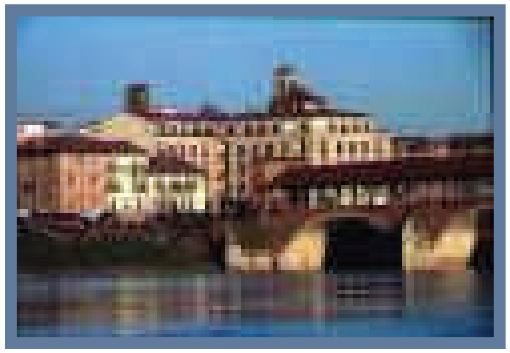


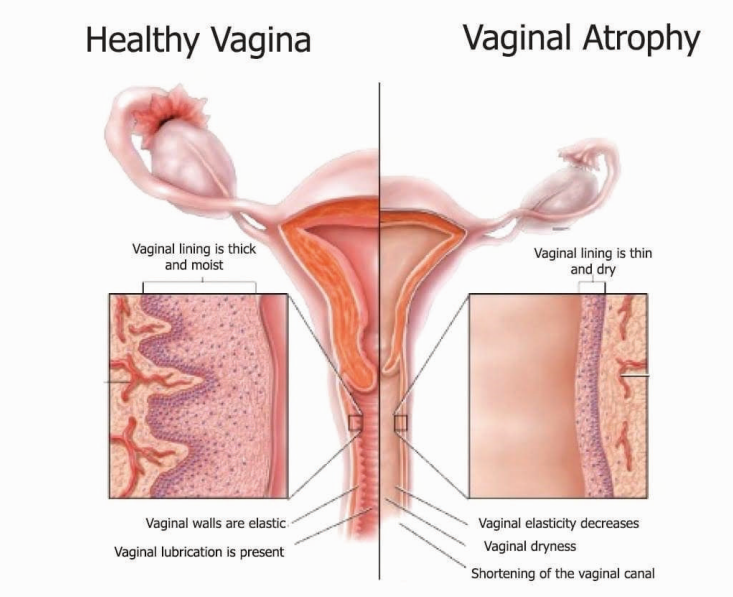
Terapia innovativa nella gestione dell'atrofia vulvo-vaginale

Rossella E. Nappi

Centro di Ricerca per la Procreazione Medicalmente Assistita,
Endocrinologia Ginecologica e della Menopausa,
IRCCS Policlinico S. Matteo, Università degli Studi di Pavia

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**



❖ **Biological etiology**:

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

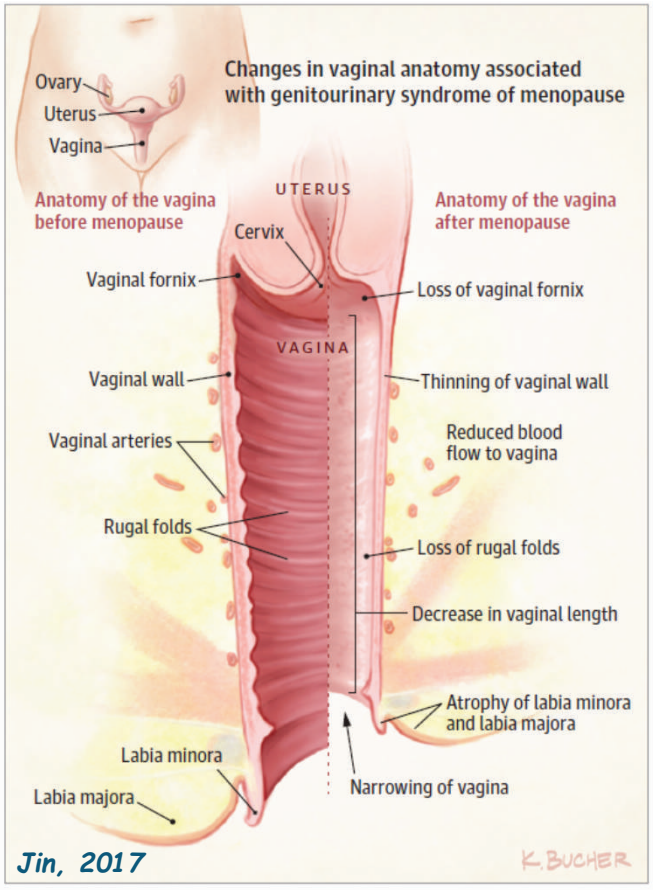
❖ **Other psychosocial modulators**:

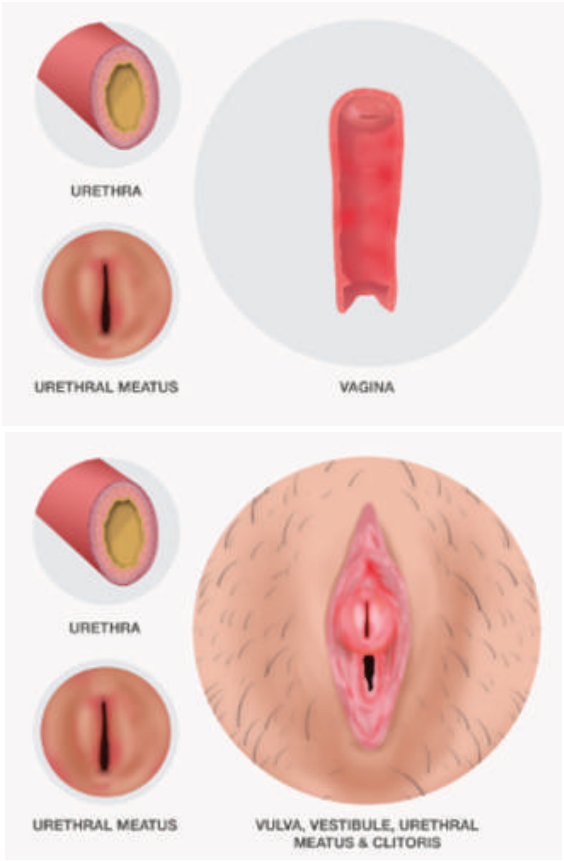
- ✓ Self-esteem
- ✓ Body image
- ✓ Personality
- ✓ Importance attributed to sexuality
- ✓ Quality and duration of the relationship
- ✓ Attitudes toward menopause and aging (norms, values, traditions…)
- ✓ Experiences
- ✓ Access

Highly prevalent
BUT
underreported and undertreated

RE Nappi, 2018

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.

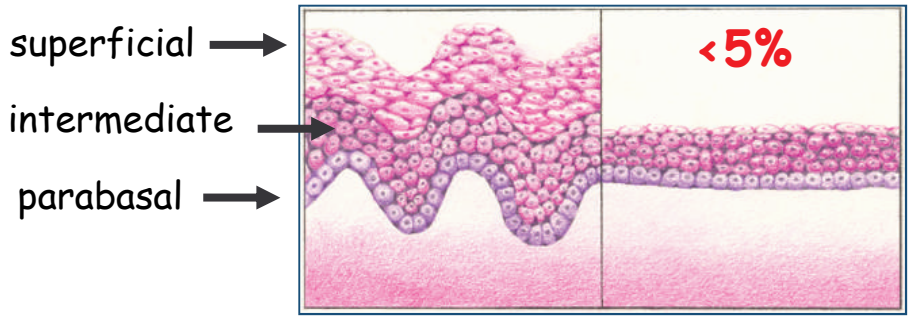
RE Nappi, 2018

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

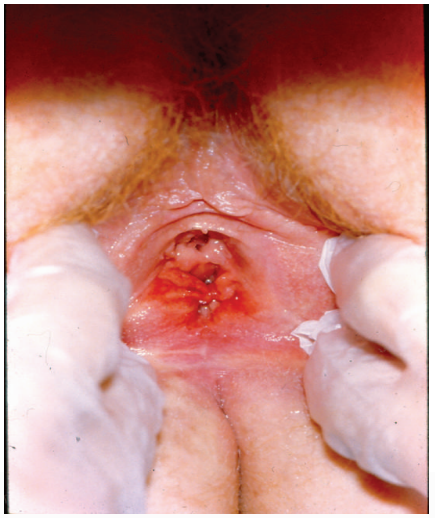
D.J. Portman*, M.L.S. Gass, on behalf of the Vulvovaginal Atrophy Terminology Consensus Conference Panel[1]

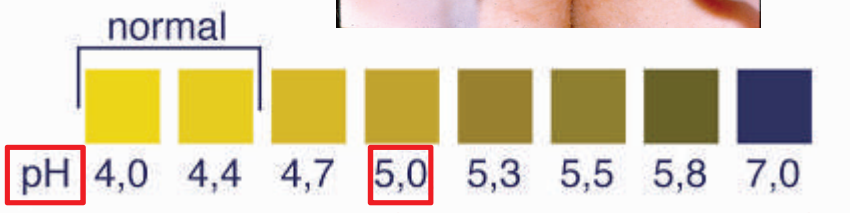
- **Genital symptoms** of dryness, burning, and irritation;
- **Sexual symptoms** of lack of lubrication, discomfort or pain, and impaired function;
- **Urinary symptoms** of urgency, dysuria and recurrent urinary tract infections.

- SCALES TO RATE SUBJECTIVE SYMPTOMS
- SCALES TO RATE OBJECTIVE SIGNS
- SUPPORTIVE FINDINGS



MATURATION INDEX





Portman et al, 2014

THERE ARE MULTIPLE PHENOTYPES OF WOMEN WITH VVA OUT THERE!

Lucia, 57 yrs

Dryness «It is an unconfortable sensation, it is more than a sexual problem…»

Dorina, 72 aa

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

Sofia, 44 yrs

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

Anna, 57 yrs

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

Maria Luisa, 61 yrs

Dysuria «I feel my bladder crying…»

Paola, 55 yrs

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

Giusy, 54 yrs

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

Maria, 68 yrs

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

RE Nappi, 2018

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

- **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

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

18th October 2010 – World Menopause Day

ENDING THE SILENT SUFFERING

Managing Vaginal Atrophy in Postmenopausal Women

SAVE THE DATE

CLIMACTERIC 2010;13:509–522

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 SUFFERING

Managing Vaginal Atrophy in Postmenopausal Women

SAVE THE DATE

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

CLIMACTERIC 2010;13:509–522

Recommendations for the management of postmenopausal vaginal atrophy

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

- **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.**

18th October 2010 – World Menopause Day

ENDING
THE SILENT
SUFFERING

Managing Vaginal Atrophy
in Postmenopausal Women

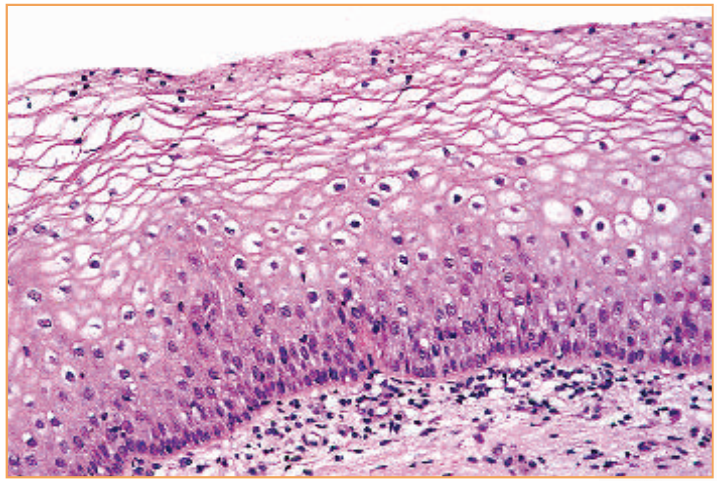
SAVE THE DATE

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

CLIMACTERIC 2010;13:509–522

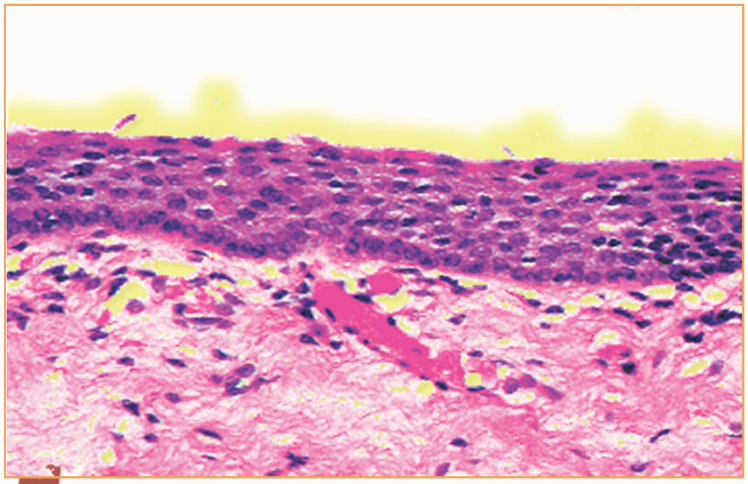
Your Vagina During Menopause

Normal Vaginal Epithelium
(Premenopausal)



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

Atrophic Vaginal Epithelium



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

HT = hormone therapy

RE Nappi, 2018

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.

De Villiers et al, 2016

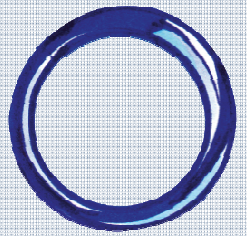
VAGINAL ESTROGEN FORMULATIONS AVAILABLE IN EUROPE

Creams

Vaginal Estriol
Estradiol or
Promestriene

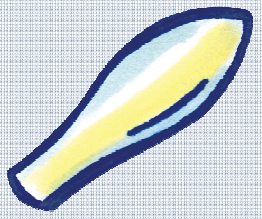
Gels

Vaginal Estriol



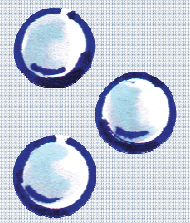
Rings

Vaginal
Estradiol
over 90 days



Suppositories

Vaginal Estriol
or
Promestriene



Tablets

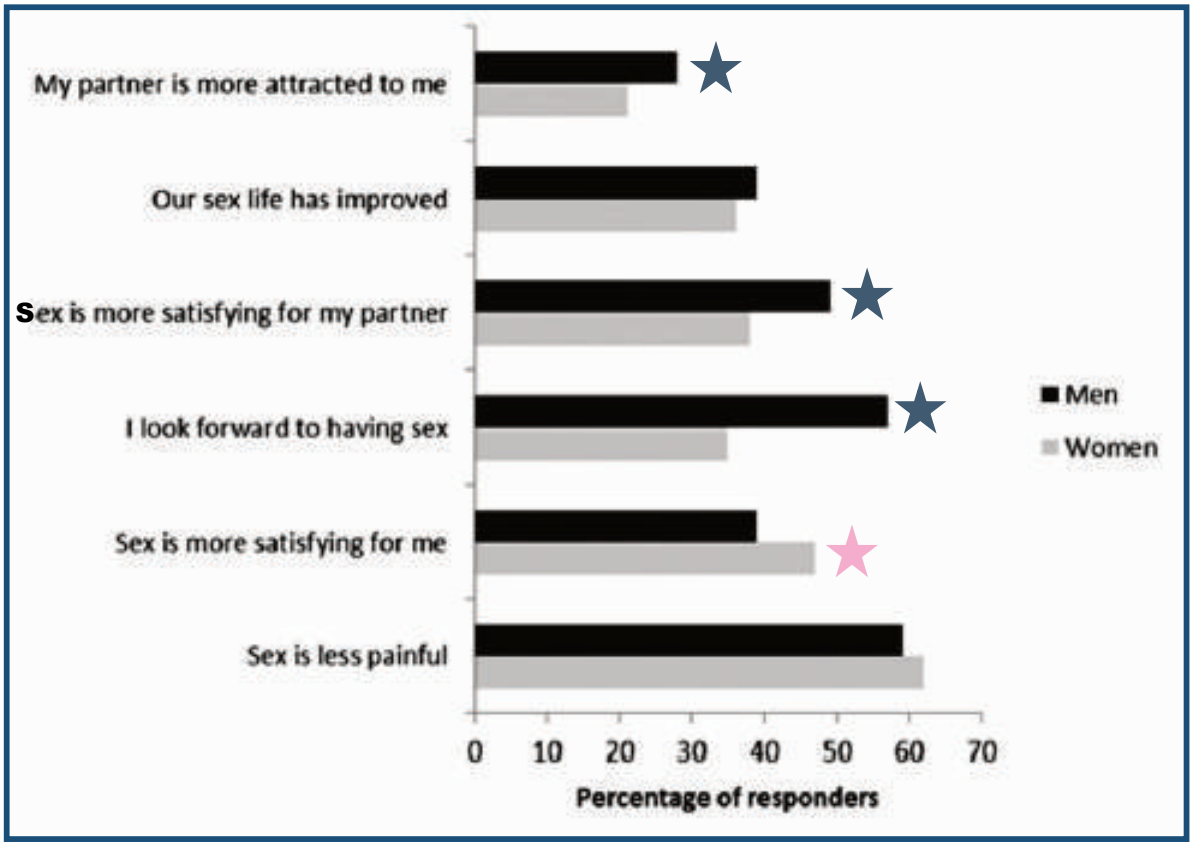
Vaginal
Estradiol

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, CINHAL 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.

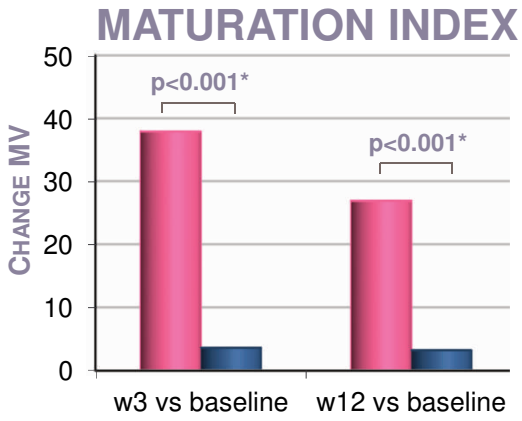
Results: We identified 188 studies, 22 of which met the inclusion criteria; 13 were controlled clinical trials and nine were quasi-experimental, and 1217 women were included. These studies confirmed the efficacy of local estrogens to treat symptoms of vulvovaginal atrophy with few adverse effects reported. 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.

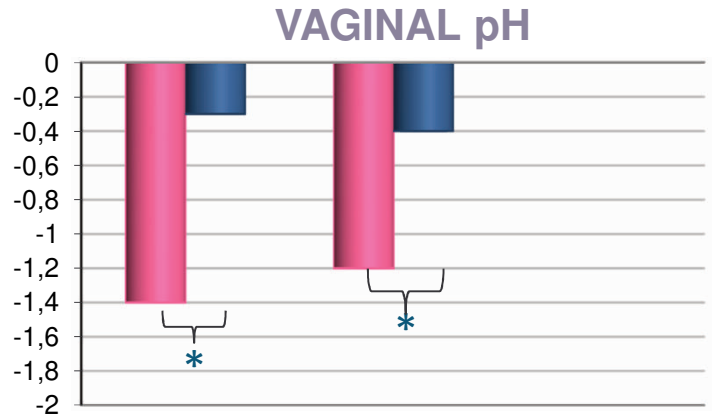
Rueda et al, 2017

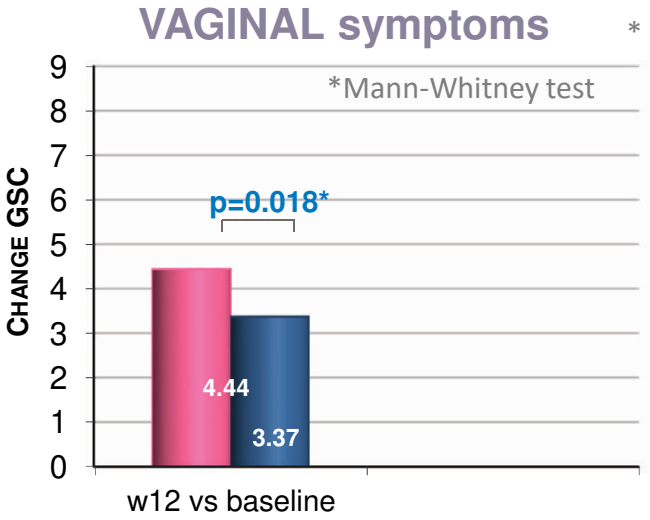
The therapeutic effect of a new ultra low concentration estriol gel formulation (0.005% estriol vaginal gel) on symptoms and signs of postmenopausal vaginal atrophy: results from a pivotal phase III study.

❖ **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.**



* Wilcoxon rank sum test





■ Vaginal Gel E3 0.005% (50 mcg)

■ Gel placebo

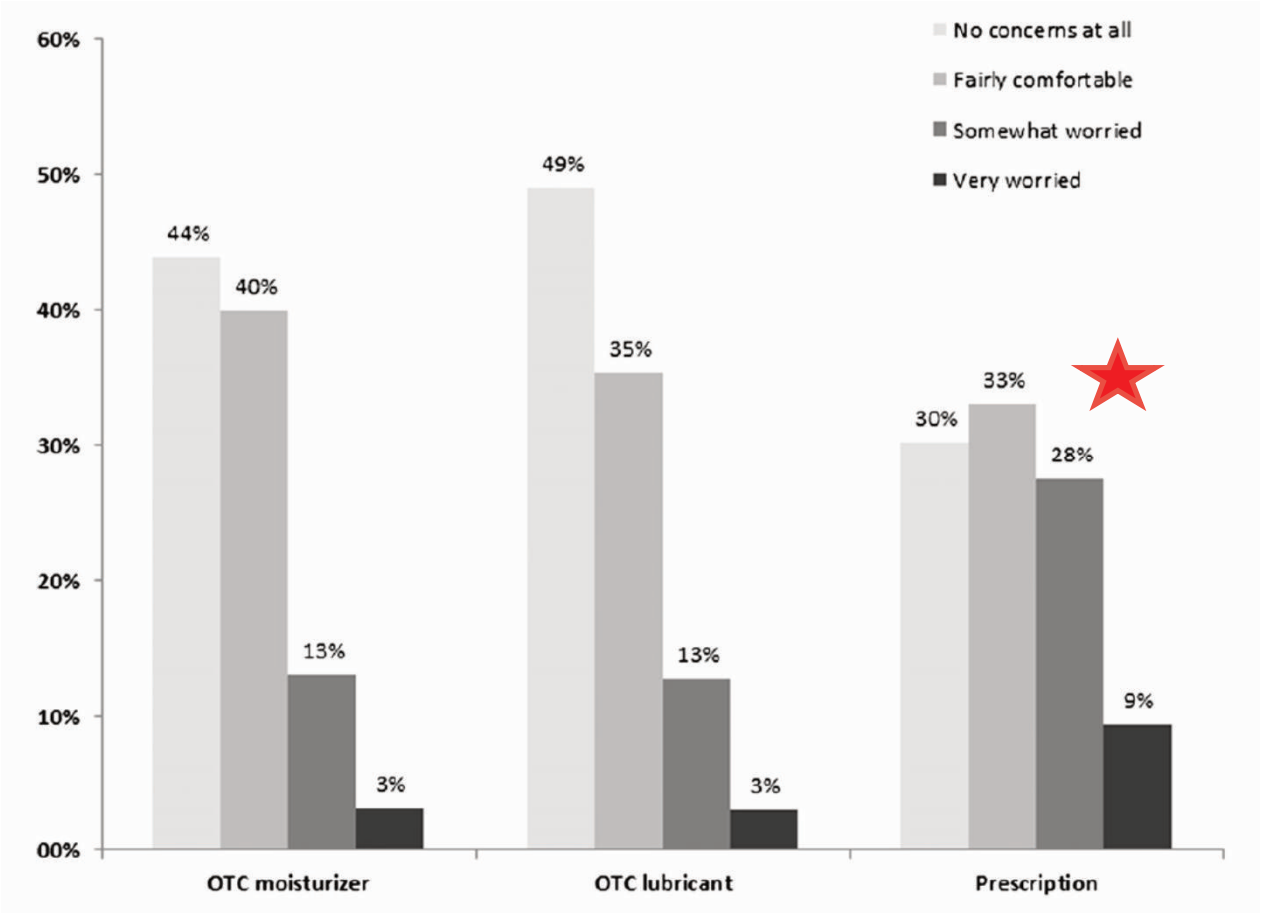
Cano et al, 2012

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



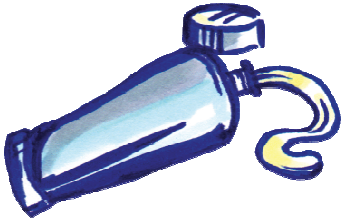
- 3768 women (45-75 yrs) in Europe (Italy, Spain, UK, Germany) currently suffering from VVA

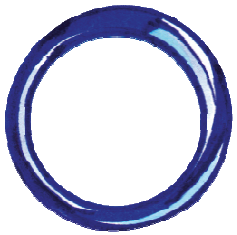
Clinical profile of women with vulvar and vaginal atrophy who are not candidates for local vaginal estrogen therapy

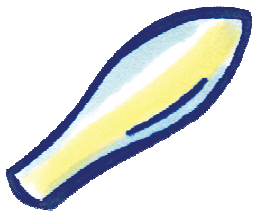
WHO ARE THEY?

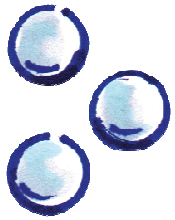
- Women with contraindication
- Women not candidates for other medical or personal reasons

- It is up to HCPs/Gynecologists to make an appropriate therapeutic decision.









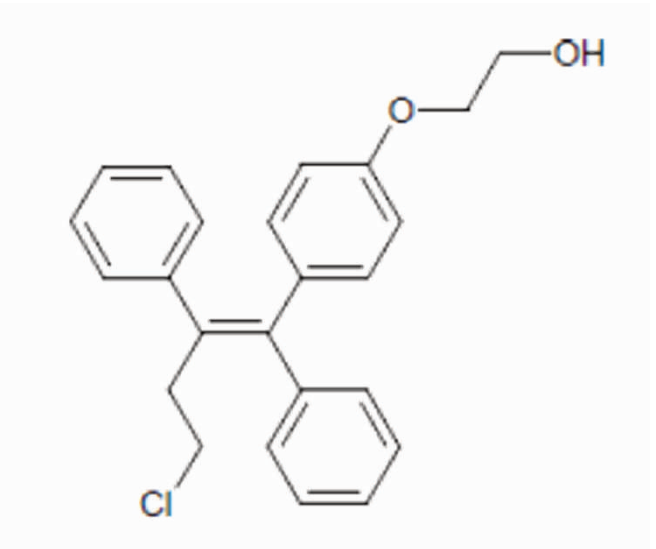
Nappi et al, 2017

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

- **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**

Struttura chimica di Ospemifene



Nappi & Cucinella, 2015; Nappi et al, 2015

OSPEMIFENE and BREAST SAFETY: preclinical data

Preclinical data suggest a neutral or anti-estrogenic action of ospemifene on breast cells.

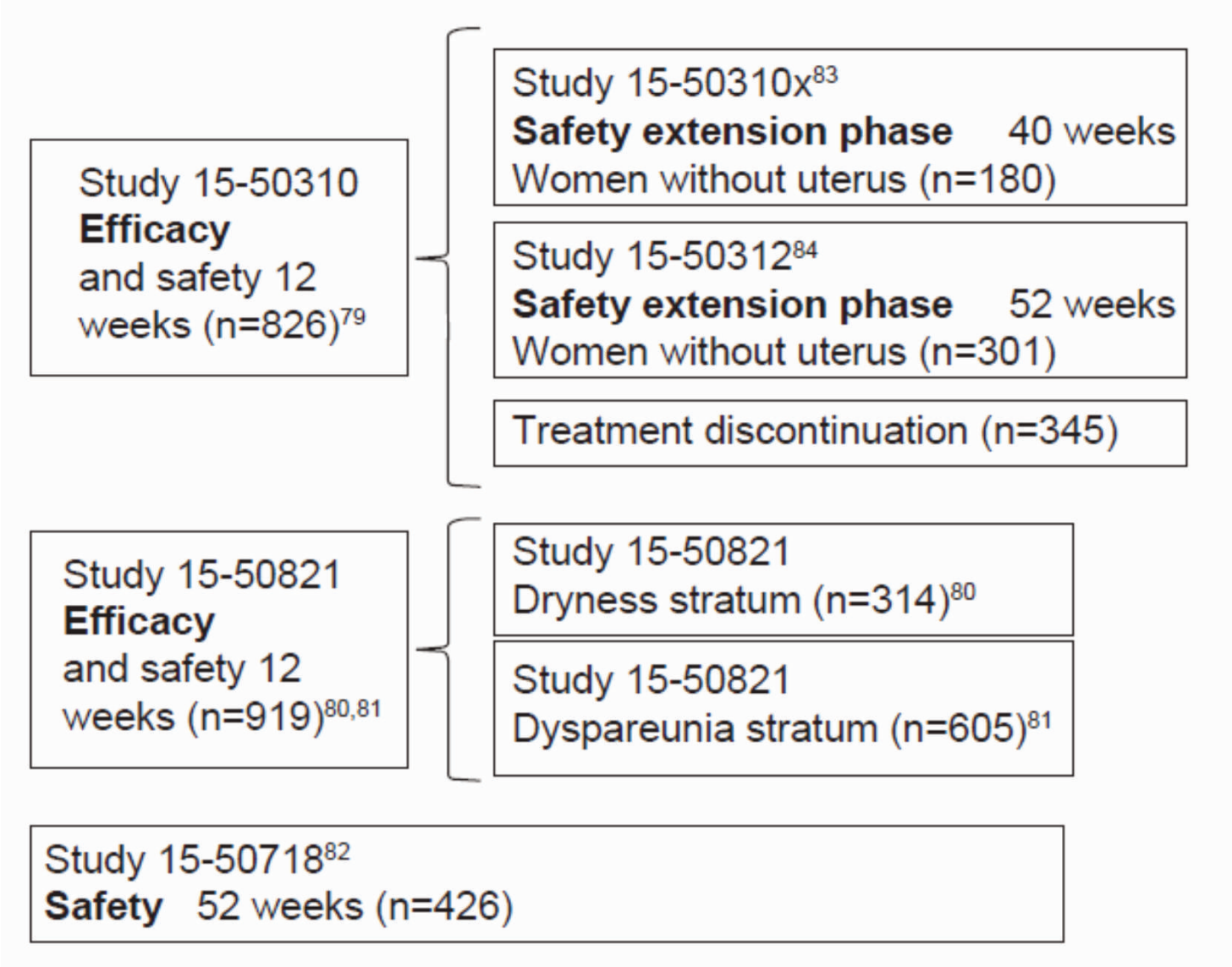
Table 2. Overview of Preclinical Data for Ospemifene in the Breast.

Study	Experimental Model	Key Results
Qu et al[14]	MCF-7 ERα$^+$ breast cancer cells grown in vivo in nude mice	Ospemifene suppressed expression of pS2, an estrogen marker
Taras et al[9]	MCF-7 ERα$^+$ breast cancer cells grown in vivo in nude mice	Ospemifene inhibited the growth of ER-dependent MCF-7 cells; no effect on ER-independent MDA-MB-231 cells
Qu et al[14]	DMBA-induced mammary carcinoma in intact and ovariectomized rats	Ospemifene inhibited tumor growth in a dose-dependent manner (by 12%, 59%, and 79%-88% in the 1-, 10-, and 50-mg/kg groups, respectively)
Wurz et al[10]	DMBA-induced mammary carcinoma in Sencar mice	Ospemifene significantly reduced DMBA-induced mammary carcinomas, similar to tamoxifen
Namba et al[8]	DCIS mouse model	Growth of transplanted cells and incidence of tumors were significantly reduced in mice treated with either ospemifene or tamoxifen compared with untreated mice
Burich et al[33]	MTag.Tg mouse breast cancer model	Ospemifene delayed the development of breast tumors, and average tumor volumes were smaller

Abbreviations: DMBA, dimethylbenzanthracene; DCIS, ductal carcinoma in situ; ER, estrogen receptor.

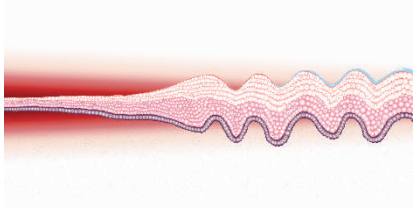
Berga SL; *Reprod Sci*. 2013 Oct;20(10):1130-6

OSPEMIFENE 60 mg: Phase III PROGRAM

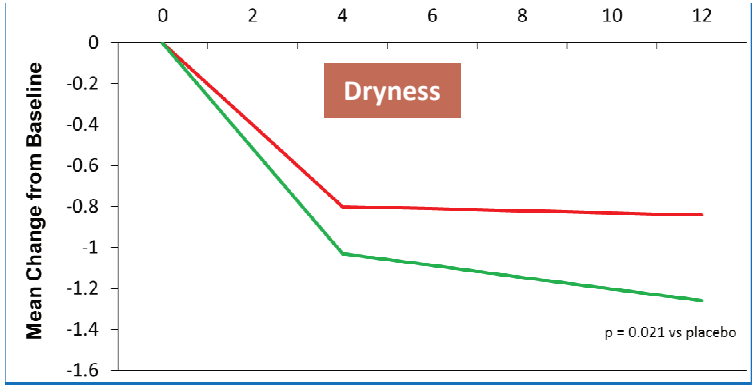


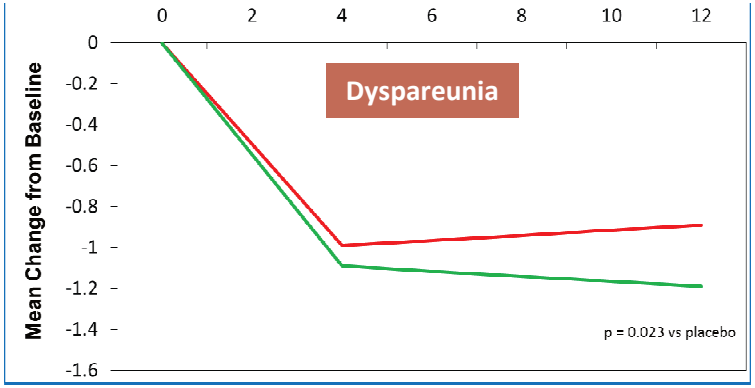
Palacios & Cancelo, 2016

MBS & Ospemifene 60 mg

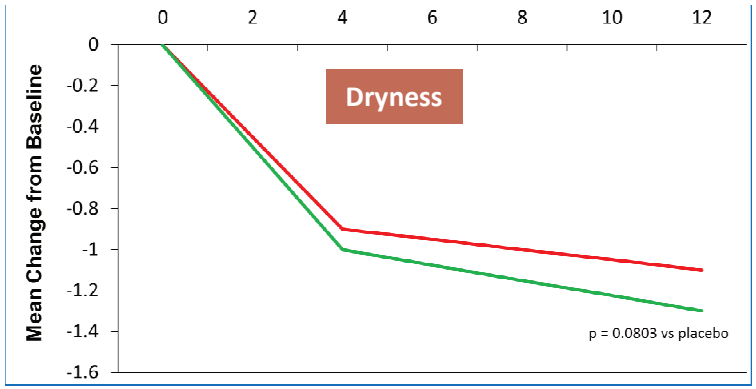


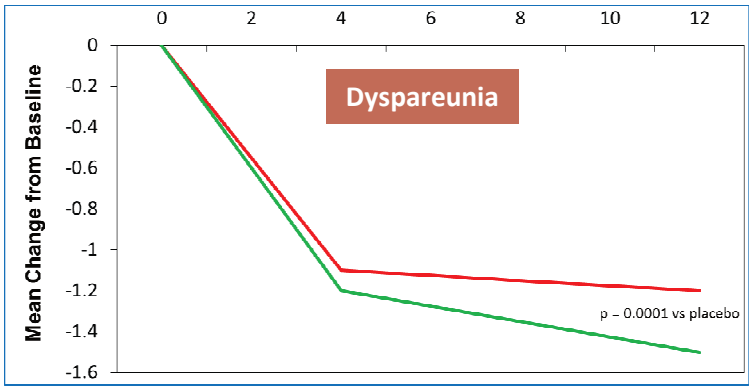
Study 15-50310 (ITT population, LOCF)





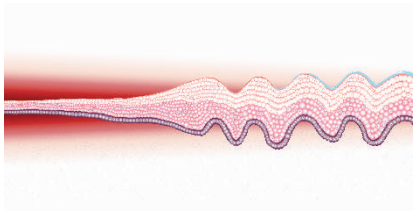
Study 15-50821 (ITT population, LOCF)

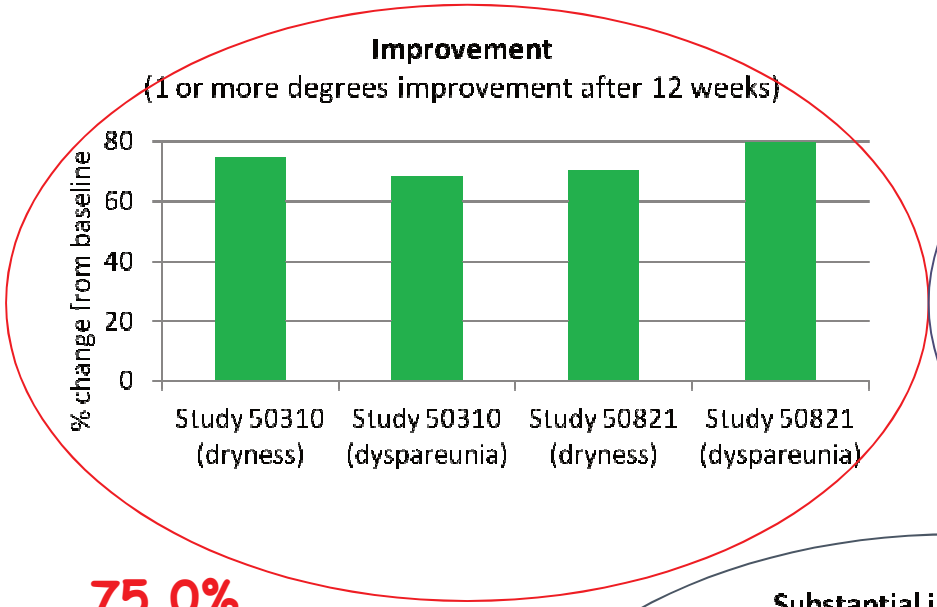




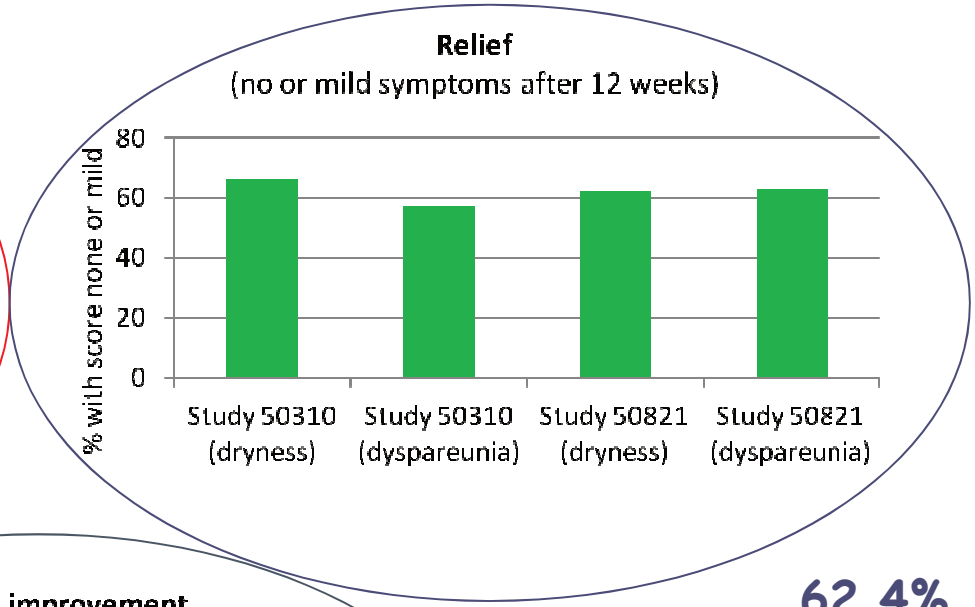
Bachmann et al, 2010; Portman et al, 2013; Portman et al, 2014

Clinical efficacy on MBS & Ospemifene 60 mg

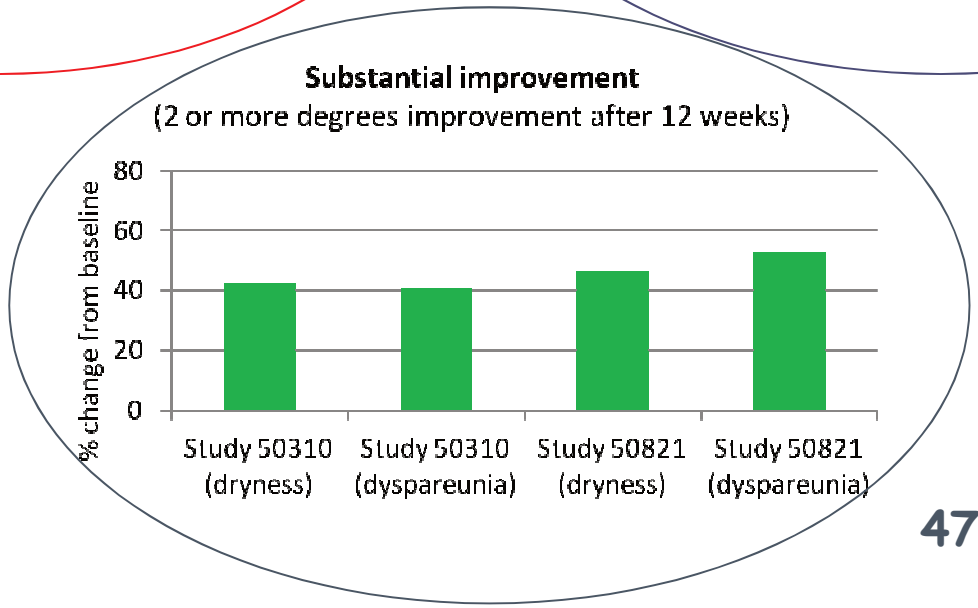




75.0%



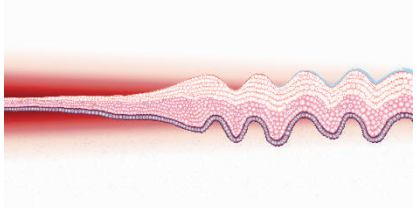
62.4%



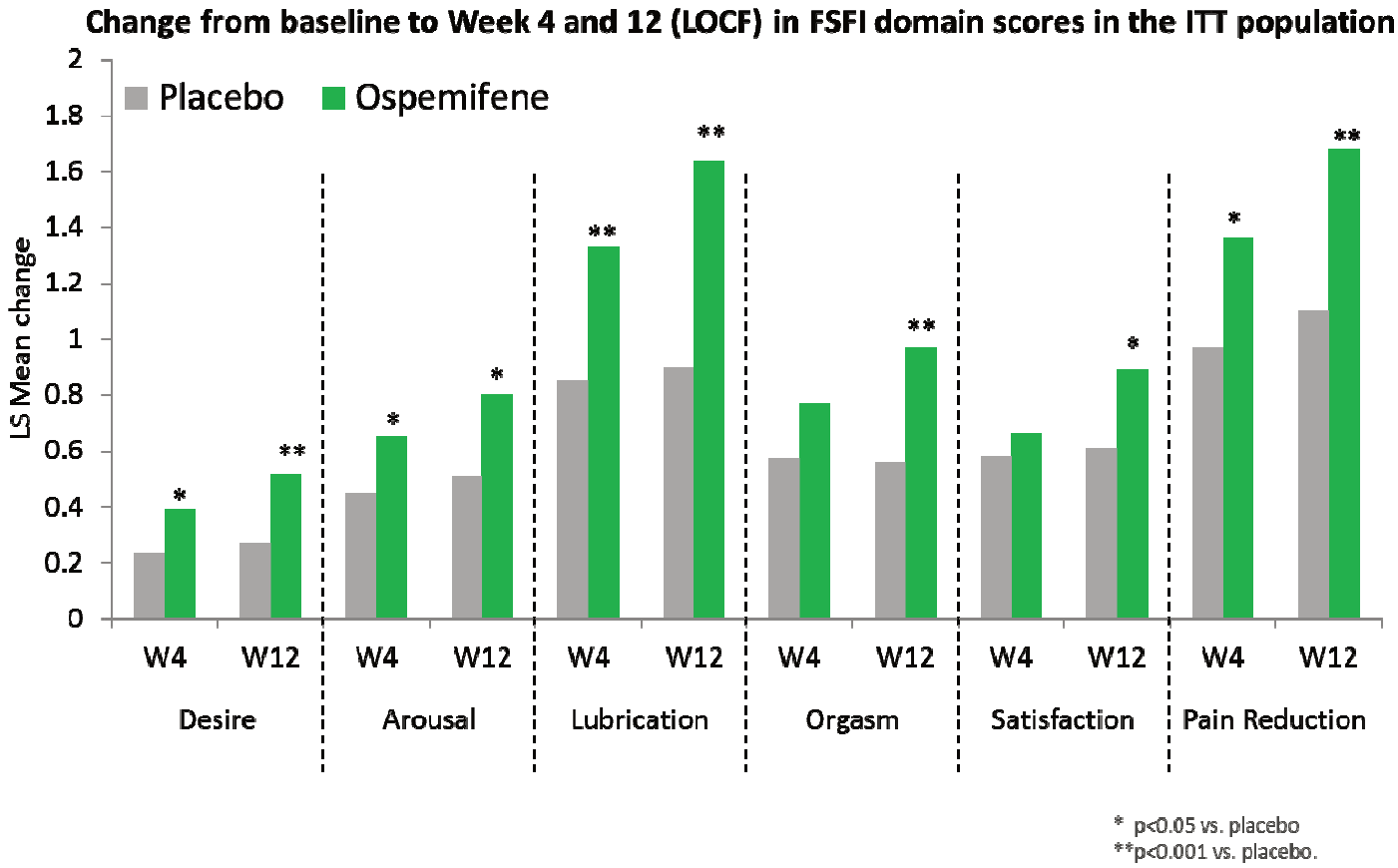
47.6%

Nappi et al, 2015

Sexual function & Ospemifene 60 mg



A significant improvement from baseline to 12 weeks



Constantine et al, 2015

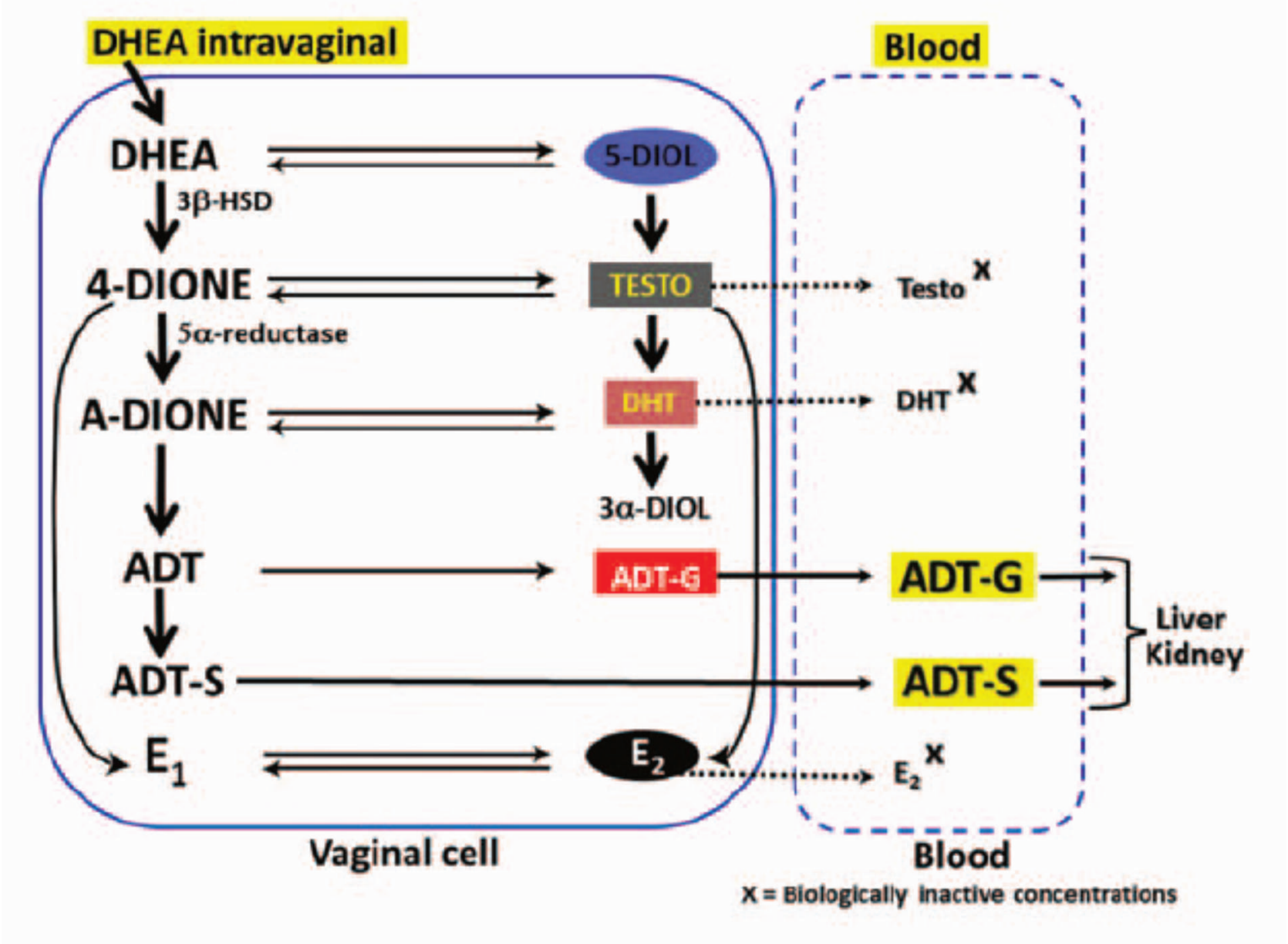
Systematic indirect comparison of ospemifene versus local estrogens for vulvar and vaginal atrophy

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 17β-estradiol 10 µg 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 µg 17β-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 µg 17β-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 µg 17β-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.

Bruyniks et al, 2017

Science of intracrinology in postmenopausal women



Labrie F et al, 2017

Concentration range of serum sex steroids in normal postmenopausal women and those with diagnosis of vulvovaginal atrophy

Abstract

Objective: The aim of the study was to determine the range of serum sex-related steroids in normal postmenopausal women and in women of the same age with a diagnosis of vulvovaginal atrophy (VVA).

Methods: Validated mass spectrometry-based assays coupled to gas or liquid chromatography were used over a 10-year period for steroid measurements. Serum samples were obtained in up to 1,512 women aged 55 to 65 years.

Results: Serum estrone sulfate (E_1S) and androsterone glucuronide (ADT-G), the main metabolites of estrogens and androgens, respectively, were 16.9% ($P = 0.005$) and 16.1% ($P = 0.001$) higher in women not diagnosed with moderate/severe VVA than those diagnosed with VVA. Serum estrone (E_1) was 14.5% ($P < 0.0001$) higher in women with no diagnosis of VVA, whereas the other steroids did not show meaningful differences. The limited biological significance of serum estradiol (E_2) and testosterone is supported by the lack of statistical significance in the serum concentrations of these two steroids between the two groups. Most importantly, for the women without a diagnosis of VVA, the normal upper limit (95^{th} centile) of serum E_2 was 9.15 pg/mL ($n = 364$) and 10.7 pg/mL ($n = 67$) for a weighted average of 9.99 pg E_2/mL. A limit of 10 pg E_2/mL has recently been found by two other laboratories. When comparing 50- to 59-year-old and 70- to 79-year-old women, serum E_2, E_1S, ADT-G, and DHEA were, respectively, 24.4%, 22.6%, 27.0%, and 85.9% higher in the younger group.

Conclusions: Somewhat higher values, namely, 16.9% and 16.1%, are observed in the serum concentrations of the estrogen (E_1S) and androgen (ADT-G) metabolites in normal compared with women with a diagnosis of VVA. Such data indicating a lower estrogenic and androgenic global exposure in women diagnosed with VVA offers an opportunity for the local intravaginal administration of DHEA to replace the deficiency in endogenous DHEA.

- **These present data illustrate lower estrogenic and androgenic global exposure in women diagnosed with VVA/GSM.**
- **DHEA is likely to be transformed intracellularly into cell-specific small amounts of estrogens and androgens that are degraded locally in the same cells into inactive sulfates and glucuronides.**

Ke et al, 2017

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.

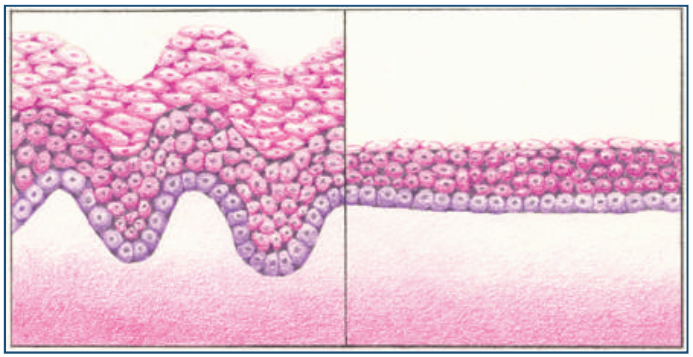
Labrie et al, 2015

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

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



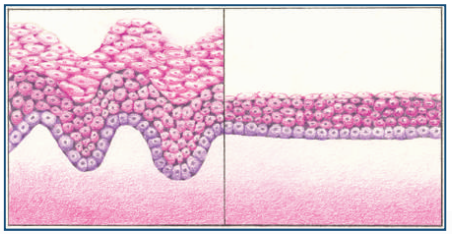
- Genes
- Life-Style
- Environment
- Health Care
- Economy

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

Nappi et al, 2016

GRAZIE PER L'ATTENZIONE!

GYNENDO-MENOPAUSE UNI-PV TEAM