaginal mucosa via phenolic derivatives, reducing oxidative mechanisms and increasing cell vitality, thereby reducing histological alterations [41, 42]. Both Vitamin E and olive oil help reduce vaginal lesions responsible for postcoital spotting and partially reverse vaginal mucosal atrophy.

Preliminary findings may serve as justification for prospective, randomized comparative studies, including a control group, aimed at confirming efficacy, safety and long-term outcomes in a more standardized setting.

CONCLUSIONS

Although topical hormone therapy is considered the “Gold Standard” for improvement of MVS according to the most recent literature data, also nonhormonal therapies are effective treatments free from side effects and contraindication [9-11, 13, 15, 16, 18, 39, 43]; in particular local vaginal hydrating and lubricating therapies should be considered the “firstline treatment”.

Topical treatment of MVS with “DuoLac-EvoGold” resulted in complete regression in approxi-

mately 60% and partial regression in 40% of cases. The symptomatology most frequently regressed, expressed by VNS score, was vaginal dryness (78.3%), dyspareunia (75%), vaginal burning (78.3%), and spontaneous pain (100%). Vaginal pH returned to normal (4-4.5) in approximately 90% of cases, reducing the risk of vaginal infections. The study of 60 MVS cases treated with “DuoLac-EvoGold” demonstrated improvement of postcoital spotting (66.7%) due to the reepithelializing effect of Vitamin E and the phenols of olive oil in improving mucosal atrophy. The mean trend of “sexual function” after therapy shows a growth trend which, in the context of this retrospective survey, indicates the efficacy of the adopted approach in improving sexual function. Unlike hormonal treatments, there are no contraindications to the use of “DuoLac-EvoGold” in patients with a positive history of endometrial or breast carcinoma.

Therefore, “DuoLac-EvoGold” is promising for the treatment of MVS both for symptom regression and for restoration of normal vaginal pH. It is a “nonhormonal topical vaginal therapy” free of side effects with good patient compliance in MVS. Furthermore, its use in MVS may represent an excellent prevention of GSM by reducing the risks of urethritis and cystitis in menopause.

Treatment showed symptomatic improvement in this limited cohort, but further prospective controlled studies are needed to confirm efficacy and safety.

COMPLIANCE WITH ETHICAL STANDARDS

Authors' contributions

A.B., M.T., L.A., D.R., G.C.DR.: Conceptualization, investigation, methodology, resources, software, visualization. A.B., M.T., L.A., D.R.: Data curation. A.B., G.C.DR.: Formal analysis. A.B., G.C.DR.: Project administration, supervision, validation, writing-original draft, writing – review & editing.

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Study registration

N/A.

Disclosure of interests

The authors declare that they have no conflict of interests.

Ethical approval

The study was conducted retrospectively using data extracted from a full anonymized database. No identifiable patient-level data were accessed for the purposes of the analysis, and no additional intervention or patient contact was performed. The requirement for Ethics Committee review was assessed according to applicable local regulations and institutional policies. Patient's anonymity has been preserved in accordance with the Declaration of Helsinki.

Informed consent

All patients signed written informed consent, all are reported under explicit consent of the patients: patient's anonymity have been preserved in accordance with the Declaration of Helsinki.

Data sharing

Data are available under reasonable request to the corresponding author.

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