

I NUTRACEUTICI AL FEMMINILE

Ferrara, 20 marzo 2015



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

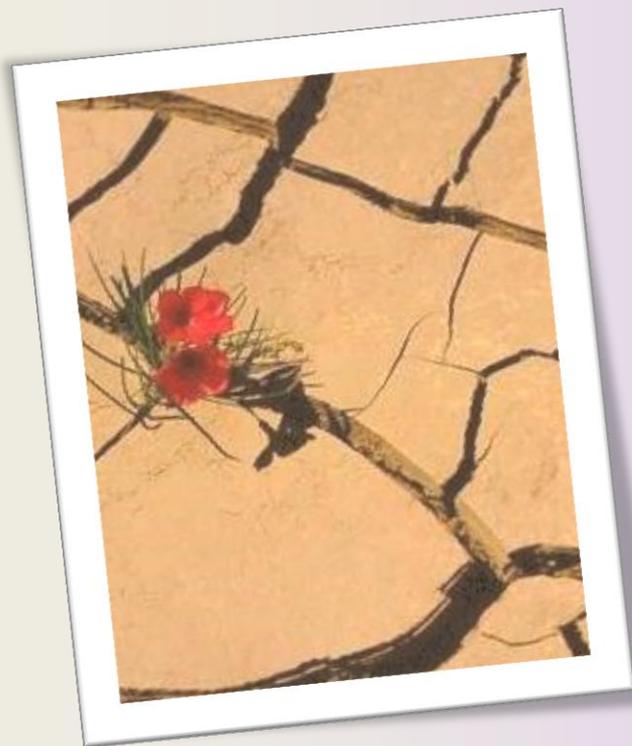
Dott.ssa Enrica Fila

Centro di Ricerca per lo Studio della Menopausa e dell'Osteoporosi



Genitourinary syndrome of menopause: New terminology for vulvovaginal atrophy from the International Society for the Study of Women's Sexual Health and The North American Menopause Society

D.J. Portman^{*}, M.L.S. Gass, on behalf of the Vulvovaginal Atrophy Terminology Consensus Conference Panel¹



“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.

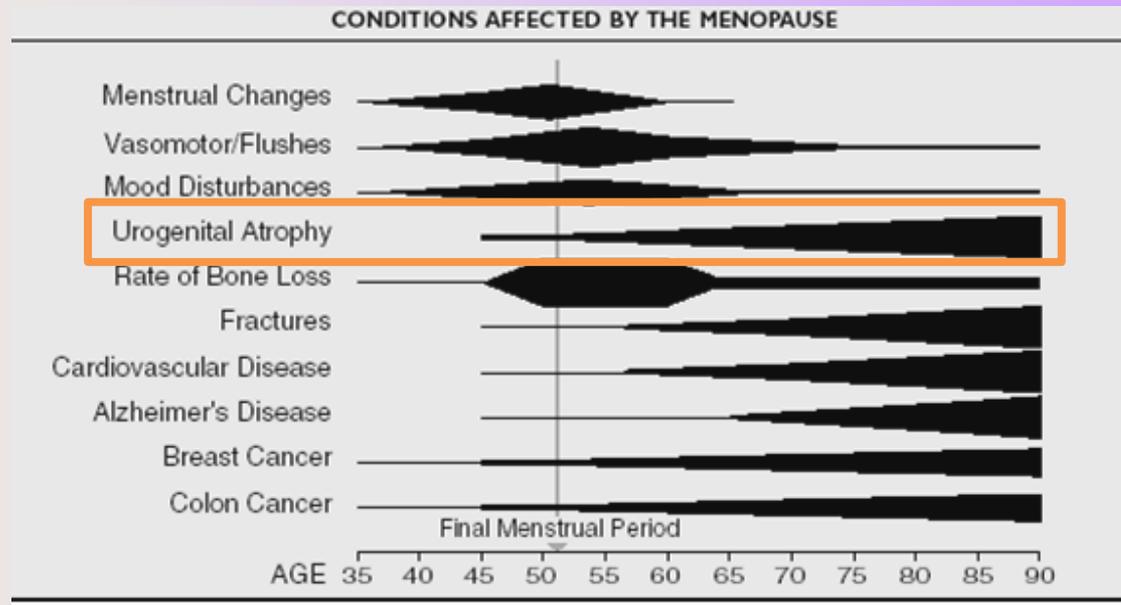
The syndrome may include but is not limited to **genital symptoms** of **dryness, burning, and irritation**; **sexual symptoms** of **lack of lubrication, discomfort or pain, and impaired function**; and **urinary symptoms** of **urgency, dysuria and recurrent UTIs.**

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**

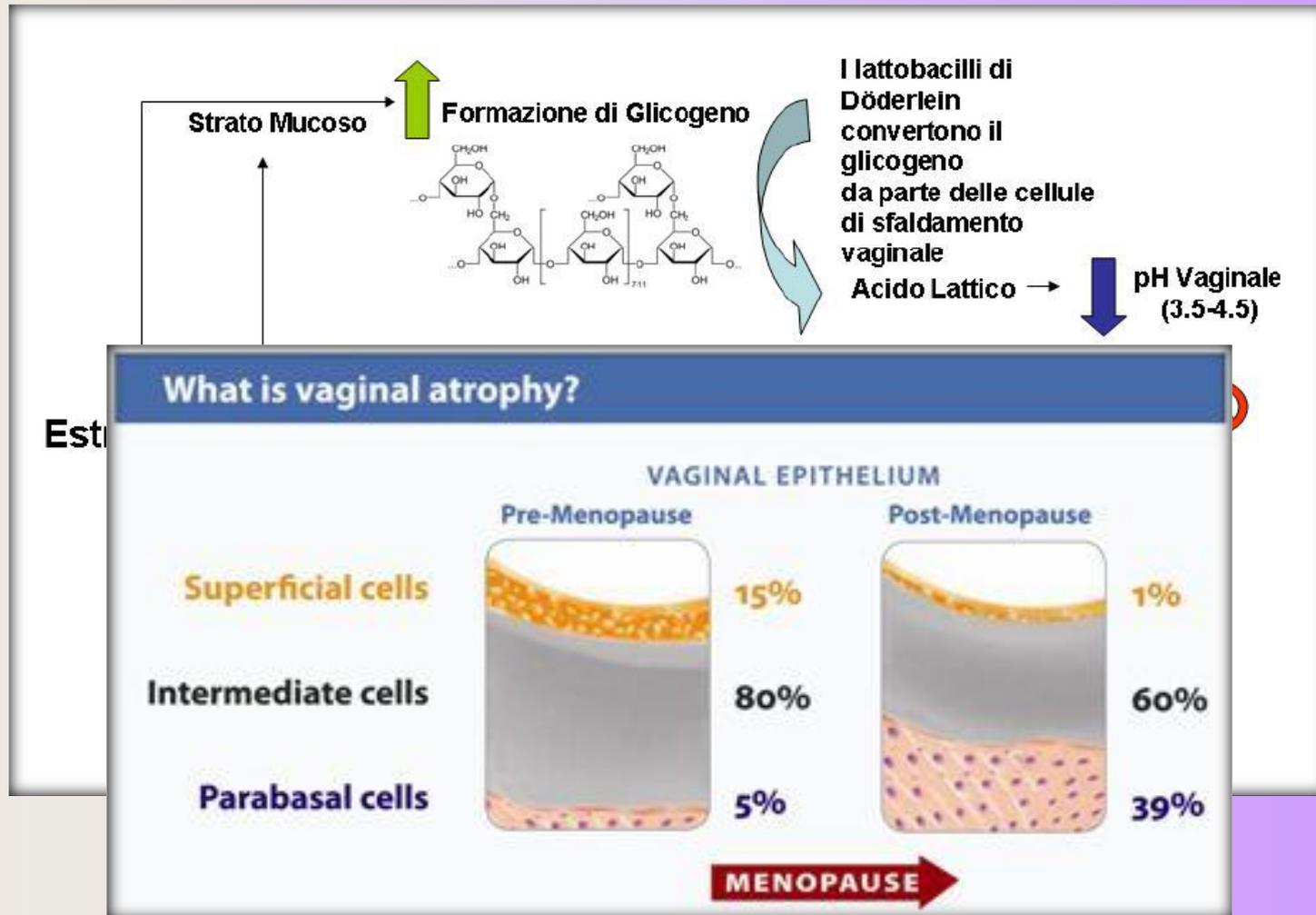
Genitourinary syndrome of menopause: New terminology for vulvovaginal atrophy from the International Society for the Study of Women's Sexual Health and The North American Menopause Society

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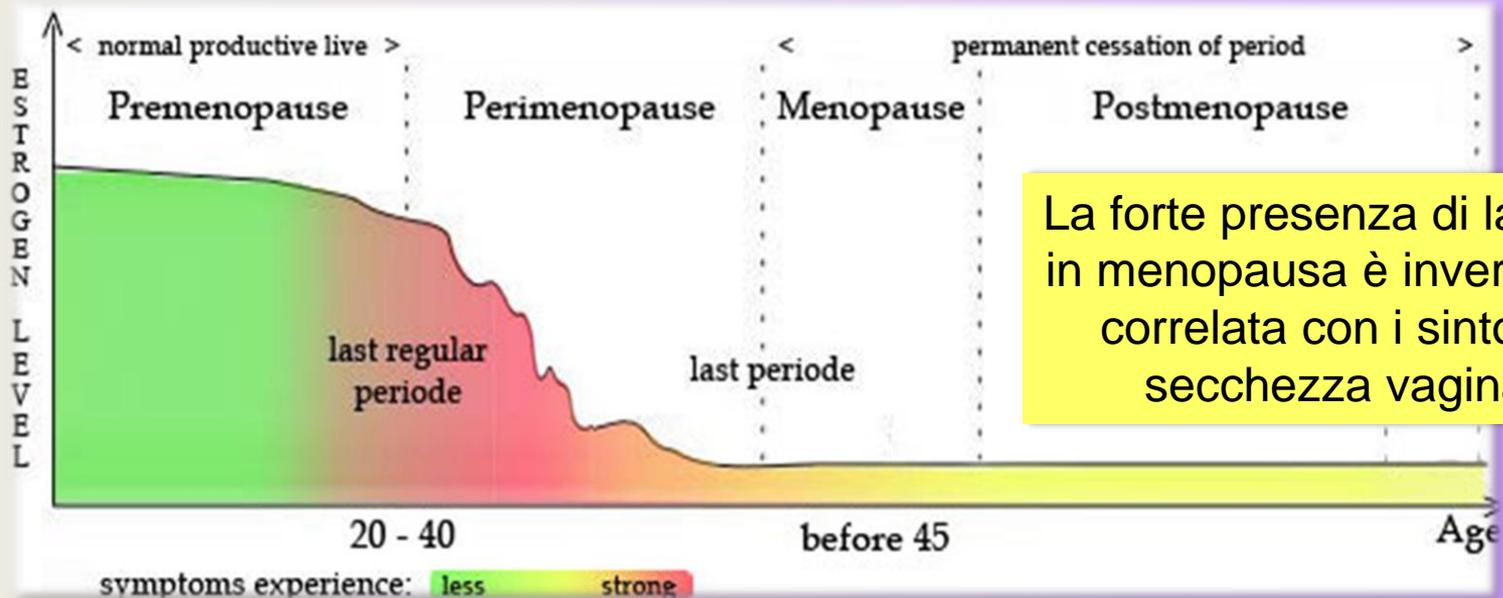
Symptoms affect **20 – 45%** of midlife and older women.

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**

LIVELLI DI ESTROGENI E CAMBIAMENTI DELLA FLORA BATTERICA VAGINALE



La forte presenza di lattobacilli in menopausa è inversamente correlata con i sintomi da secchezza vaginale .

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.**



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Médecine et
maladies infectieuses

Médecine et maladies infectieuses 43 (2013) 185–188

Original article

Recurrent cystitis in post-menopausal patients more or less than 65 years of age

Cystites récidivantes chez les femmes ménopausées de plus ou moins de 65 ans

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Available online 22 April 2013

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)



INTERNATIONAL MENOPAUSE SOCIETY

THE SOCIETY FOR THE STUDY OF ALL ASPECTS OF THE CLIMACTERIC IN MEN AND WOMEN

Raccomandazioni per la gestione dell'atrofia vaginale postmenopausale

1 Ottobre 2010

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

TABLE 1. *Examples of nonhormonal therapeutic options for dyspareunia secondary to VVA*

Lubricants

Water based

Astroglide Liquid
 Astroglide Gel Liquid
 Astroglide
 Just Like Me
 K-Y Jelly
 Pre-Seed
 Slippery Stuff
 Liquid Silk

Silicone based

Astroglide X
 ID Millennium
 K-Y Intrigue
 Pink
 Pjur Eros

Oil based

Elégance Women's Lubricants
 Olive oil

Moisturizers

Replens
 Me Again
 Vagisil
 Femeinease
 K-Y SILK-E
 Luvena
 Silken Secret



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*
- Isobutilammidi 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



- **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

78

CNS & Neurological Disorders - Drug Targets, 2013, 12, 78-83

New Insights in Mast Cell Modulation by Palmitoylethanolamide

D. De Filippis^{1,3}, L. Negro^{2,3}, M. Vaia², M.P. Cinelli¹ and T. Iuvone^{*,1,2}

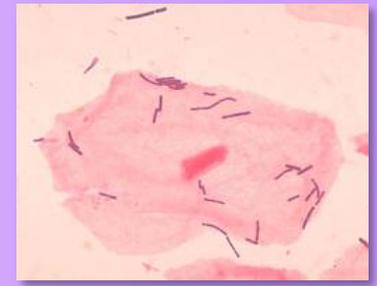
¹Endocannabinoid Research Group; Dept. of Experimental Pharmacology, ²Via D. Montesano and ³Department of Biomorphological and Functional Sciences, Via Pansini-University of Naples, "Federico II"- Naples, Italy

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.

Differences in the vaginal lactobacilli of postmenopausal women and influence of rectal lactobacilli

L. Petricevic, K. J. Domig*, F. J. Nierscher, M. J. Sandhofer, I. Krondorfer*, W. Kneifel* and H. Kiss

Department of Obstetrics and Fetomaternal Medicine, Medical University of Vienna, Vienna; *Department of Food Science and Technology, BOKU – University of Natural Resources and Life Sciences, Vienna, Austria



Rectal lactobacilli may affect the intermediate vaginal flora of postmenopausal women → **atrophic colpitis** with depleted numbers of lactobacilli in postmenopausal women **may effectively be treated by oral application of probiotics.**

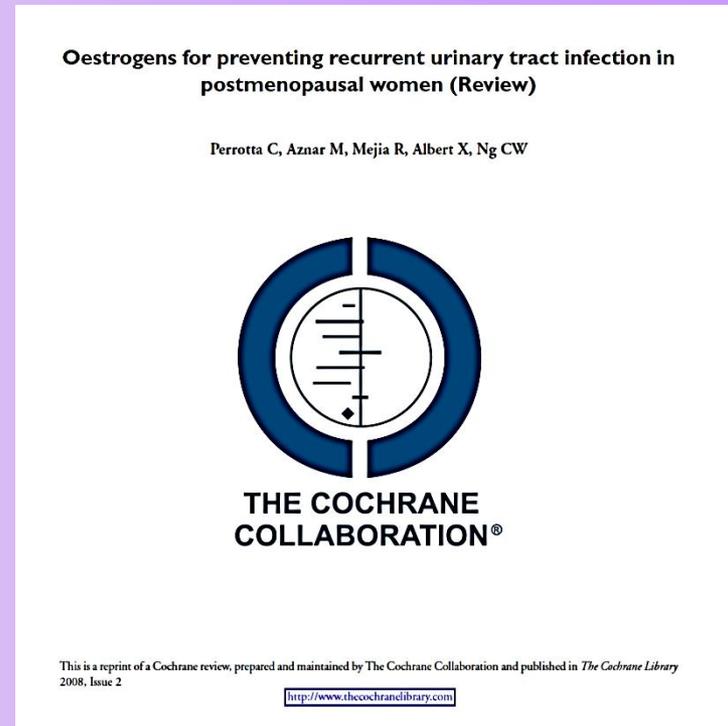
In its position statement on the various strategies to improve vaginal health, the **Spanish Menopause Society addresses the option of using probiotics.** The recommendations say: ‘Despite the limited evidence available for postmenopause, we recommend using probiotics with *Lactobacillus* as an adjunct 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).



Vaccinium macrocarpon (VM), o 'Mirtillo rosso americano' o *Cranberry*

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).



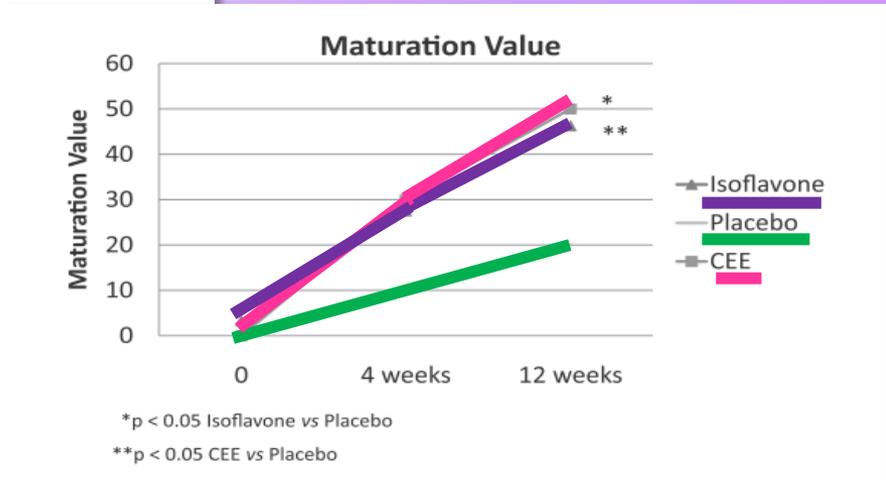
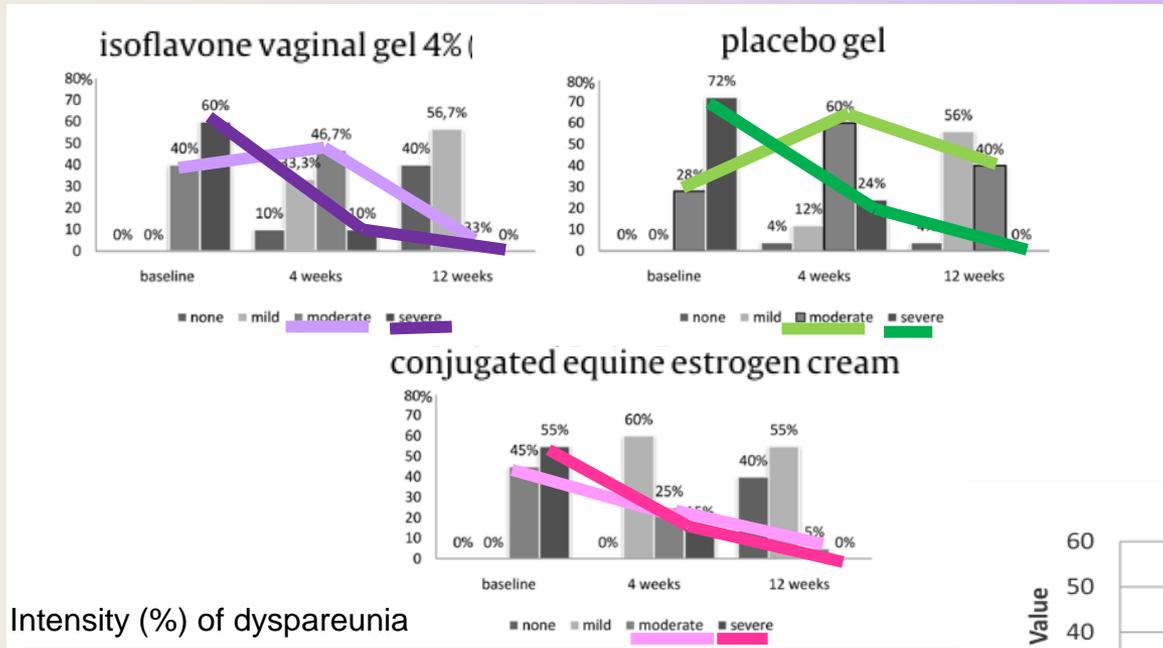
Di Pierro, 2009

Effective treatment of vaginal atrophy with isoflavone vaginal gel[☆]

Maturitas

Sonia M. Rolim Rosa Lima^a, Silvia Saito Yamada^a, Benedito Fabiano Reis^{a,b,*}, Sostenes Postigo^a,
 Maria Antonieta L. Galvão da Silva^c, Tsutomu Aoki^a

2012



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

Parameters	isoflavone vaginal gel 4%			placebo gel		
	Basal	12 weeks	<i>p</i> value	Basal	12 weeks	<i>p</i> value
Vaginal pH	<u>7.1 ± 0.9</u>	<u>5.4 ± 0.8</u>	0.000*	<u>7.4 ± 0.8</u>	<u>7.1 ± 0.8</u>	0.172

Parameters	Group	Mean	
		Basal	12 weeks
Thickness	Isoflavones	153.5 ± 66.1	259.8 ± 56.9
	Placebo	145.3 ± 60.5	191.9 ± 83.7
ER positive	Isoflavones	58.5 ± 33.9	82.6 ± 17.4
	Placebo	73.4 ± 24.5	83.7 ± 8.8

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 Iemmo · 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, colposcopic 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, colposcopic 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.

The role of soy isoflavones in menopausal health: report of The North American Menopause Society/Wulf H. Utian Translational Science Symposium in Chicago, IL (October 2010).

North American Menopause Society.

«Only two studies have explored the potential benefits of isoflavones for the treatment of postmenopausal vaginal dryness.»

Fertil Steril. 2005 Jan;83(1):137-42.

Lack of effect of isoflavonoids on the vagina and endometrium in postmenopausal women.

Nikander E¹, Rutanen EM, Nieminen P, Wahlström T, Ylikorkala O, Tiitinen A.

PATIENT(S): Sixty-four postmenopausal women with a history of breast cancer.

INTERVENTION(S): The women took (in a randomized order) 114 mg of isolated isoflavonoids or placebo in tablets daily for 3 months; the treatment regimens were crossed over after a 2-month washout period. The subjects were studied before and on the last day of each treatment period.

MAIN OUTCOME MEASURE(S): Vaginal dryness, maturation index (MI) of vaginal epithelium, endometrial thickness, histology, and expression of estrogen (E) and progesterone (P) receptors and the proliferation marker Ki-67 in the endometrium.

RESULT(S): Isolated isoflavones did not relieve vaginal dryness. Maturation index values remained unchanged during the isoflavone regimen, but decreased during the placebo regimen. No changes were found in any of the variables measured in the endometrium.

CONCLUSION(S): Daily administration of 114 mg of isolated isoflavones for 3 months had no effect on the subjective perception of vaginal dryness or on objective findings in the vagina or endometrium. This implies safety with regard to the endometrium.

The role of soy isoflavones in menopausal health: report of The North American Menopause Society/Wulf H. Utian Translational Science Symposium in Chicago, IL (October 2010).

North American Menopause Society.

Only two studies have explored the potential benefits of isoflavones for the treatment of postmenopausal vaginal dryness.»

Maturitas. 2006 May 20;54(2):135-40. Epub 2005 Nov 16.

The effect of a soy-rich diet on urogenital atrophy: a randomized, cross-over trial.

Manonai J¹, Songchitsomboon S, Chanda K, Hong JH, Komindr S.

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.

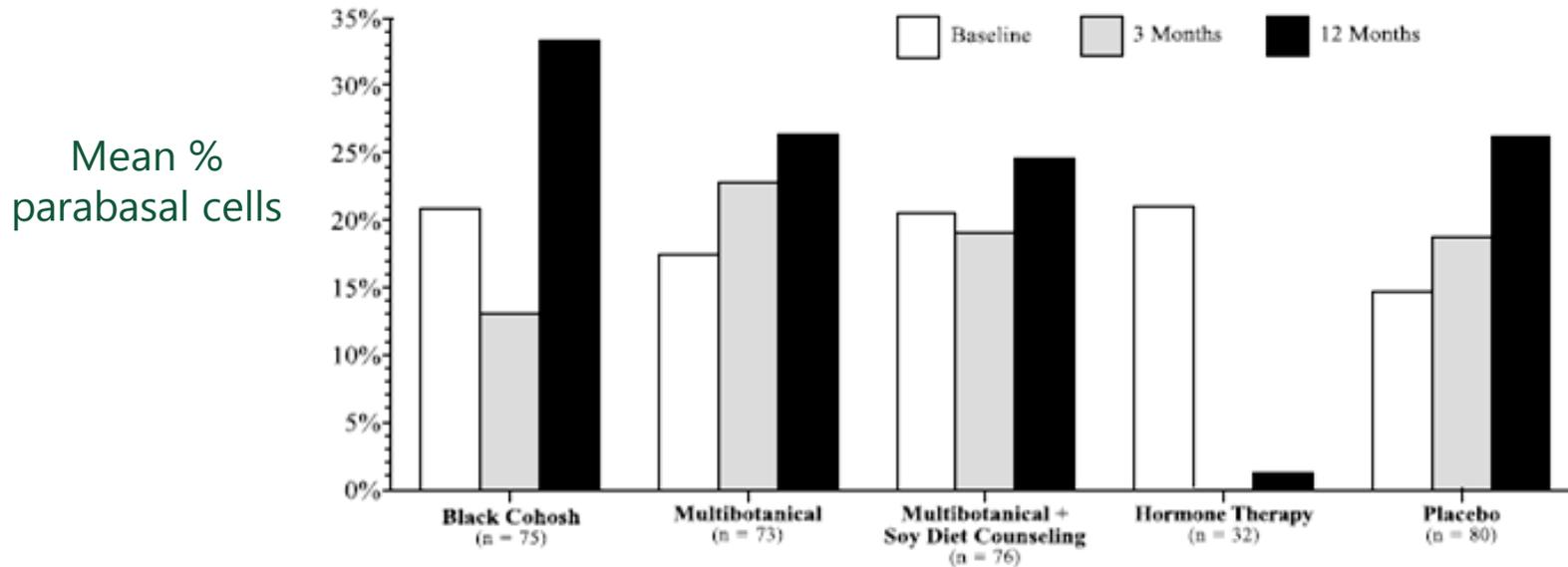
CONCLUSION: A soy-rich diet did not relieve the urogenital symptoms or restore the vaginal epithelium or improve the vaginal health in perimenopausal and postmenopausal Thai women.

Vaginal, endometrial, and reproductive hormone findings: randomized, placebo-controlled trial of black cohosh, multibotanical herbs, and dietary soy for vasomotor symptoms: the Herbal Alternatives for Menopause (HALT) Study

Susan D. Reed, MD, MPH,^{1,2,4} Katherine M. Newton, PhD,¹ Andrea Z. LaCroix, PhD,^{1,4}
Louis C. Grothaus, MS,¹ Verena S. Grieco, MD,³ and Kelly Ehrlich, MA¹ 2008

N. 351 casi

GYNECOLOGIC FINDINGS FROM THE HALT STUDY



Daily supplementation with Black cohosh, multibotanical herbs and multibotanical herbs + soy didn't demonstrate efficacy in the treatment of vaginal dryness, evaluated with vaginal cytology.

EDITORIAL

Herbal alternatives as substitutes for hormone therapy in urogenital atrophy: scientific evidence is needed

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)

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

2015

Genitourinary symptoms such as vaginal dryness or pain with intercourse/sexual activity?^b

Yes

No

Free of breast cancer, endometrial cancer, and other hormone-sensitive cancers?

Avoid HT

Yes

No

Vaginal lubricants and/or moisturizers. Consider low-dose vaginal estrogen if response is inadequate.

Ospemifene may be an option for women who prefer non-estrogen oral therapy if no contraindications.

Vaginal lubricants and/or moisturizers

FITOESTROGENI
?

Contraindications for vaginal estrogen:

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

Contraindications for Ospemifene:

- all of those for vaginal estrogen
- past or current venous or arterial thromboembolic disease.