



ATROFIA VULVO-VAGINALE: PROSPETTIVE DI CURA

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Sexual well-being after menopause: An International Menopause Society White Paper

J. A. Simon^a, S. R. Davis^b, S. E. Althof^{c,d}, P. Chedraui^e, A. H. Clayton^f, S. A. Kingsberg^g, R. E. Nappi^h,
S. J. Parishⁱ and W. Wolfman^{j,k}

Climacteric, 2018

- ❖ Positive sexual function at midlife can enhance personal and relationship quality, improve longevity and enhance quality of life.
- ❖ Yet many women suffer from low desire, arousal and orgasmic dysfunction with or without sexual pain **due to VVA/GSM following menopause.**
- ❖ Both women and their practitioners are reluctant to bring sexual problems to light, and so they often go untreated, resulting in detrimental effects in the relationship despite safe and effective available treatments.
- ❖ It is hoped that this short 'how to' manuscript can help those practitioners caring for menopausal women to open the dialog and provide or facilitate appropriate treatment.

18th October 2018 -
World Menopause Day



18th October 2010 -
World Menopause Day



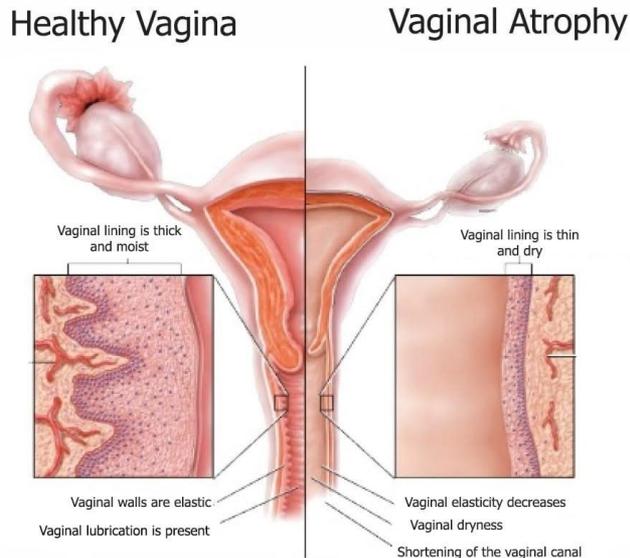
ENDING
THE SILENT
SUFFERING

Managing Vaginal Atrophy
in Postmenopausal Women

SAVE THE DATE

VVA/GSM - A MULTIDIMENSIONAL ISSUE

- A **chronic condition** affecting a very large number of postmenopausal women with a significant impact on **sexual health** and **quality of life**



❖ Other psychosocial modulators:

- ✓ Self-esteem
- ✓ Body image
- ✓ Personality
- ✓ Importance attributed to sexuality
- ✓ Quality and duration of the relationship
- ✓ Attitudes toward menopause and aging (norms, values, traditions...)
- ✓ Experiences
- ✓ Access

❖ Biological etiology:

- ✓ Hormonal changes
- ✓ Aging *per se*
- ✓ Life-style factors
- ✓ Sexual activity
- ✓ Comorbidities
- ✓ Partner's Health
- ✓ Others...

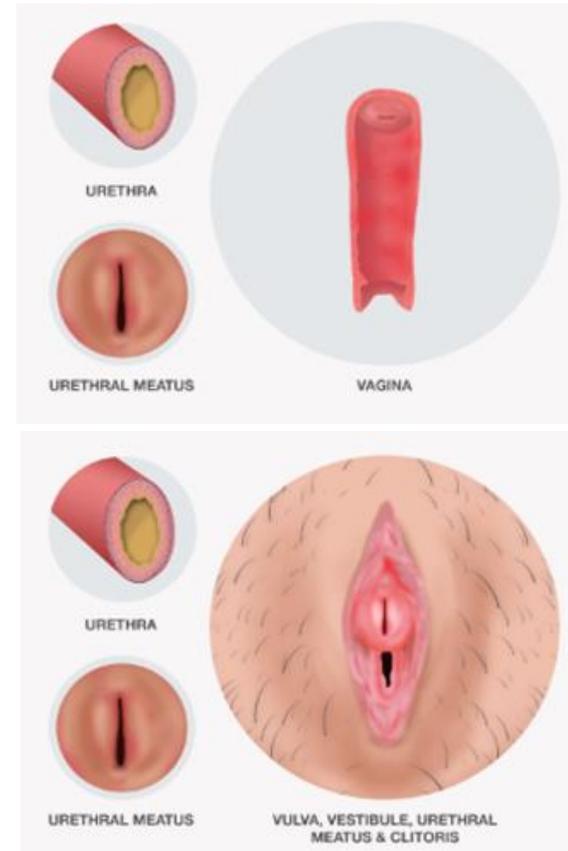
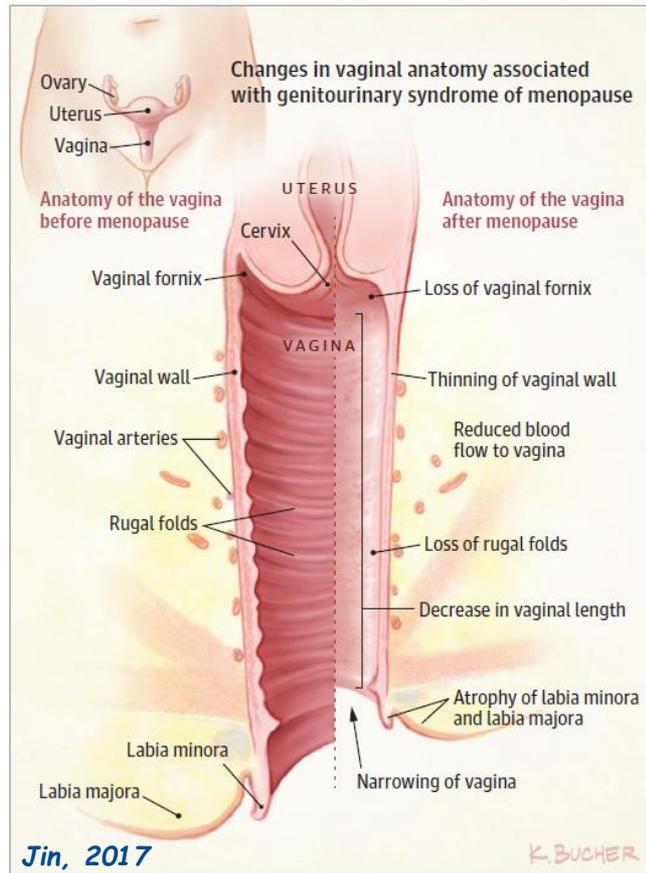
Highly prevalent

BUT

underreported and undertreated



FROM VVA TO GSM



J Simon et al, 2018

- An evolving concept including other dimensions of women's uro-genital and sexual well-being with a significant impact on QoL.
- A collection of symptoms and signs associated with a decrease in estrogen and androgens involving changes to the labia majora/minora, clitoris, vestibule/introitus, vagina, pelvic floor, urethra and bladder.

RE Nappi, 2018

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

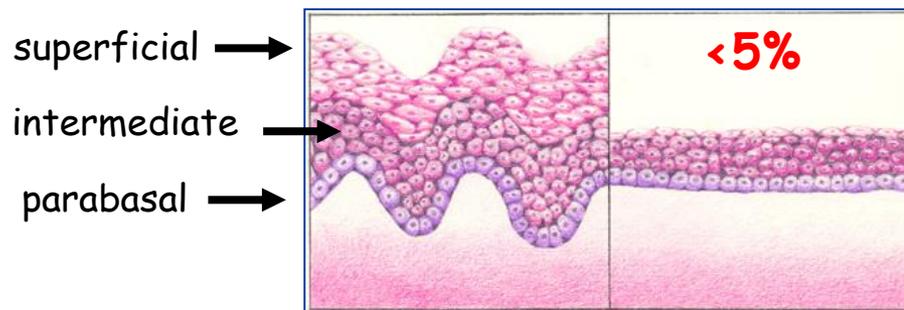
D.J. Portman*, M.L.S. Gass, on behalf of the Vulvovaginal Atrophy Terminology Consensus Conference Panel¹

- ❖ Genital symptoms of **dryness, burning, and irritation**;
- ❖ Sexual symptoms of **lack of lubrication, discomfort or pain, and impaired function**;
- ❖ Urinary symptoms of **urgency, dysuria and recurrent urinary tract infections**.

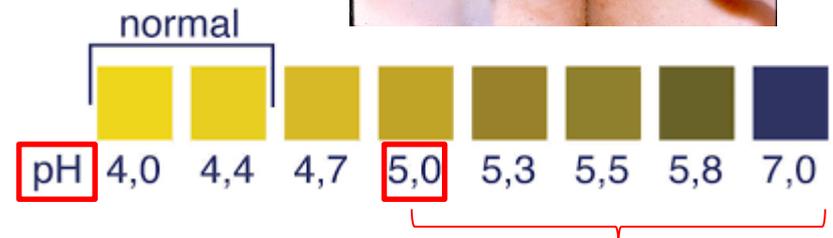
❖ **SCALES TO RATE SUBJECTIVE SYMPTOMS**

❖ **SCALES TO RATE OBJECTIVE SIGNS**

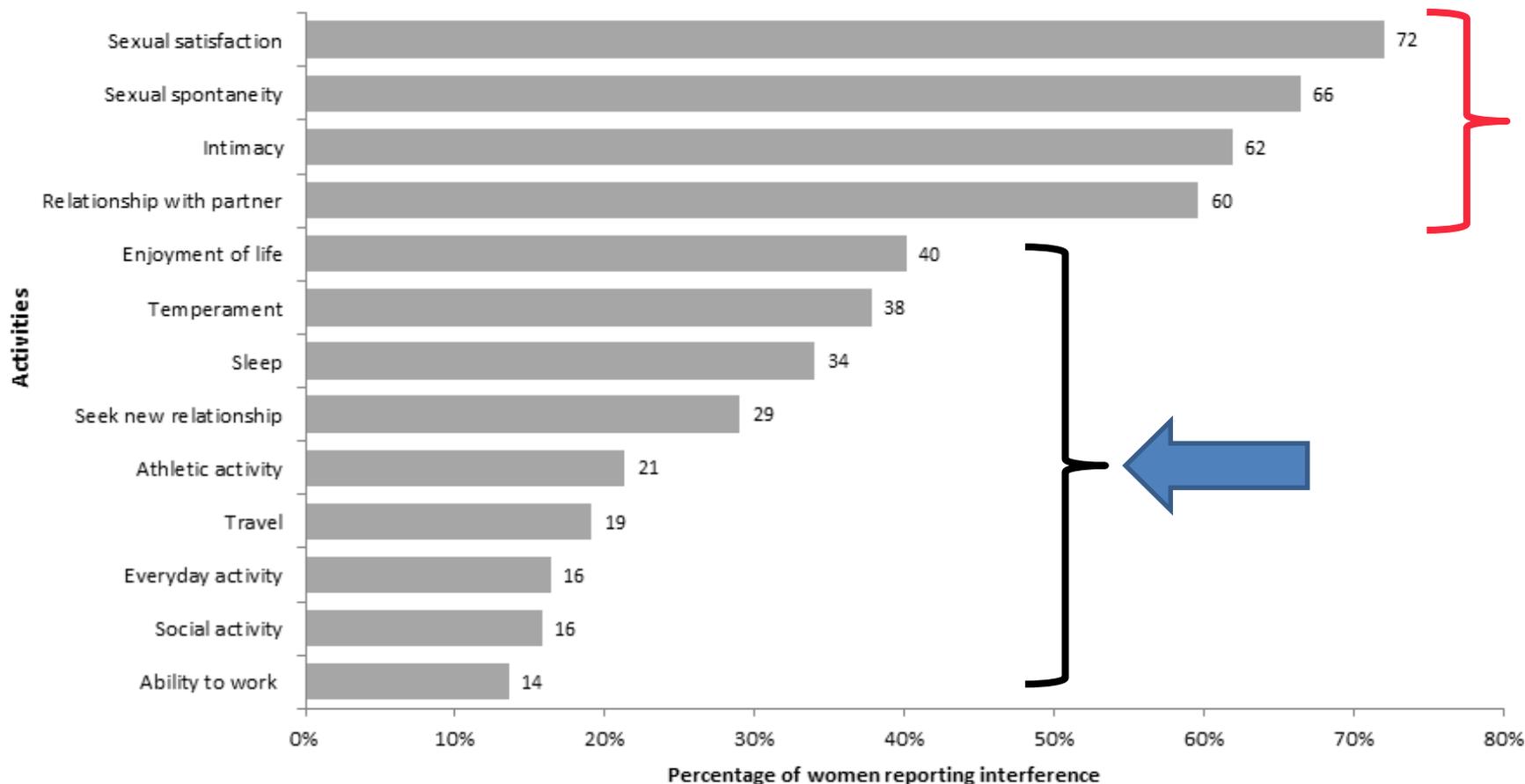
❖ **SUPPORTIVE FINDINGS**



MATURATION INDEX



VVA symptom interference with sexual life and other dimensions - REVIVE



- 3768 women (45-75 yrs) in Europe (Italy, Spain, UK, Germany)

The REVIVE (REal Women's Views of Treatment Options for Menopausal Vaginal ChangEs) survey in Europe: Country-specific comparisons of postmenopausal women's perceptions, experiences and needs

Maturitas 91 (2016) 81–90

Rossella E. Nappi^{a,*}, Santiago Palacios^b, Martire Particco^c, Nick Panay^d

Table 2
VVA treatment status according to discussion with HCP.

Treatment status	Discussed VVA symptoms with HCP				Did not discuss VVA symptoms with HCP			
	Italy (n= 666)	Germany (n= 640)	Spain (n= 551)	UK (n= 446)	Italy (n= 219)	Germany (n= 289)	Spain (n= 159)	UK (n= 464)
Current treatment users, n (%)	455 (68.3)	359 (56.1)	365 (66.2)	185 (41.5)	78 (35.6)	50 (17.3)	48 (30.2)	75 (16.2)
OTC only	387 (58.1)	154 (24.1)	249 (45.2)	72 (16.1)	66 (30.1)	32 (11.1)	43 (27.0)	57 (12.3)
Rx only	23 (3.5)	139 (21.7)	69 (12.5)	79 (17.7)	4 (1.8)	8 (2.8)	2 (1.3)	7 (1.5)
Rx + OTC	1 (0.3)	37 (5.8)	16 (2.9)	17 (3.8)	–	1 (0.3)	–	–
Other (Laser, etc.)	44 (6.7)	29 (4.5)	31 (5.6)	17 (3.8)	8 (3.7)	9 (3.1)	3 (1.9)	11 (2.4)
Lapsed on treatment, n (%)	144 (21.6)	157 (24.5)	126 (22.9)	153 (34.3)	35 (16.0)	52 (18.0)	24 (15.1)	55 (11.9)
Naive to treatment, n (%)	67 (10.1)	124 (19.4)	60 (10.9)	108 (24.2)	106 (48.4)	187 (64.7)	87 (54.7)	334 (72.0)



- European women shared the same expectation of improving the quality of their sex lives.
- The opportunity for that varied among different countries in relation to the healthcare system and to the **effective communication** achieved with healthcare professionals when managing VVA.
- Overall, women who discussed VVA with a HCP were twice as likely to be current medication users (59.7% vs 22.7% for those who had not discussed VVA).
- 3768 women (45–75 yrs) in Europe (Italy, Spain, UK, Germany) currently suffering from VVA

THERE ARE MULTIPLE PHENOTYPES OF WOMEN WITH VVA OUT THERE!



Lucia, 57 yrs

Dryness «It is an uncomfortable sensation, it is more than a sexual problem...»



Sofia, 44 yrs

FSD «My premature menopause has killed my desire and I feel no arousal down there...»



Maria Luisa, 61 yrs

Dysuria «I feel my bladder crying...»



Giusy, 54 yrs

Itching/No sexual activity «I am afraid of the pain...»



Dorina, 72 aa

rUTIs «This year I had 10 prescriptions of antibiotics...»



Anna, 57 yrs

Dyspareunia «Any time I have sex, cystitis is there!»



Paola, 55 yrs

Burning «After my breast cancer, nothing between us has been the same...»



Maria, 68 yrs

Urgency «I have to rush to the bathroom so many times...»

Update on management of genitourinary syndrome of menopause: A practical guide

Santiago Palacios^a, Camil Castelo-Branco^b, Heather Currie^c, Velja Mijatovic^d,
Rossella E. Nappi^e, James Simon^f, Margaret Rees^{g,*}

2015

- 5. Management
- 5.1. Hormonal therapies
- 5.1.1. Topical and systemic hormone therapy
- 5.1.2. Tibolone
- 5.1.3. Ospemifene
- 5.1.4. Vaginal dehydroepiandrosterone
- 5.2. Non hormonal therapies
- 5.3. Laser
- 5.4. Alternative and complementary therapies ..

- TAILOR THE RIGHT TREATMENT TO THE RIGHT WOMAN
- USE MULTIPLE TREATMENTS FOR DIFFERENT PHENOTYPES



Recommendations for the management of postmenopausal vaginal atrophy



D. W. Sturdee and N. Panay, on behalf of the International Menopause Society Writing Group*

Restoration of urogenital physiology

Alleviation of symptoms

**18th October 2010 –
World Menopause Day**



**ENDING
THE SILENT
SUFFERING**

Managing Vaginal Atrophy
in Postmenopausal Women

SAVE THE DATE

- **Treatment should be started early and before irrevocable atrophic changes have occurred.**
- **Treatment needs to be continued to maintain the benefits.**

Recommendations for the management of postmenopausal vaginal atrophy



D. W. Sturdee and N. Panay, on behalf of the International Menopause Society Writing Group*

Restoration of urogenital physiology

Alleviation of symptoms

- **Systemic HRT relieves vaginal atrophy in about 75% of women**
- **Combination of systemic and local therapy may be required initially for some women**

**18th October 2010 –
World Menopause Day**



**ENDING
THE SILENT
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- **All local estrogen preparations are effective and patient preference will usually determine the treatment used**

SAVE THE DATE

Recommendations for the management of postmenopausal vaginal atrophy



D. W. Sturdee and N. Panay, on behalf of the International Menopause Society Writing Group*

**18th October 2010 –
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**ENDING
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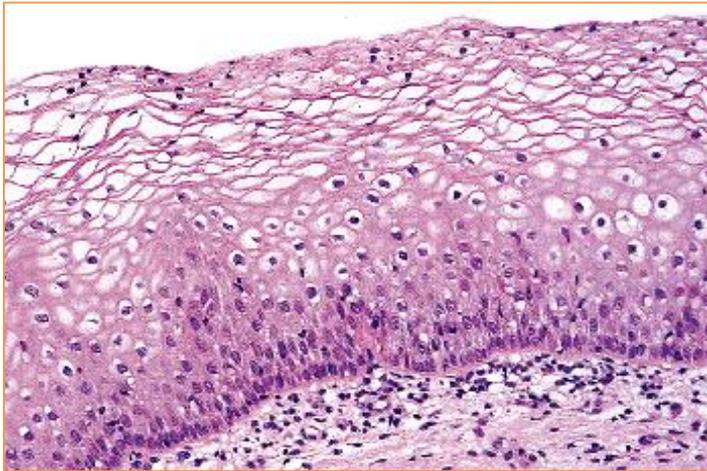
SAVE THE DATE

- There are some data suggesting that moisturizers and some other substances may have a longer-lasting effect if used consistently
- Non-hormonal options are primarily indicated in women wishing to avoid hormonal therapy or in high-risk individuals with a history of hormone-sensitive malignancy such as breast or endometrial cancer.

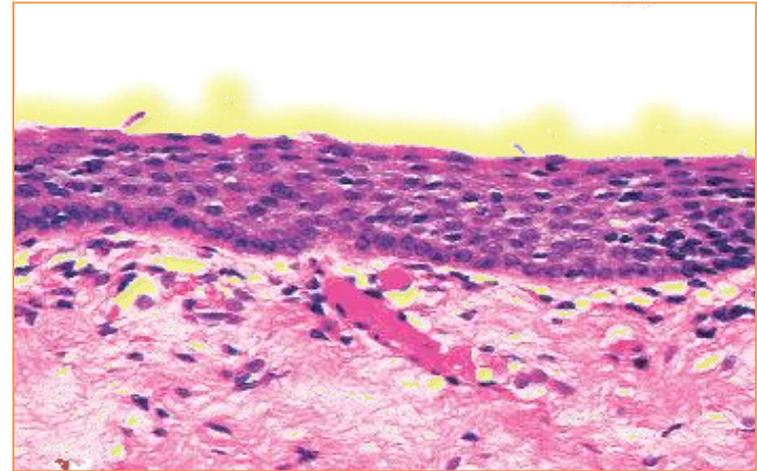
- If estrogen is ineffective or undesired, vaginal lubricants and moisturizers can relieve symptoms due to dryness.

Your Vagina During Menopause

Normal Vaginal Epithelium
(Premenopausal)



Atrophic Vaginal Epithelium



HT can **revitalize** the vaginal epithelium and **restore** vaginal health

Moisturizers and lubricants just **"gloss over"** the problem

HT = hormone therapy

Revised Global Consensus Statement on Menopausal Hormone Therapy

- MHT, including tibolone, is effective in the treatment of **vulvovaginal atrophy (VVA)**, now also considered as a component of the genitourinary syndrome of menopause (**GSM**).
- Local low-dose estrogen therapy is preferred for women whose symptoms are limited to **vaginal dryness** or associated **discomfort with intercourse** or for the prevention of **recurrent urinary tract infections**.
- Ospemifene, an oral selective estrogen receptor modulator, is also licensed in some countries for the treatment of **dyspareunia attributed to VVA**.

VAGINAL ESTROGEN FORMULATIONS AVAILABLE IN EUROPE



Creams

**Vaginal Estriol
Estradiol or
Promestriene**

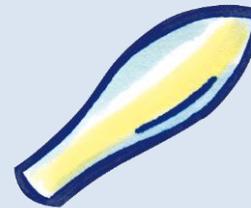
Gels

Vaginal Estriol



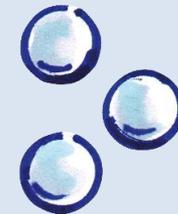
Rings

**Vaginal
Estradiol
over 90 days**



Suppositories

**Vaginal Estriol
or
Promestriene**



Tablets

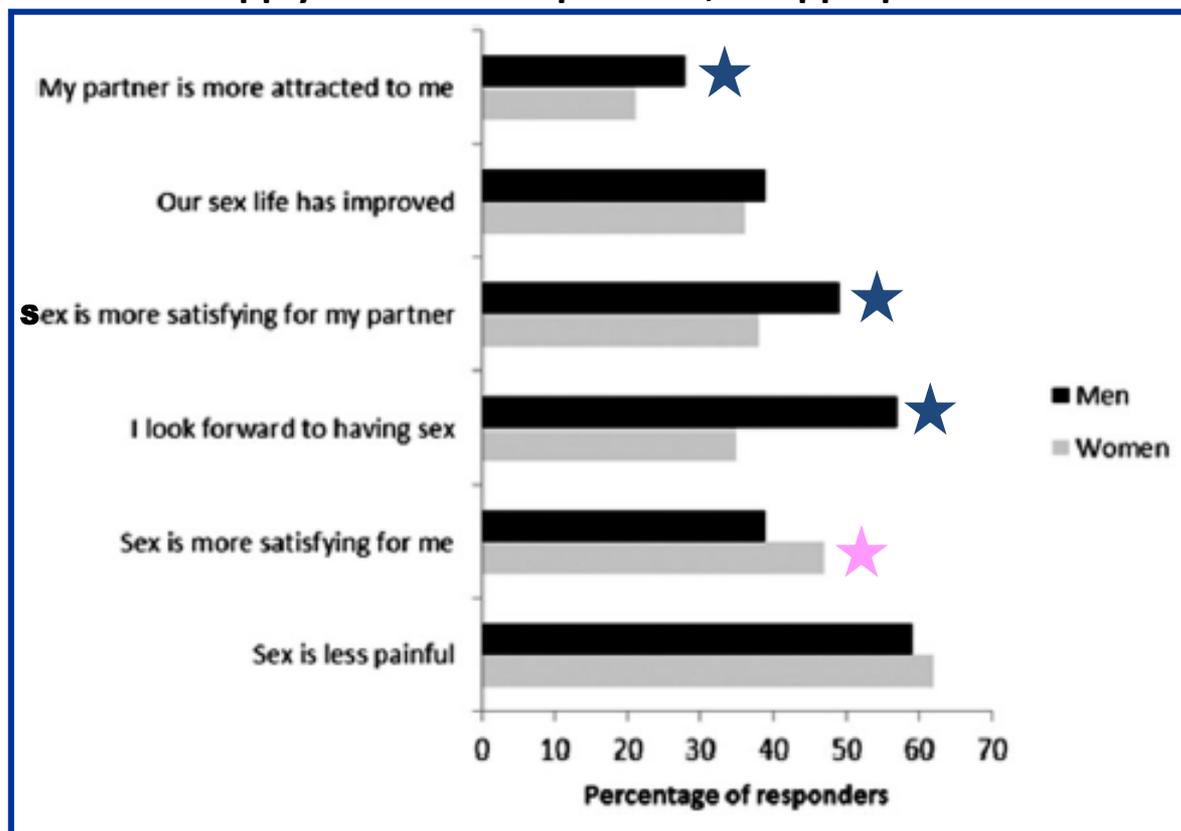
**Vaginal
Estradiol**

The CLOSER (CLarifying Vaginal Atrophy's Impact On SEx and Relationships) Survey: Implications of Vaginal Discomfort in Postmenopausal Women and in Male Partners

Rossella E. Nappi, MD, PhD,* Sheryl Kingsberg, PhD,† Ricardo Maamari, MD, NCMP,‡ and James Simon, MD, CCD, NCMP, FACOG§

J Sex Med 2013;10:2232–2241

Questions were asked to the women and corresponding questions for men were rephrased slightly to apply to the men's partners, as appropriate.



- Impact of local estrogen therapy on sex life (41% of the sample)

The efficacy and safety of estriol to treat vulvovaginal atrophy in postmenopausal women: a systematic literature review

ABSTRACT

Objectives: To evaluate the efficacy and safety of estriol for the treatment of vulvovaginal atrophy in postmenopausal women.

Methods: A systematic literature review was performed. We searched the following electronic databases: Medline, Cochrane, Embase, Lilacs, CINAHL and Google Scholar. The studies selected included controlled clinical trials and quasi-experimental studies. Selections were made in pairs and independently, first by title and abstract and then complete texts.

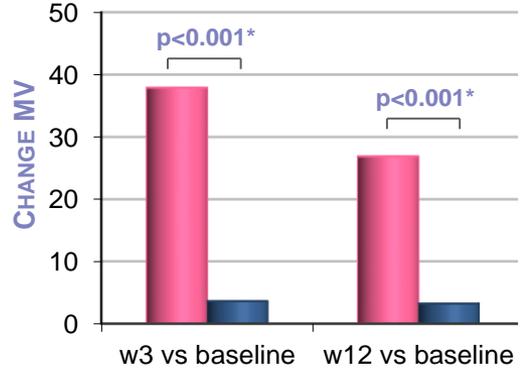
Results: We identified 188 studies, 22 of which met the inclusion criteria; 13 were controlled clinical trials and nine were quasi-experimental, and 1217 women were included. These studies confirmed the efficacy of local estrogens to treat symptoms of vulvovaginal atrophy with few adverse effects reported. Following treatment, serum estriol levels rose, peaking at 1 h. At the 6-month follow-up, there was no increase in serum estriol in treated women.

Conclusions: The available evidence (of low and moderate quality) shows that, when administered vaginally, estriol preparations appear to be safe for women who have risk factors related to systemic estrogen therapy.

The therapeutic effect of a new ultra low concentration estriol gel formulation (0.005% estriol vaginal gel) on symptoms and signs of postmenopausal vaginal atrophy: results from a pivotal phase III study.

❖ A total of 167 women were treated (114 received E3 and 53 received placebo) daily for 3 weeks and then twice weekly up to 12 weeks.

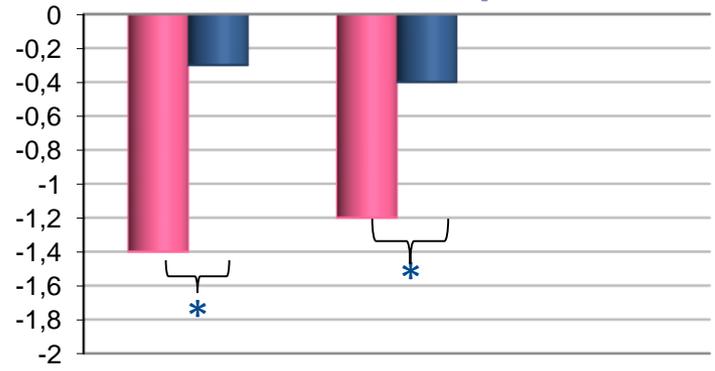
MATURATION INDEX



* Wilcoxon rank sum test

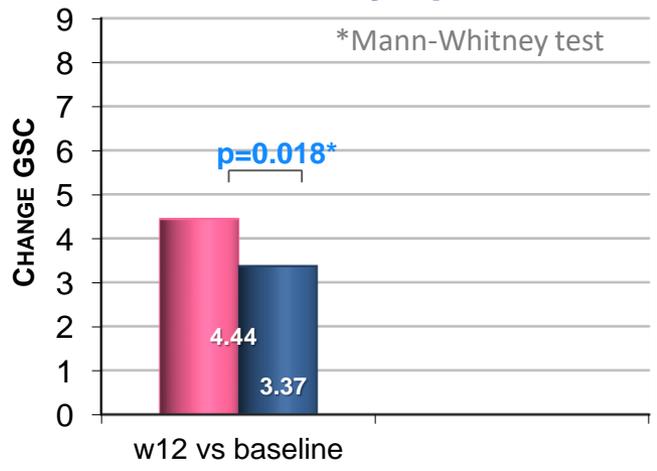
■ Vaginal Gel E3 0.005% (50 mcg)
 ■ Gel placebo

VAGINAL pH



VAGINAL symptoms

* P < 0.001, Wilcoxon



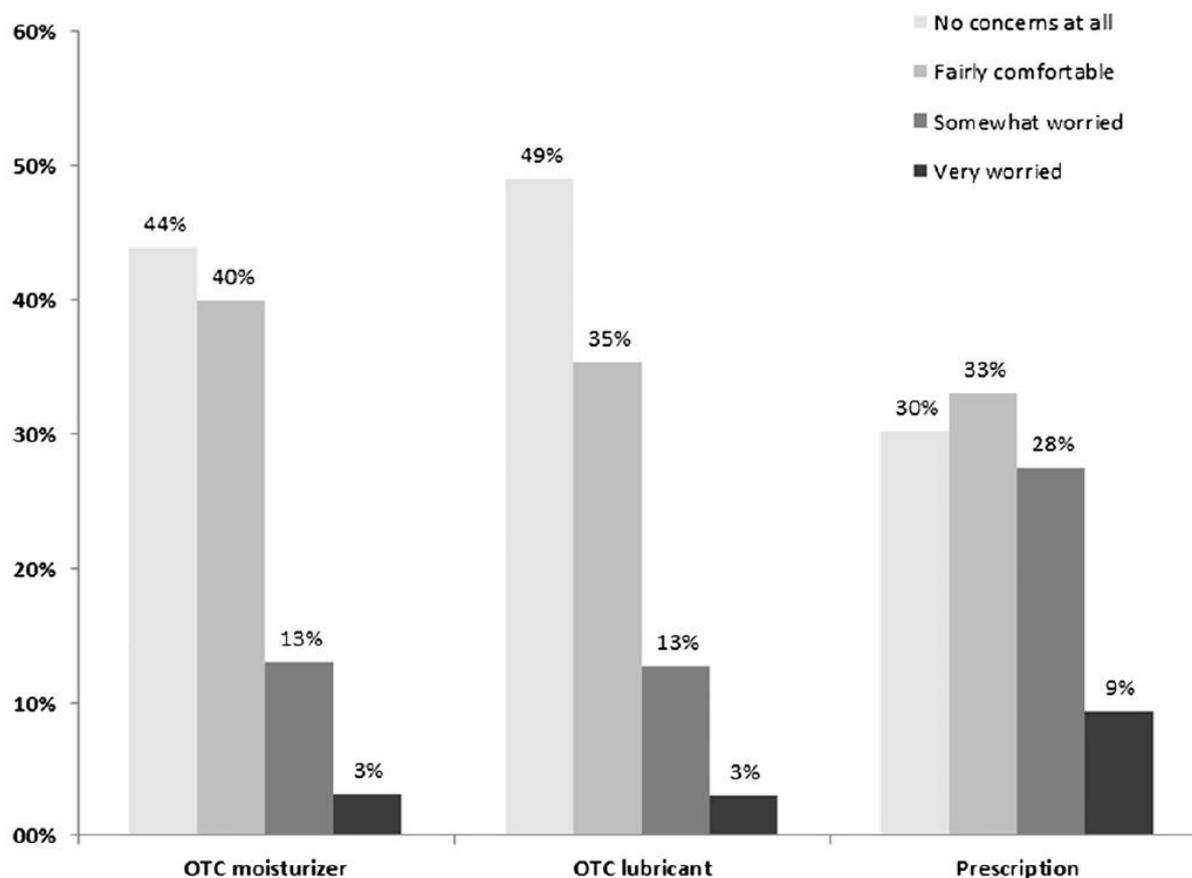
*Mann-Whitney test

Vulvar and vaginal atrophy in four European countries: evidence from the European REVIVE Survey

R. E. Nappi^a, S. Palacios^b, N. Panay^c, M. Particco^d and M. L. Krychman^e

CLIMACTERIC, 2016
VOL. 19, NO. 2, 188–197

Proportion of participant's concerned with long-term use of their current VVA medication



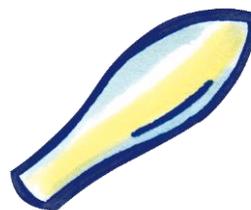
- 3768 women (45–75 yrs) in Europe (Italy, Spain, UK, Germany) currently suffering from VVA

Clinical profile of women with vulvar and vaginal atrophy who are not candidates for local vaginal estrogen therapy



WHO ARE THEY?

- Women with contraindication
- Women not candidates for other medical or personal reasons
- It is up to HCPs/Gynecologists to make an appropriate therapeutic decision.

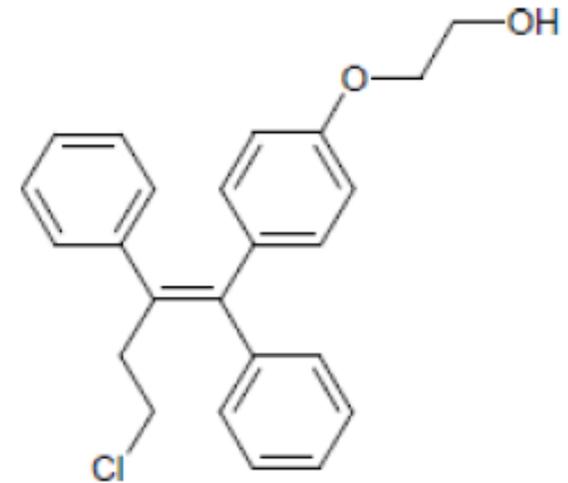


OSPEMIFENE 60 mg è stato recentemente approvato per la seguente indicazione:

Trattamento dei sintomi moderati/severi di atrofia vulvo-vaginale (AVV) in donne in post-menopausa che non sono candidate per la terapia estrogenica locale

Struttura chimica di Ospemifene

- **Modulatore selettivo dei recettori per gli estrogeni (SERM)**
- **Ospemifene ha azione agonista su epitelio vaginale**
- **Più di 7 donne su 10 hanno avvertito un miglioramento della secchezza vaginale e della dispareunia dopo 12 settimane di terapia verso placebo**

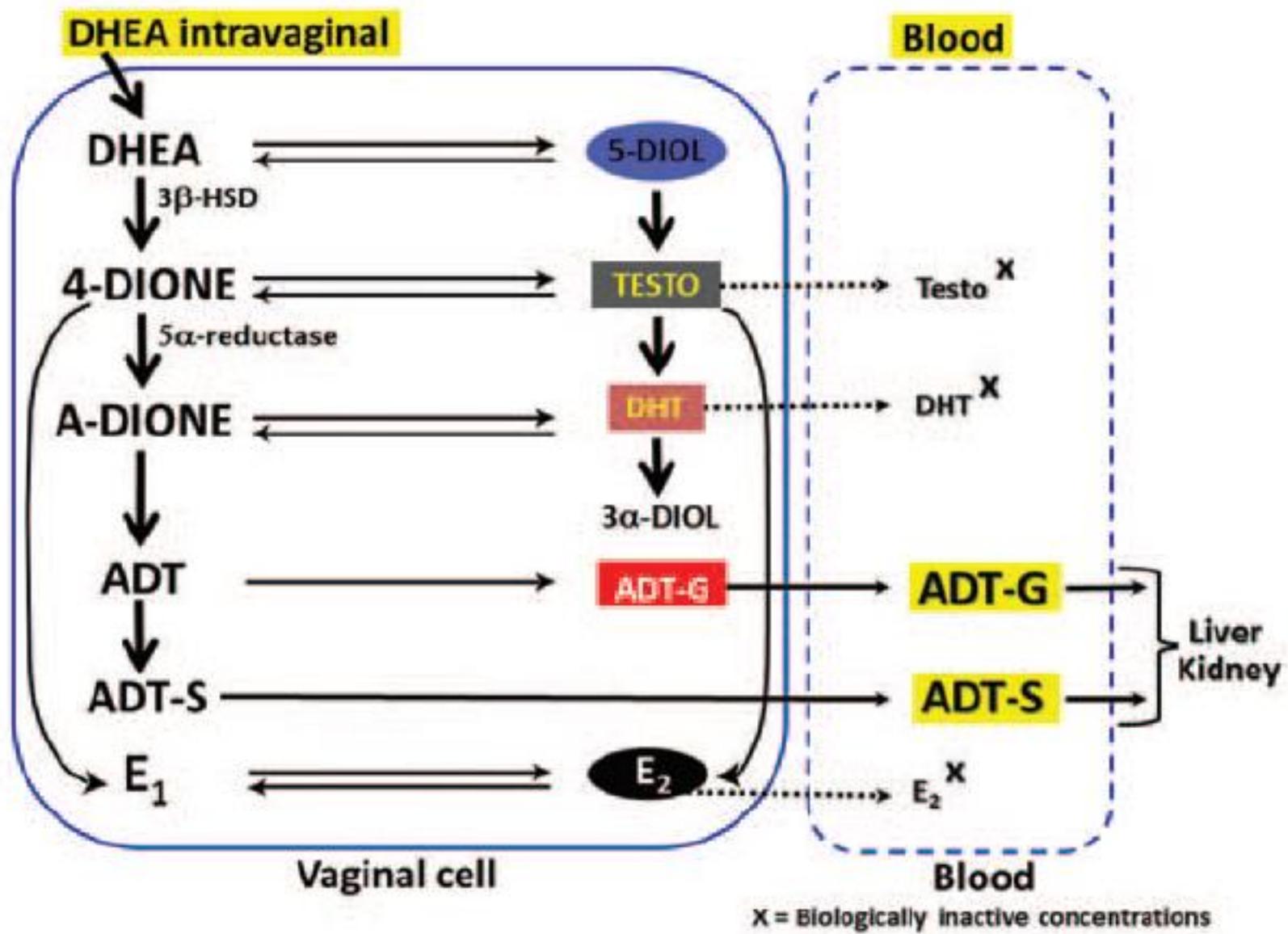


Systematic indirect comparison of ospemifene versus local estrogens for vulvar and vaginal atrophy

ABSTRACT

In the absence of a direct head-to-head study, we performed an indirect historical comparison of ospemifene 60 mg (Senshio[®]) vs. local vaginal estrogens in moderate or severe vulvar and vaginal atrophy (VVA). A literature search was carried out of clinical efficacy/safety trials of local vaginal estrogens in VVA approved in Europe. For efficacy comparison, studies had to be placebo-controlled and of 12 weeks' duration. For safety comparison, studies had to be ≥ 40 weeks' duration. Efficacy endpoints were the difference between active and placebo in change from baseline to week 12 for symptoms, vaginal pH, and maturation value (MV). Safety endpoints were endometrial safety, breast safety, thrombosis, and adverse events. The 12-week improvement over placebo in symptom score was not different for ospemifene 60 mg and 17 β -estradiol 10 μ g and for ospemifene 60 mg and estriol gel. After 12 weeks, the percentages with vaginal pH < 5.0 and < 5.5 were better for ospemifene 60 mg than 10 μ g 17 β -estradiol. Week-12 pH changes were comparable with estriol pessaries or gel and ospemifene 60 mg. The 12-week MV improvements over placebo were similar or better with ospemifene 60 mg compared with 10 μ g 17 β -estradiol and with estriol pessaries or gel. There was no increased vaginal bleeding, endometrial hyperplasia, or carcinoma (including breast cancer) relative to placebo and no signal for increased risk of venous thromboembolism with ospemifene 60 mg or 10 μ g 17 β -estradiol, but the confidence intervals for both products do not exclude an increased risk. This historical indirect comparison suggests that ospemifene 60 mg has an efficacy, safety, and tolerability profile comparable to or better than local vaginal estrogens in the treatment of VVA.

Science of intracrinology in postmenopausal women



Efficacy of intravaginal dehydroepiandrosterone (DHEA) on moderate to severe dyspareunia and vaginal dryness, symptoms of vulvovaginal atrophy, and of the genitourinary syndrome of menopause

Conclusions: The daily intravaginal administration of 0.50% (6.5 mg) DHEA (Prasterone) has shown clinically and highly statistically significant effects on the four coprimary parameters suggested by the US Food and Drug Administration. The strictly local action of Prasterone is in line with the absence of significant drug-related adverse events, thus showing the high benefit-to-risk ratio of this treatment based upon the novel understanding of the physiology of sex steroids in women.

Labrie et al, 2016

Effect of Intravaginal Prasterone on Sexual Dysfunction in Postmenopausal Women with Vulvovaginal Atrophy

Conclusion. The present data show that all the six domains of the FSFI are improved over placebo (from $P = 0.047$ to 0.0005), thus confirming the previously observed benefits of intravaginal DHEA on female sexual dysfunction by an action exerted exclusively at the level of the vagina, in the absence of biologically significant changes of serum steroids levels.

Labrie et al, 2015

Serum steroid concentrations remain within normal postmenopausal values in women receiving daily 6.5 mg intravaginal prasterone for 12 weeks

The present data shows that a low daily intravaginal dose (6.5 mg) of DHEA (prasterone) which is efficacious on the symptoms and signs of VVA, permits to achieve the desired local efficacy without systemic exposure, in agreement with the stringent mechanisms of menopause established after 500 million years of evolution where each cell in each tissue is the master of its sex steroid exposure.

Martel et al, 2016

Light and Energy Based Therapeutics for Genitourinary Syndrome of Menopause: Consensus and Controversies

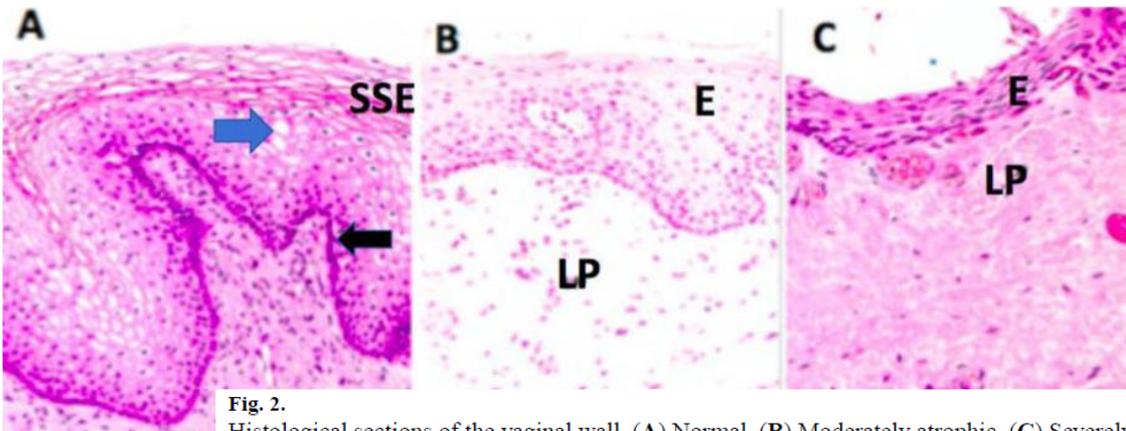
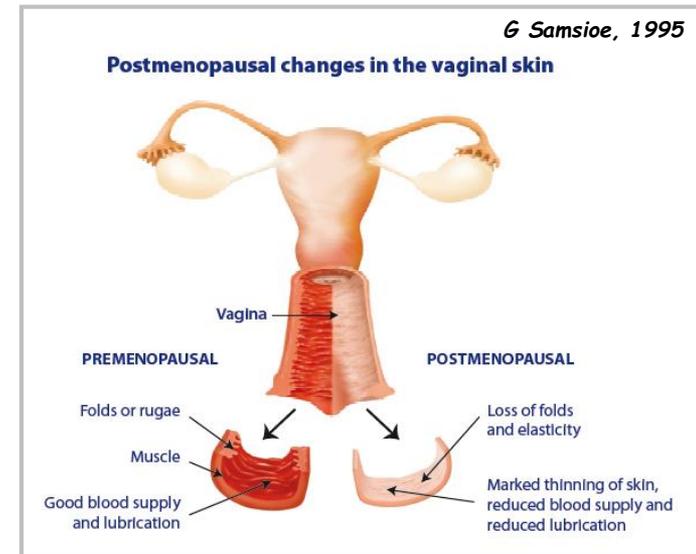
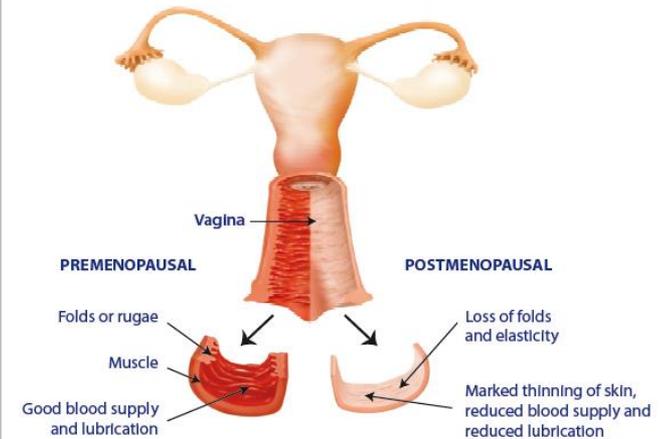


Fig. 2. Histological sections of the vaginal wall. (A) Normal. (B) Moderately atrophic. (C) Severely atrophic. (A) Estrogenized vaginal histology. The two upper layers of the vaginal wall are shown: stratified, squamous epithelium (SSE), and the lamina propria (LP). The stratified squamous epithelium is rich in glycogen (larger cells with abundant clear cytoplasm—blue arrow) and is nonkeratinizing. The basal cell layer (black arrow) consists of a single layer of columnar cells. (B) Moderately atrophied vagina: Atrophy is shown by thinner epithelium (E) and loss of maturation (smaller cell size with less cytoplasm) on the surface. (C) Marked vaginal atrophy. (Courtesy: Lev-Sagie A).



G Samsioe, 1995

Postmenopausal changes in the vaginal skin



- Recent technological developments triggered an unprecedented wave of publications, assessing the efficacy of **fractional laser**, and **radiofrequency** on the vaginal wall in reversing natural aging processes.
- Studies have shown that a certain degree of thermal energy deposited on the vaginal wall stimulates proliferation of
 - the **glycogen-enriched epithelium**,
 - **neovascularization**,
 - and collagen **formation in the lamina propria**,and improves natural lubrication and control of urination.

Tadir et al, 2017

Turning the spotlight on lasers

Hillard, 2017

...from the evidence to date, the use of vaginal laser treatment certainly appears successful and promises to be a potential addition to our array of treatments for VVA, particularly for those women with previous breast cancer.

Seeing the light: the need for randomized trials of vaginal laser in postmenopausal women

Mitchell, 2017

...the field is encouraged to demand more trials to rigorously evaluate the true efficacy of laser products for postmenopausal vulvovaginal symptoms.

Laser therapy for the genitourinary syndrome of menopause. A systematic review and meta-analysis

Pitsouni et al, 2017

- Laser-therapy seems a promising and safe non-pharmaceutical therapeutic option for GSM in both clinical and pathophysiological aspect.
- However, quality of the body of evidence is "low" or "very low", the possible placebo effect of the treatment has not yet been ruled out or estimated

Management of genitourinary syndrome of menopause in women with or at high risk for breast cancer: consensus recommendations from The North American Menopause Society and The International Society for the Study of Women's Sexual Health

Faubion et al, 2018

- Available data suggest the **VEL or CO2 lasers have the potential to ameliorate distressing GSM for survivors of breast cancer** without the need for local hormone intervention.
- Placebo or active-controlled trials, long-term safety follow-up, and additional economic analyses are needed.

GSM TREATMENT OPTIONS IN BREAST CANCER SURVIVORS

Table 2 Different Options for Genitourinary Syndrome of Menopause Treatment in BCSs

Pharmacological Intervention

Nonhormonal vaginal moisturizers and lubricants (first-line therapy; transient benefit, low compliance)

Low-dose vaginal estrogens (LETs) (for BCSs who do not respond to nonhormonal intervention, after discussion of risk and benefits; caution in women receiving AIs. Great efficacy, even at ultra-low doses)

Oral ospemifene (no clinical trials available in BCSs; in healthy women the efficacy is comparable with LETs, no endometrial or breast stimulation after 12 months of therapy)

Androgen therapy (experimental; concerns regarding possible aromatization of androgens to estrogen in BCSs)

Nonpharmacological Interventions

Vaginal laser (no clinical trials available in BCSs; short follow-up for evaluating its efficacy in healthy women)

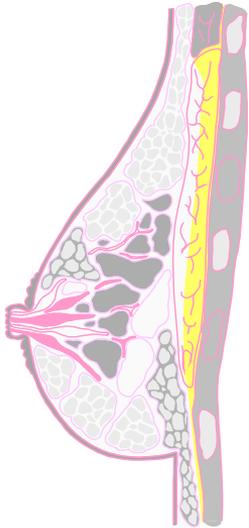
Couple counseling

Management of psychosocial distress

Regular sexual activity

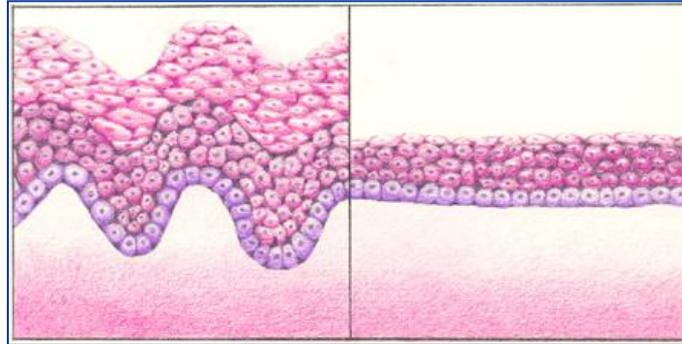
Need for larger clinical trials:

- Vaginal dilators of graduated size
- Pelvic floor physical therapy
- Topical liquid lidocaine



VVA/GSM

IS A CHRONIC CONDITION WITH AN IMPACT ON
SEXUALITY, URO-GENITAL HEALTH AND QOL



- Genes
- Life-Style
- Environment
- Health Care
- Economy



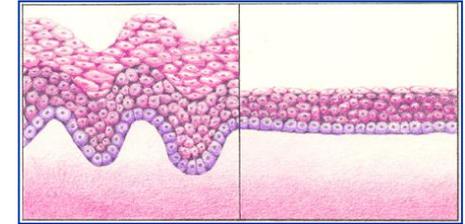
**THE RIGHT TO HAVE WRINKLES
ALSO DOWN THERE!**

RE Nappi, 2018

Diagnosis and management of symptoms associated with vulvovaginal atrophy: expert opinion on behalf of the Italian VVA study group*

HCPs/GYNECOLOGISTS PLAY A CRUCIAL ROLE

1. Facilitating the discussion
2. Recognizing the condition
3. Being sensible to the impact on sex & QoL
4. Educating about risk factors and consequences
5. Understanding needs, expectations
6. Removing barriers, fears, misconceptions
7. Considering all the potential options according to
 - Benefits/Risks Balance
 - Psychosocial Profile
8. Having the objective to effectively treat VVA
9. Starting early to obtain a better response to treatments
9. Improving long-term adherence



GRAZIE PER L'ATTENZIONE!



GYNENDO-MENOPAUSE UNI-PV TEAM