Sindrome genito-urinaria in postmenopausa: approccio terapeutico non ormonale.

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"A collection of symptoms and signs associated with a decrease in estrogen and other sex steroids involving changes to the labia majora/minora, clitoris, vestibule/introitus, vagina, urethra and bladder."

The syndrome may include but is not limited to genital symptoms of dryness, burning, and irritation; sexual symptoms of lack of lubrication, discomfort or pain, and impaired function; and urinary symptoms of urgency, dysuria and recurrent UTIs.

Women may present with some or all of the signs and symptoms, which must be bothersome and should not be better accounted for by another diagnosis.”

VVA is chronic, progressive, and, unlike vasomotor symptoms, will not resolve with time and without treatment.
This aspect of menopause is often overlooked and undermanaged, because only a minority seek medical help for the problem.
• **Densità** ER > a livello vaginale e progressivamente ridotta in corrispondenza di genitali esterni e cute

• **ER α** presenti nei tessuti vaginali sia in premenopausa che in postmenopausa

• **ER β** scarsamente o per nulla espressi nel tessuto vaginale in postmenopausa

• ER sono presenti a livello dell’uretra del **trigono** vescicale e della **muscolatura** del pavimento pelvico
Nelle varie fasi della vita della donna l’ecosistema microbico vaginale va incontro a significativi cambiamenti strutturali che sono direttamente influenzati dai livelli di estrogeni circolanti. La progressiva diminuzione di estrogeni durante la perimenopausa si traduce in una riduzione dei batteri produttori di acido lattico ad una selezione di specie che includono solamente batteri anaerobi ed enterobatteri.
In postmenopausa la vagina presenta un **basso numero di specie microbiche con minor capacità transizionale verso e da organismi tipici della vaginosi batterica** (BV-like) (2% of the time) in confronto a ciò che accade in premenopausa (17% transizione). ** Questa stabilità sembra essere protettiva** in quanto la diversificazione della flora batterica vaginale in postmenopausa è associata ad un aumento dei sintomi da secchezza vaginale.

Si pensa generalmente che in menopausa i lactobacilli siano assenti a livello vaginale, ma studi sull’ecosistema microbico vaginale mostrano che i Lattobacilli Iners e Crispatus sono le più comuni specie batteriche presenti in donne asintomatiche in menopausa.

Una specie di batteri produttori di acido lattico, precedentemente classificata come specie di lattobacilli è ora identificata come Atopobium vaginae. In premenopausa la presenza di tale specie è associata con i sintomi della vaginosi batterica, mentre rappresenta la normale flora vaginale di pazienti in postmenopausa con lattobacilli ridotte o assenti.
METHODS: Post-menopausal patients for at least one year, having presented with at least three episodes of cystitis in the year before the first consultation in the clinic, having received 20 days of antibiotics at most during the acute phase.

The analysis of a series of post-menopausal patients with recurrent cystitis did not reveal any difference in clinical, radiological, or biological presentation whether patients were more or less than 65 years of age.

The incidence of recurrent cystitis is increased in postmenopausal patients, probably because of hormonal depletion.
Therapeutic goals

- Alleviate symptoms of VVA
- Preserve sexual function
- Decrease the anatomic changes due to atrophy
- Prevent and treat infections
The North American Menopause Society Recommendations for Clinical Care of Midlife Women

Jan L. Shifren, MD, NCMP, Margery L.S. Gass, MD, NCMP,
for the NAMS Recommendations for Clinical Care of Midlife Women Working Group 2014

GENITOURINARY SYNDROME OF MENOPAUSE/
SYMPTOMATIC VULVOVAGINAL ATROPHY

1) Women with GSM/VVA should consider nonhormonal vaginal lubricants and moisturizers as initial therapy. (Level II)

2) Low-dose vaginal ET (available as a cream, tablet, or ring) is a highly effective treatment for persistent symptoms of GSM/VVA. (Level I)

3) The estrogen agonist/antagonist ospemifene is an oral agent for the treatment of moderate to severe dyspareunia due to GSM/VVA. (Level I)
La **terapia estrogenica** per via sistemica e topica rappresenta il **trattamento più efficace** per l’atrofia vaginale postmenopausale.

Per le donne in cui le **terapie ormonali sono sconsigliate**, l’uso di **idratanti vaginali** migliora la lubrificazione.

**I fitoestrogeni possono esercitare dei benefici urogenitali** (come gli isoflavoni della soia e del trifoglio rosso per via orale, Woods R et Al, 2004), **ma la sicurezza non è stata dimostrata in donne con tumori estrogeno-sensibili.**
Vaginal ET: Effectiveness

- Typically provides **greater benefit than nonhormonal** interventions
- Preferred mode of delivery when **vaginal symptoms are the only complaint**
- Shown in clinical trials to be **more effective than systemic oral ET** (that conversely, may worsen incontinence)
- May also reduce risk of urinary urgency and recurrent urinary tract infections
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<thead>
<tr>
<th>Lubricants</th>
<th>Moisturizers</th>
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<td><strong>Water based</strong></td>
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<tr>
<td>Astroglide Liquid</td>
<td>Replens</td>
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<td>Astroglide Gel Liquid</td>
<td>Me Again</td>
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<td>Astroglide</td>
<td>Vagisil</td>
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<tr>
<td>Just Like Me</td>
<td>Feminase</td>
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<td>K-Y Jelly</td>
<td>K-Y SILK-E</td>
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<td>Pre-Seed</td>
<td>Luvena</td>
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<td>Slippery Stuff</td>
<td>Silken Secret</td>
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<td>Liquid Silk</td>
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<td>Astroglide X</td>
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<td><strong>Oil based</strong></td>
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<td>Elégance Women’s Lubricants</td>
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<td>Olive oil</td>
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Abbreviation: VVA, vulvovaginal atrophy.
**Derivati botanici**

Preparazioni con principi attivi di grado ‘cosmetico’ e di derivazione estrattiva con proprietà lenitive, antinfiammatorie ed anti-prurito, ma anche anti-microbiche (report clinici)

- Acido 18-beta glicirretico da Glycyrrhiza glabra
- Bisabololo da Matricaria chamomilla
- Curcumina da Curcuma longa
- Isobutilammid da Zanthoxylum bungeanum
- Olio essenziale da Melaleuca alternifolia

Dopo 10 giorni trattamento con **Crema e Detergente** in soggetti con diagnosi di VVA per almeno per i 7 giorni successivi di washout (n.15 pazienti):

- **Prurito e bruciore** risultavano scomparsi
- **Secchezza** ↓ dell’85%
- **EO**: area vulvovaginale non iperemica ed eutrofica, con un’evidente riduzione dell’assottigliamento della mucosa

*Di Pierro, 2009*
• **Tocoferolo acetato (vitamina E) topica**
  Forma un film protettivo, persistente ed omogeneo, favorendo il ripristino della normale idratazione della superficie vaginale

• **Aliamidi**
  Palmitoiletanolamide (PEA), Adelmidrol

The ability of PEA to modulate MC behaviour (**MC number, activation state**), more than the only **blockage of MC degranulation**, may provide new impetus to MC pharmacology, in view of the central role that these cells play in the development of the inflammatory process from its promotion to progression and chronicity.
In its position statement on the various strategies to improve vaginal health, the Spanish Menopause Society addresses the option of using probiotics. The recommendations say: ‘Despite the limited evidence available for postmenopause, we recommend using probiotics with *Lactobacillus* as an adjunct for treating recurrences of urogenital infections’.
Si definisce infezione ricorrente del tratto urinario (RUTI) la comparsa di tre episodi di infezioni del tratto urinario (UTI) nei precedenti 12 mesi o la comparsa di due episodi negli ultimi 6 mesi.

I fattori di rischio principali associati alle RUTI in postmenopausa sono il prolasso vescicale, il cistocele, il residuo post-minzionale e l’incontinenza urinaria (Foxman 2000; Raz 2000), tutte condizioni associate ad una diminuzione degli estrogeni.

CONCLUSIONI: Sulla base dei soli due studi che confrontano gli estrogeni vaginali con placebo, gli estrogeni vaginali riducono il numero delle UTI in postmenopausa.

Bevande o compresse a base di mirtillo rosso hanno un qualche ruolo nella strategia della prevenzione (Jepson 2004).
Attività preventiva nei confronti delle infezioni vescicali, soprattutto nei quadri di ricorrenza.

Il meccanismo d’azione più probabile sembra essere legato alla capacità di ridurre l’adesione delle cellule batteriche alla superficie della mucosa vescicale, limitando l’adesività, e quindi la capacità proliferativa dei patogeni, con particolare riferimento ad E. coli.

In soggetti con diagnosi di UTI ricorrente, somministrato in condizioni di urino-coltura negativa, riduce la manifestazione di UTI nei mesi seguenti, con una risposta probabilmente dose-dipendente, (riduzione del fenomeno di circa il 90% ad 1 cp/die e del 100% a 2 cp/die).

Vaccinium macrocarpon (VM), o ‘Mirtillo rosso americano’ o Cranberry

Di Pierro, 2009
Effective treatment of vaginal atrophy with isoflavone vaginal gel☆

Sonia M. Rolim Rosa Lima⁹, Silvia Saito Yamada⁹, Benedito Fabiano Reis⁹,¹,²,* Sostenes Postigo⁹, Maria Antonieta L. Galvão da Silva⁹, Tsutomo Aoki⁹

Intensity (%) of dyspareunia
Effects of *Glycine max* (L.) *Merr.* soy isoflavone vaginal gel on epithelium morphology and estrogen receptor expression in postmenopausal women: A 12-week, randomized, double-blind, placebo-controlled trial

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<th>Parameters</th>
<th>isoflavone vaginal gel 4% (</th>
<th>placebo gel</th>
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<tbody>
<tr>
<td></td>
<td>Basal 12 weeks p value</td>
<td>Basal 12 weeks p value</td>
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<tr>
<td>Vaginal pH</td>
<td>7.1 ± 0.9 5.4 ± 0.8 0.000</td>
<td>7.4 ± 0.8 7.1 ± 0.8 0.172</td>
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<th>Parameters</th>
<th>Group</th>
<th>Mean Basal 12 weeks</th>
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<tbody>
<tr>
<td>Thickness</td>
<td>Isoflavones 153.5 ± 66.1 259.8 ± 56.9</td>
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<td></td>
<td>Placebo   145.2 ± 60.5 191.9 ± 82.7</td>
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<tr>
<td>ER positive</td>
<td>Isoflavones 58.5 ± 33.9 82.6 ± 17.4</td>
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<tr>
<td></td>
<td>Placebo   73.4 ± 24.5 83.7 ± 8.8</td>
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**Conclusion:** *Glycine max* (L.) *Merr.* at 4% vaginal gel on a daily basis in postmenopausal women led to improvements in vaginal atrophy symptoms, maturation values, vaginal pH, morphology and expression of estrogen receptors in vaginal epithelium. Isoflavones proved good treatment options for relief of vulvovaginal atrophy.
The effect of vaginally administered genistein in comparison with hyaluronic acid on atrophic epithelium in postmenopause

Maria Le Donne · Carmela Caruso · Alfredo Mancuso · Gregorio Costa · Raffaella Iemma · Giovanni Pizzimenti · Vittorio Cavallari

Abstract

Purpose  The quality of life in postmenopause is seriously affected by the symptoms related to vaginal atrophy. To evaluate in a 3-month, prospective, randomized, double blind, study whether vaginal suppositories containing genistein might improve genital symptoms, colposcopical and cytologic findings or modify DNA cytometric features in postmenopausal women affected by vaginal atrophy, in comparison with vaginal suppositories containing hyaluronic acid (HA).

Methods  A total of 62 postmenopausal women were randomly assigned to receive intravaginally 97 μg of genistein (group A, n = 31) or 5 mg of HA (group B, n = 31) daily for 15 days continuously/month for 3 months. Vaginal and cervical smear, colposcopy, vaginal biopsy were performed before and at the end of the study. Maturation value (MV) was calculated. Flow cytometric analysis of DNA ploidy (DI) and S-phase fraction (SPF) were performed.

Results  After 90 days of study, a significant improvement was obtained in genital symptoms, colposcopy scores and MV (p < 0.001) in both groups; the improvement obtained by genistein was more effective especially regarding genital score (p value between groups 0.001). No significant change was found in SPF value and DI.

Conclusion  Both treatments improved genital symptoms, colposcopical features and MV, although genistein was more effective on genital score. Both treatments did not significantly influence flow cytometry parameters, although genistein showed slight decrease in DI, with a normalization of the aneuploid content present in some cases that could represent an additional application of intravaginal phytoestrogen therapy, providing an alternative therapy of vaginal atrophy in postmenopausal patients. The results of this investigation should be considered preliminary and need to be verified in larger, prospective studies.
Only two studies have explored the potential benefits of isoflavones for the treatment of postmenopausal vaginal dryness.
Only two studies have explored the potential benefits of isoflavones for the treatment of postmenopausal vaginal dryness.

*Abstract*

**OBJECTIVE:** To evaluate the effect of a soy-rich diet on urogenital symptoms, vaginal health index, and vaginal cytology in perimenopausal and postmenopausal women.

**MATERIALS AND METHODS:** Thirty-six perimenopausal and postmenopausal women (mean age 52.5+/−5.1 years) participated in a randomized, cross-over trial with two 12-week diet periods and two 4-week washout periods before and between treatments. The study diet consisted of a control diet (soy-free diet) and an isocaloric soy-rich diet (25 g soy protein in various forms of soy food containing more than 50 mg/day of isoflavones substituted for an equivalent amount of animal protein). Subjects were assessed for urogenital symptoms, vaginal health index, vaginal pH and vaginal cytology. The single physician and the single cytopathologist were blinded with regard to onset, period and randomization number. Statistical analyses were performed using paired t-test or Wilcoxon Signed Ranks Test, significance was set as P<0.05.

**RESULTS:** Good compliance to the diet was shown by the significant elevation of serum levels of daidzein and genistein during the soy-rich diet period. The symptoms of urge incontinence and vaginal dryness had significantly increased after 12-week of soy-free diet. All other urogenital symptoms did not change in both periods. The vaginal health index, the vaginal pH, the karyopyknotic index, and the maturation value were not significantly changed in both periods.

**CONCLUSION:** A soy-rich diet did not relieve the urogenital symptoms or restore the vaginal epithelium or improve the vaginal health in perimenopausal and postmenopausal Thai women.
Daily supplementation with Black cohosh, multibotanical herbs and multibotanical herbs + soy didn’t demonstrate efficacy in the treatment of vaginal dryness, evaluated with vaginal citology.
Herbal products have not demonstrated any beneficial effect in clinical trials. (NAMS, 2013)

While neither of these studies demonstrated a positive effect of isoflavones on vaginal atrophy, both imply at least a mild protective effect, demonstrated by a worsening of dryness or vaginal epithelium maturity in the placebo groups. (Bedell et Al, 2014)

Drawing any definite conclusion was difficult because of the limited number of RCTs, the small sample sizes, weak methodology and considerable heterogeneity of the included studies. (Ghazanfarpour et Al, 2015)
Contraindications for Ospemifene:
- all of those for vaginal estrogen
  - past or current venous or arterial thromboembolic disease.

Contraindications for vaginal estrogen:
- unexplained vaginal bleeding
- known or suspected breast cancer or other estrogen-dependent neoplasia.

Algorithm and mobile app for menopausal symptom management and hormonal/non-hormonal therapy decision making: a clinical decision-support tool from The North American Menopause Society