ATROFIA VULVO-VAGINALE: NUOVE OPZIONI TERAPEUTICHE

Prof.ssa Maria Cristina Meriggiola
Dott.ssa Stefania Alvisi
Ginecologia e Fisiopatologia della Riproduzione Umana
Policlinico S. Orsola - Università di Bologna

Ferrara 17-18 Maggio 2019
«XXIII Congresso Nazionale A.GI.CO.»

Contents lists available at ScienceDirect

Maturitas

journal homepage: www.elsevier.com/locate/maturitas

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]

«..a more accurate and inclusive term that describes the multiple changes occurring in the external genitalia, pelvic floor tissues, bladder and urethra, and the sexual sequelae of loss of sexual function and libido, caused by hypoestrogenism during the menopause transition and postmenopause.
These genitourinary changes primarily occur in response to reduced oestrogen levels and ageing, and do not settle with time».

L'Atrofia Vulvo-Vaginale (AVV) è da considerarsi parte della "Sindrome Genitourinaria della Menopausa (GSM)"

- *Nella donna in post-menopausa all'esame obiettivo* ***la prevalenza di GSM varia dal 67 al 98%.*** *Può essere* ***diagnosticata*** *fino al 20% delle donne* ***in premenopausa.***

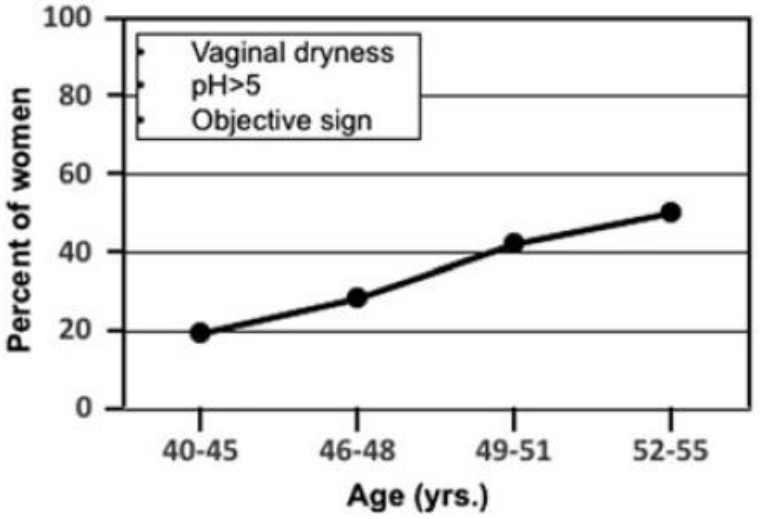
Nappi 2014; Cagnacci, 2019

- *Nel* ***50% delle donne è sintomatica****:* ***secchezza vaginale*** *è il sintomo più frequentemente riportato dalle donne, seguito dalla* ***dispareunia****, dal* ***prurito****, dal* ***bruciore*** *e dalla* ***disuria.***

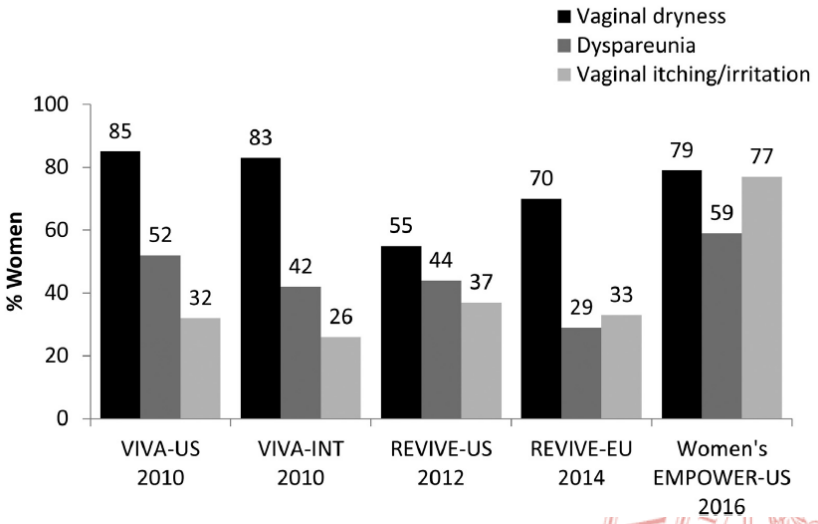
Palma, 2018; Palacios, 2018; Krychman, 2017

- *Ha un importante* ***impatto sulla qualità di vita.***

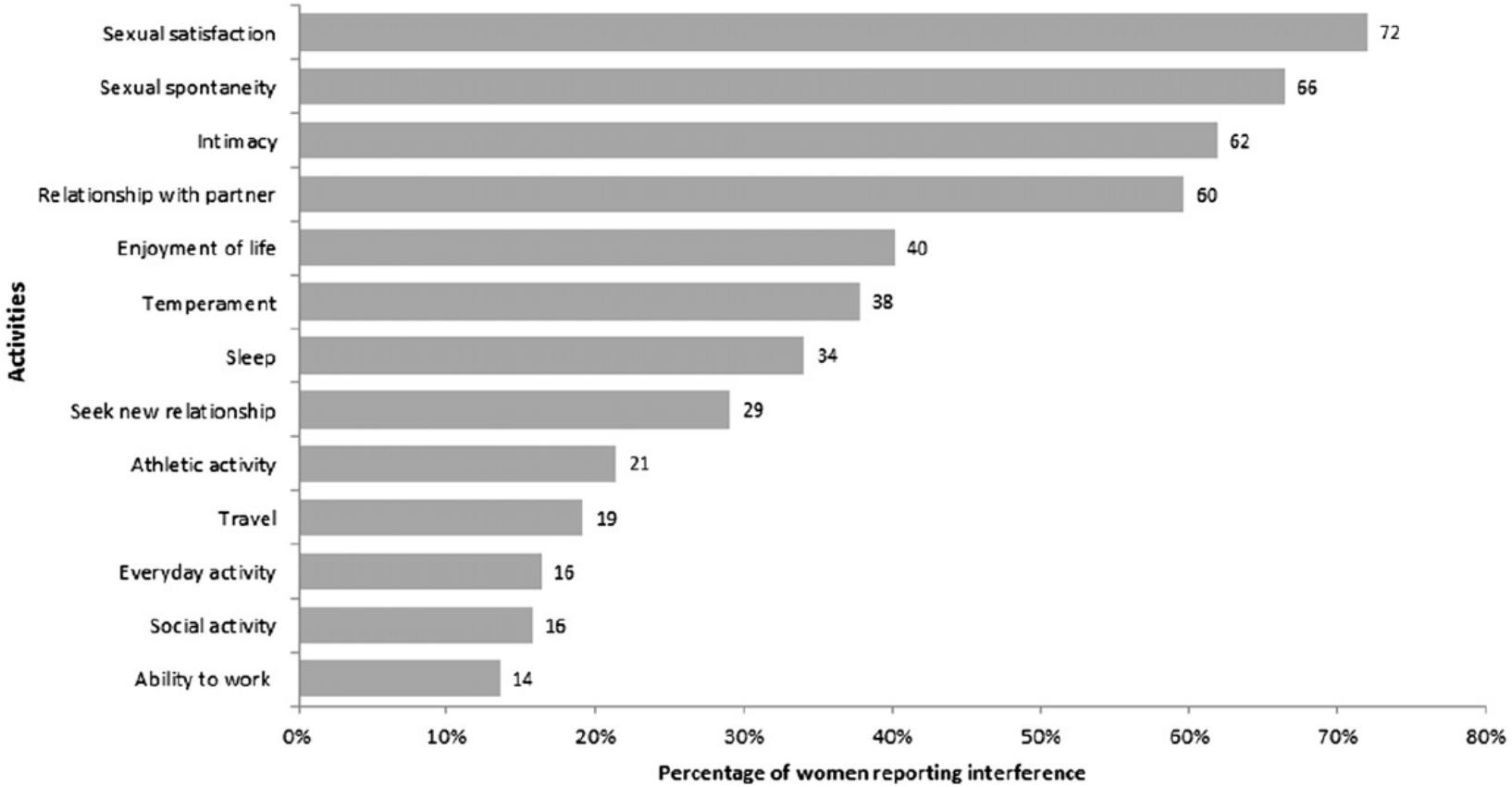
Nappi, 2018



Prevalence of vaginal atrophy in the women under survey.



INTERFERENZA DEI SINTOMI DELLA AVV CON VARI ASPETTI DELLA QUALITA' DI VITA



Nappi RE, 2016

39-50% delle donne non discute di AVV con il proprio medico

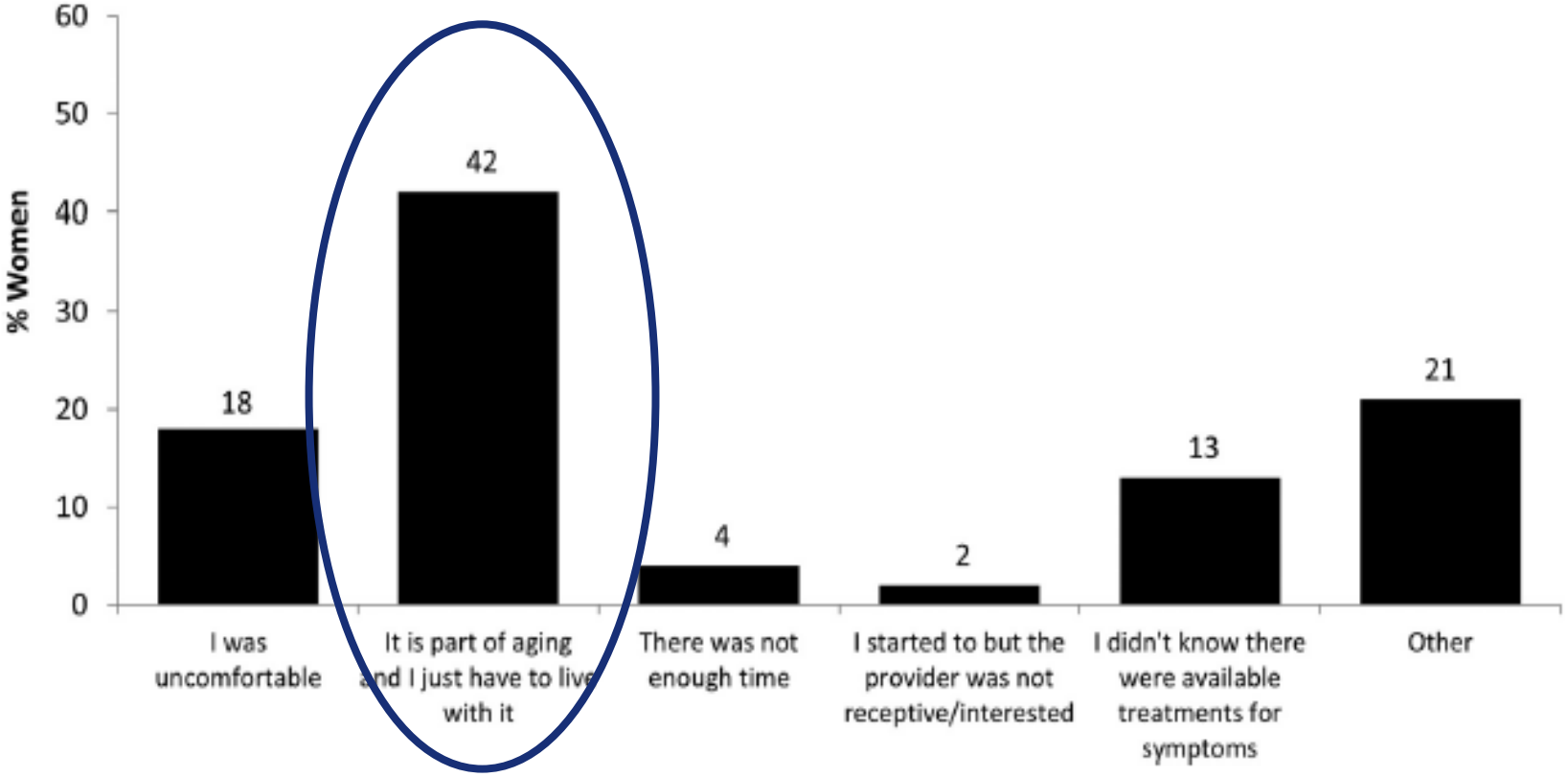
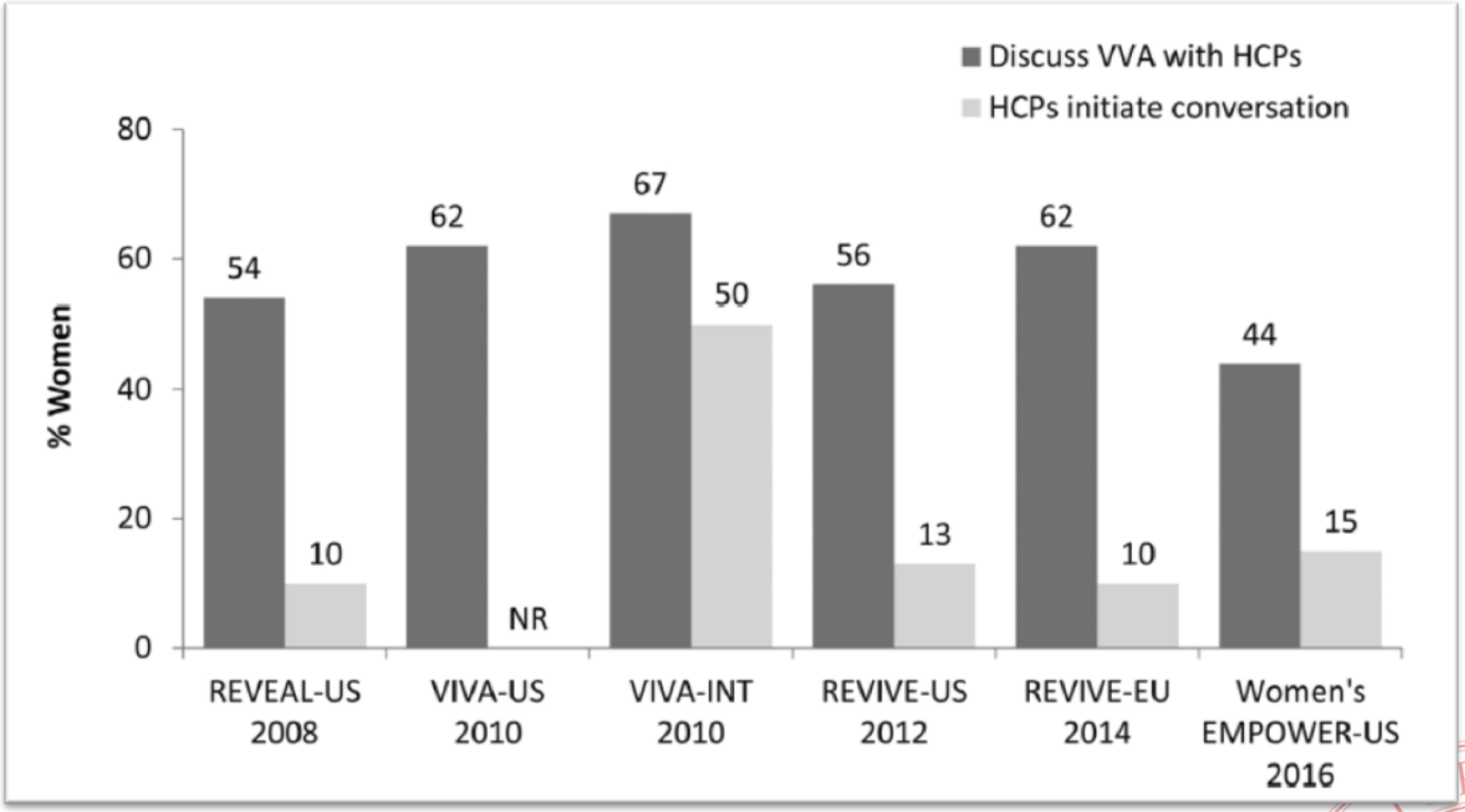


Figure 3. Reasons for not discussing vaginal health with health care professionals (n = 1,046).

The Women's EMPOWER Survey. 2018

Discussion of vulvar and vaginal symptoms with HCPs



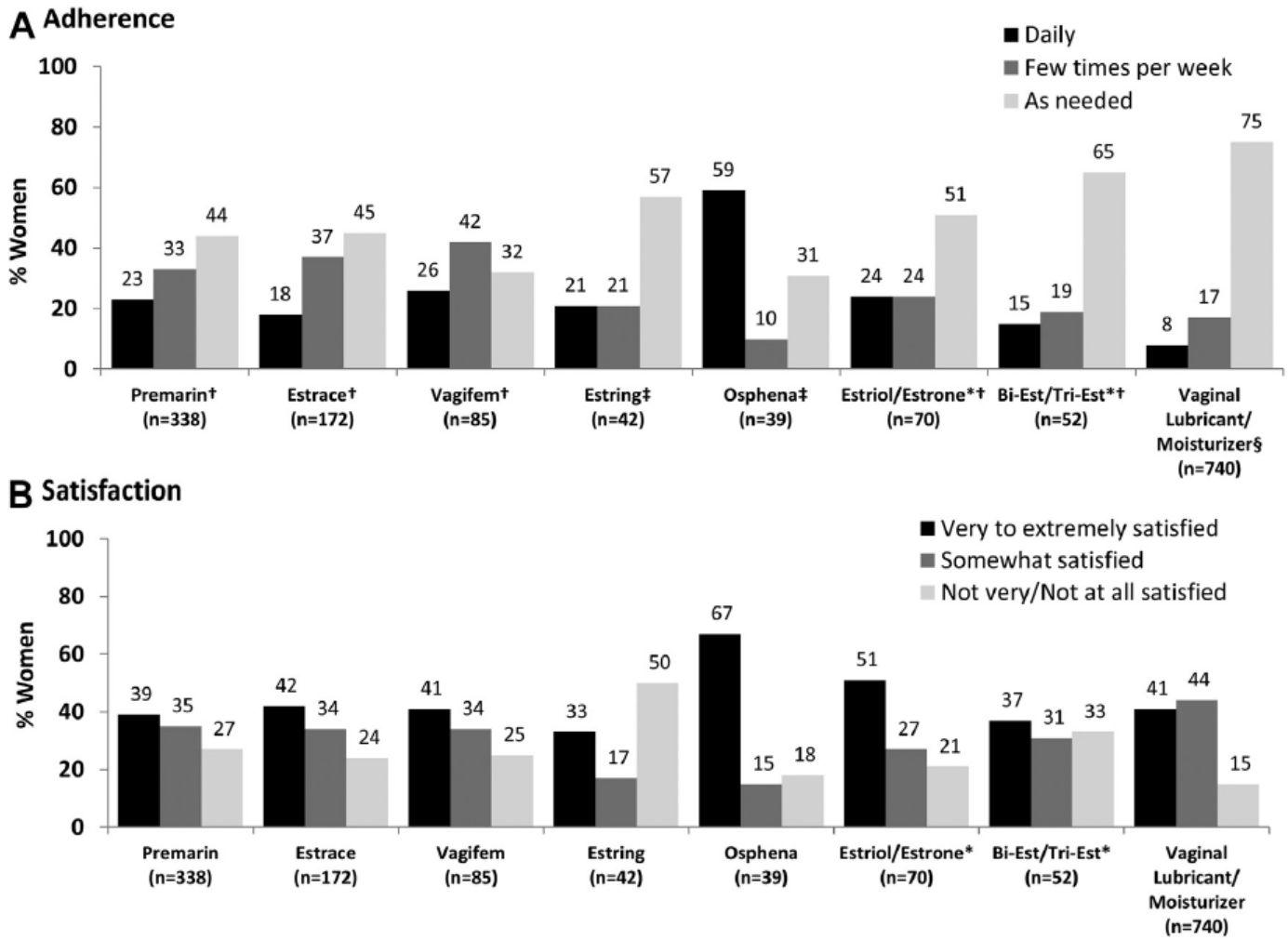
The Women's EMPOWER Survey. 2018

Raccomandazioni per il trattamento dell'AVV

Recommendations for the management of post-menopausal vaginal atro	International Menopause Society
European guidelines for treat VVA with low-dose vaginal o	e and Andropause
Management of symptomati 2013 position statement of T	opause Society
BMS Consensus Statements: (2014)	se Society
Hormone therapy in perimen Interdisciplinary S3 Guidelin Germany	Gynaecology and
Position of the Spanish Men postmenopausal women	use Society
Raccomandazioni clinico-pratiche in peri-postmenopausa e terza eta'	Associazione Ostetrici Ginecologi Ospedalieri Italiani
Documento Congiunto SIGiTE-SIM 2013 – Gestione del Trattamento Ormonale Sostitutivo nella donna in menopause	SIGiTE, SIM

- ***Menopausal Hormone Therapy (MHT)***
- ***Low-dose vaginal estrogen***
- ***Vaginal moisturizers and lubricants***
- ***Alternative treatments***
- ***Laser-therapy***
- ***Ospemifene***
- ***Prasterone (DHEA)***

Adherence to and satisfaction with, respectively, currently and formerly used therapies for VVA



*Vaginal cream prepared by local pharmacy; Indication for product is: †A few times per week; ‡Daily; §As needed.

Kingsberg S, 2017

OSPEMIFENE

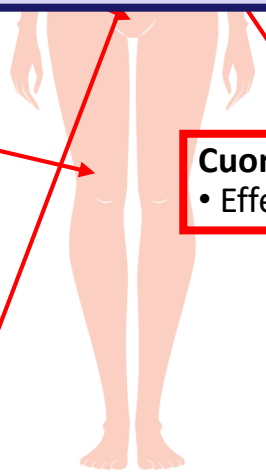
Modulatore selettivo dei recettori per gli estrogeni (SERM)

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

Osso
• Effetto **agonista**/estrogenico in studi pre-clinici

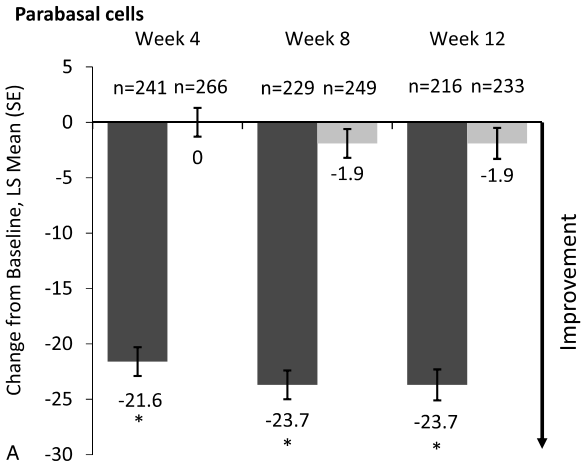
Cuore
• Effetto complessivamente **neutro**

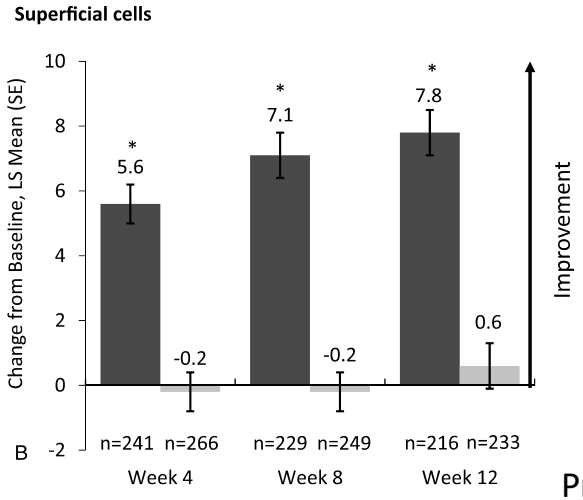
Endometrio
• Azione complessivamente **neutra**

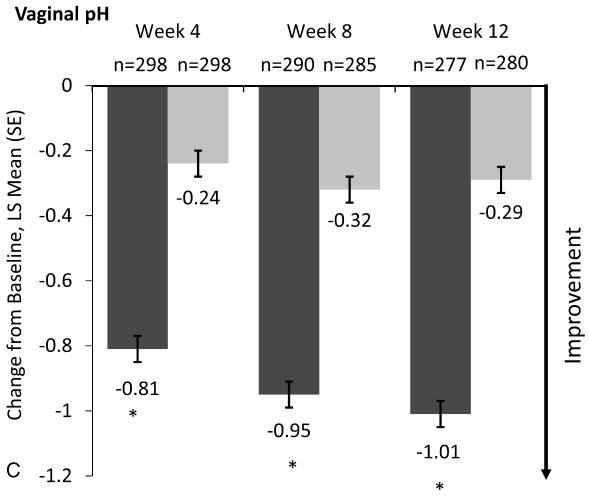


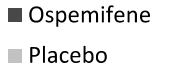
Berga SL, 2013; Kangas L & Unkila M, 2013

Effetti di ospemifene sulla mucosa vaginale

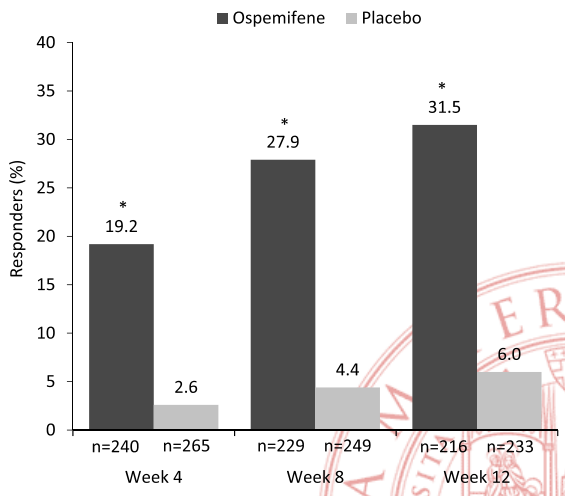








Proportion of responders with ospemifene and placebo

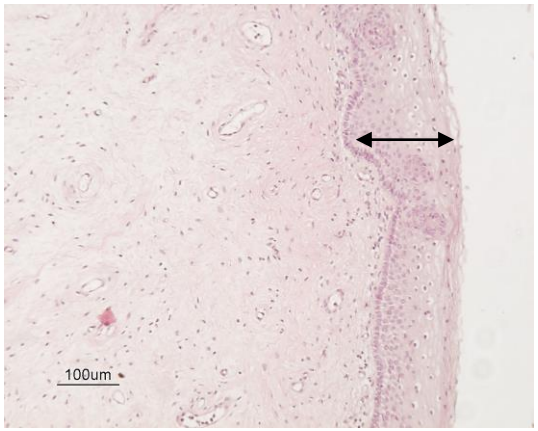


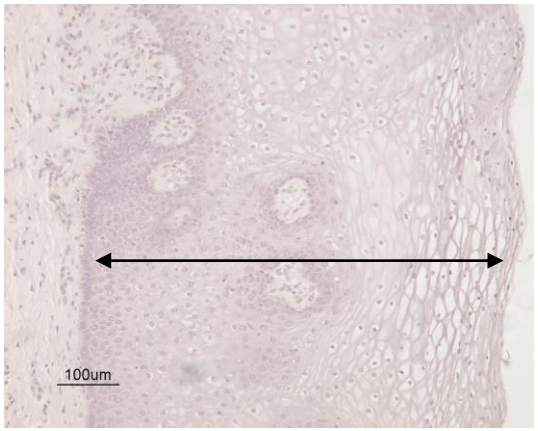
Archer DF, 2019

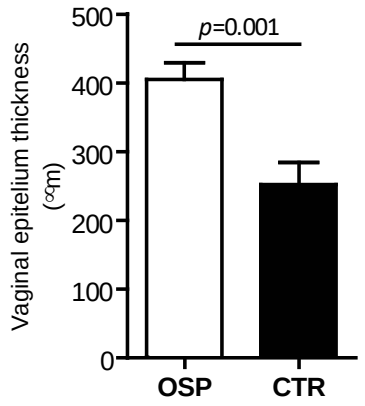
Aumento dello spessore dell'epitelio vaginale e vulvare *in donne in postmenopausa che hanno assunto ospemifene per 32+ 4 gg*

CONTROL (CTL) **OSPEMIFENE (OSP)**

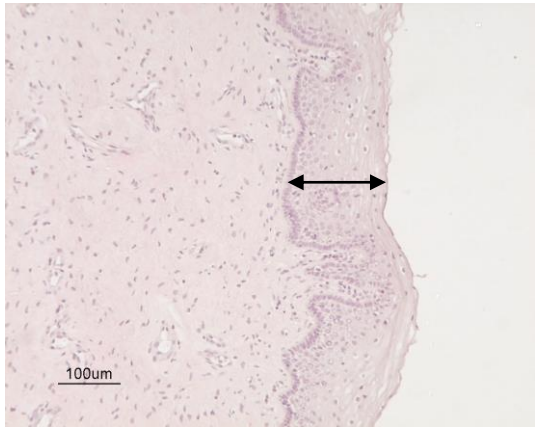
VAGINA

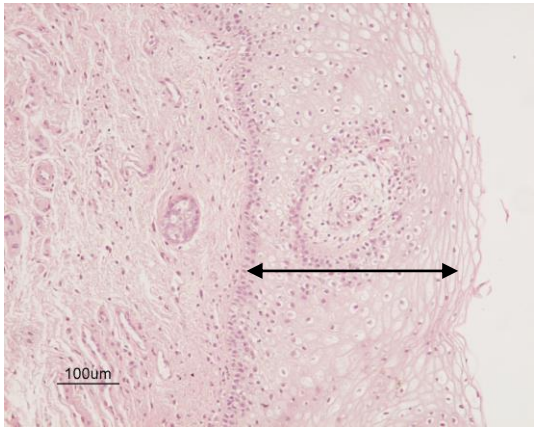


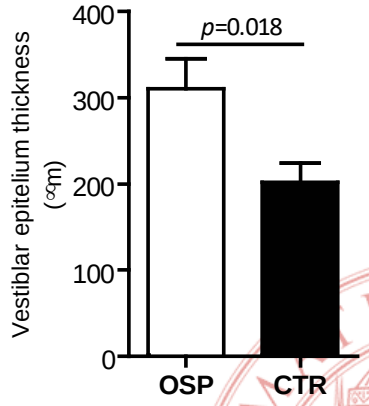




VULVA

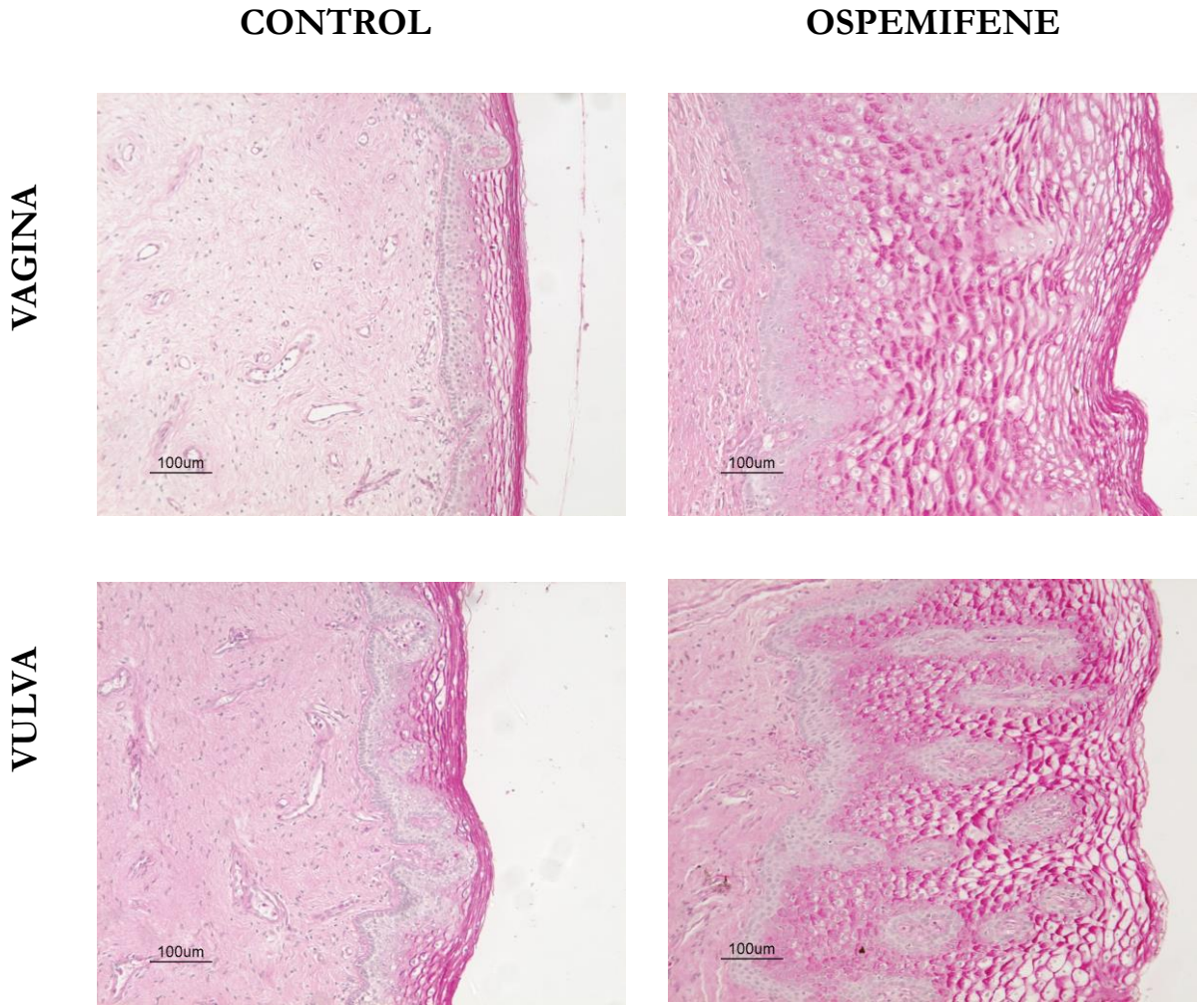






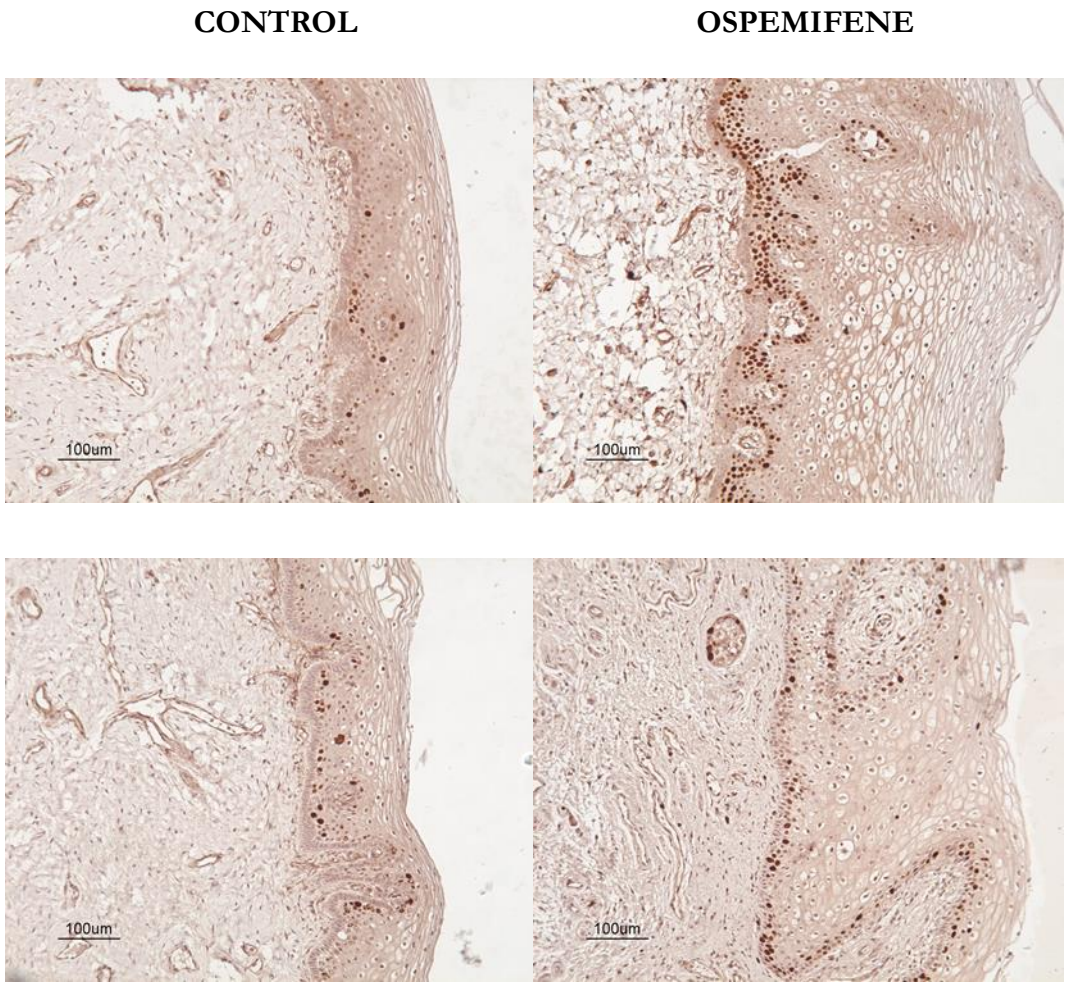
Alvisi S et al., Journal of Sexual Medicine, 2018

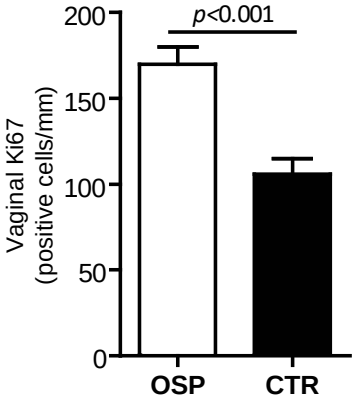
Aumento del contenuto di glicogeno dell'epitelio vaginale e vulvare *in donne in postmenopausa che hanno assunto ospemifene per 32+ 4 gg*

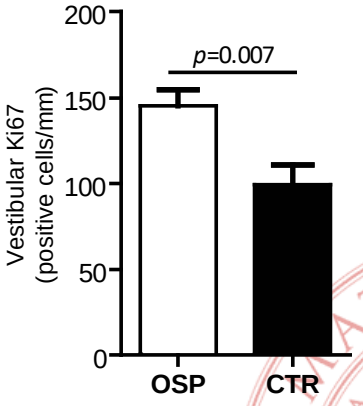


Alvisi S et al., Journal of Sexual Medicine, 2018

Aumento della proliferazione dell'epitelio vaginale e vulvare *in donne in postmenopausa che hanno assunto ospemifene per 32± 4 gg*





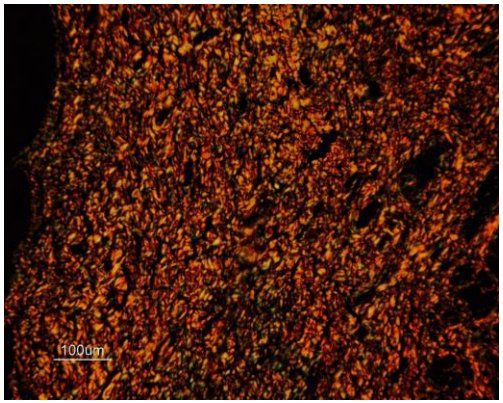


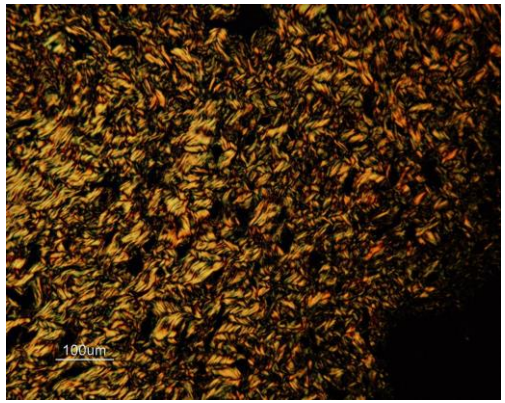
Alvisi S et al., Journal of Sexual Medicine 2018

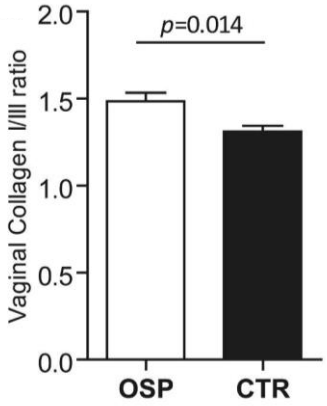
Maggior concentrazione di fibre collagene di tipo I rispetto al tipo III a livello vaginale e vulvare *dopo assunzione di ospemifene* per 32+4 gg

OSPEMIFENE (OSP) **CONTROLLO (CTL)**

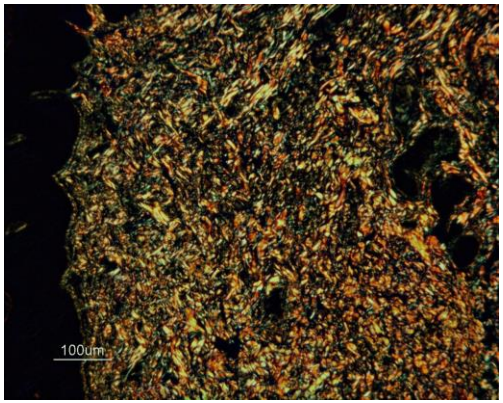
VAGINA

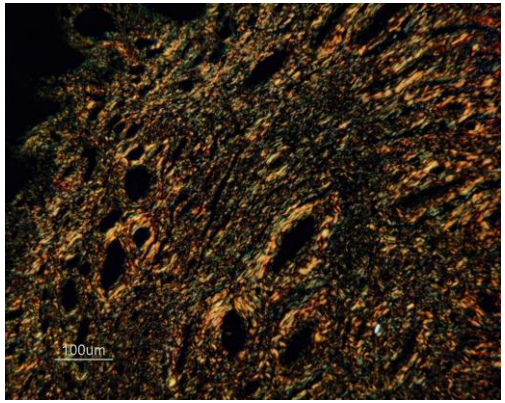


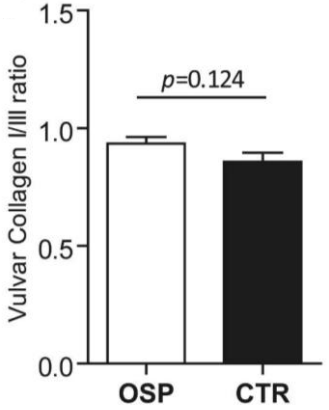




VULVA







Alvisi S et al., Journal of Sexual Medicine 2018

Ospemifene: segni e sintomi di atrofia a livello vulvare

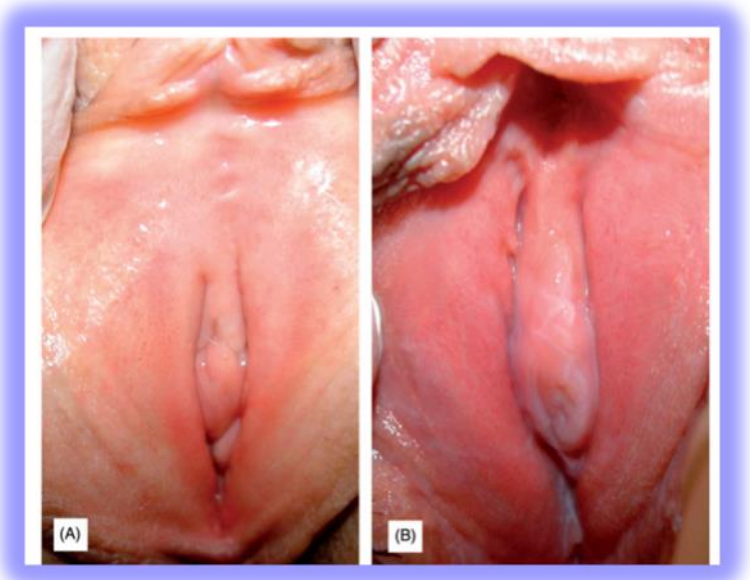


Table 2. Distribution of symptoms and signs at baseline and after 60 d of therapy with ospemifene 60 mg.

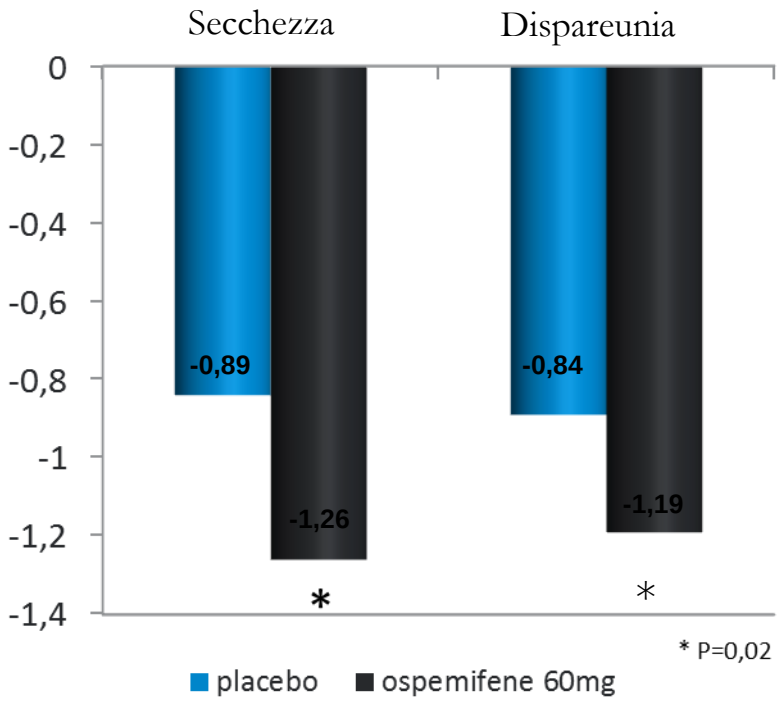
Symptoms and signs	Basal	After treatment (60 d)	*p* value
Burning	7.48 ± 1.09	2.81 ± 1.34	.01
Dryness	6.83 ± 1.13	4.10 ± 1.21	.03
Dyspareunia	8.04 ± 0.99	5.35 ± 1.19	.01
Cotton swab test[a]	2.81 ± 0.44	1.25 ± 0.78	.01
Vulvar vestibule trophism[b]	11.2 ± 2.31	4.2 ± 1.31	.02

Data are presented as the mean values ± standard deviation.
Score from 0 to 3; [a]0: absent; 1: mild; 2: strong; 3: severe;
[b]Observations for petechiae, pallor, friability, dryness, and redness in the mucosa. Ratings were based on a 4-point scale (0: none; 1: mild; 2: moderate; 3: severe).
$p < .05$ is considered statistically significant refers to Student's *t*-test results.

Murina et al., 2017

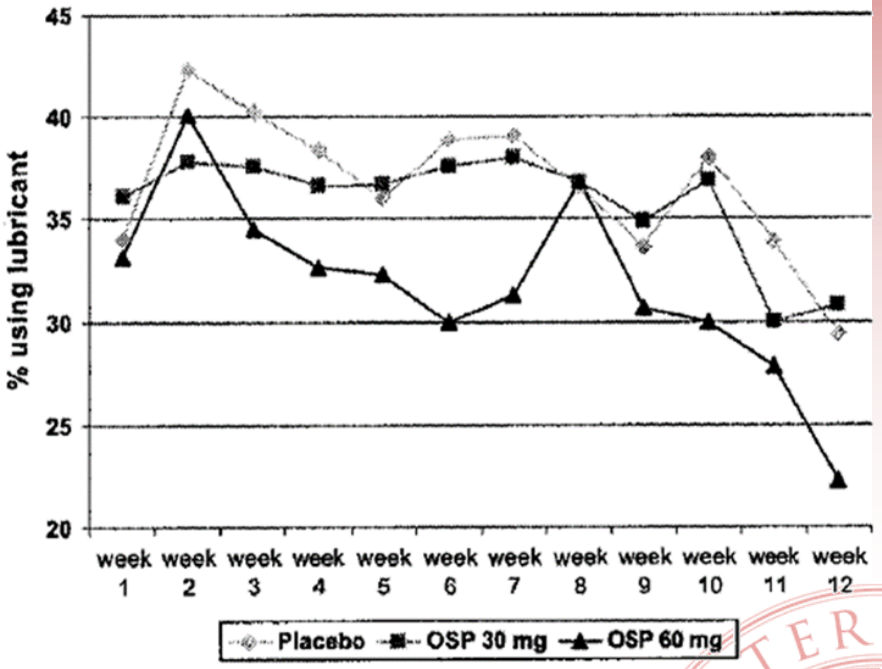
Ospemifene: effetto sui sintomi più fastidiosi

Variazione rispetto al basale del punteggio di severità del sintomo più fastidioso



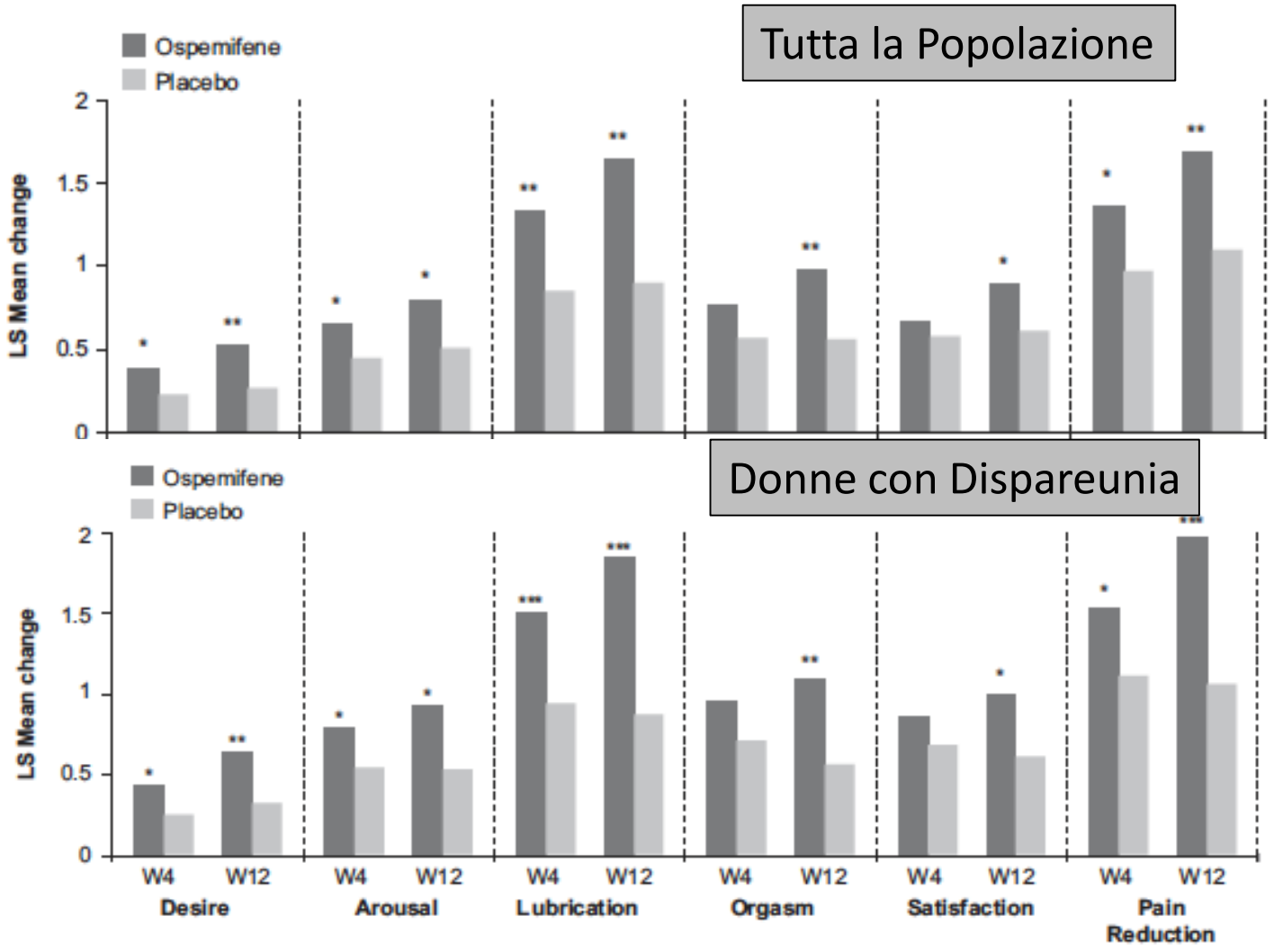
*p<0.05 vs placebo
Adattato da Bachmann, 2010

Utilizzo settimanale di lubrificante



Bachmann GA, et al. Menopause 2010

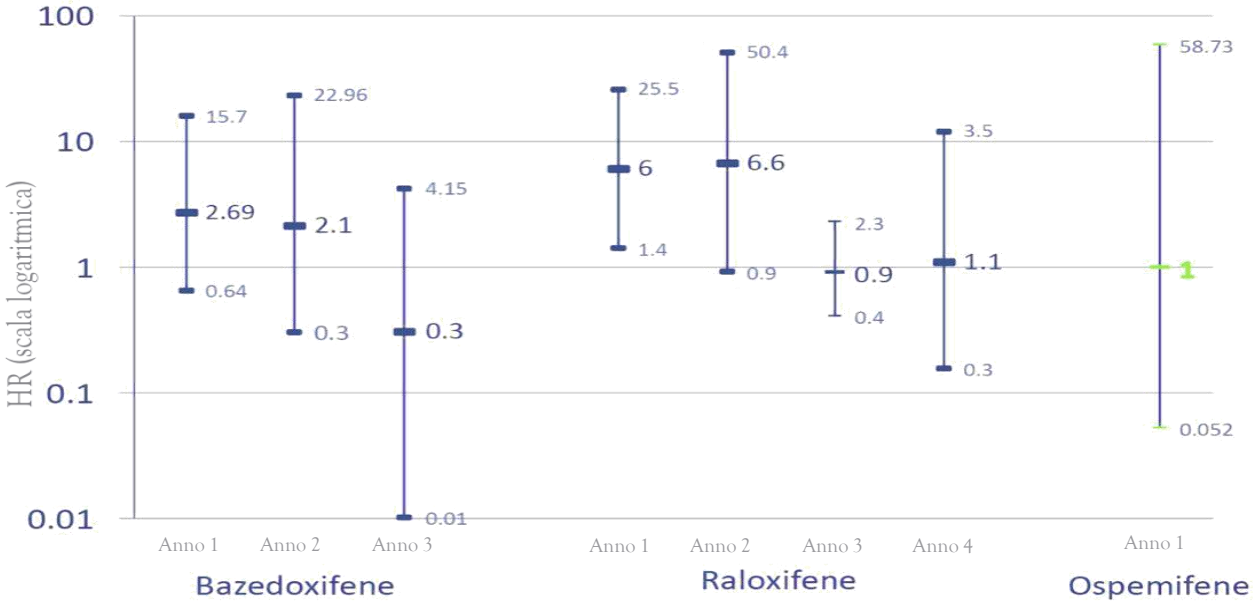
Ospemifene: effetto sulla sessualità (FSFI)



Constantine et al., Climacteric 2014

Effetto di ospemifene sul rischio tromboembolico

Rischio relativo per TEV per anno dall'inizio del trattamento per i vari SERM vs placebo, rischio più alto con raloxifene e bazedoxifene nel primo anno, rischio più basso negli anni successivi



Questi dati non indicano un rischio aumentato per ospemifene

Rabe T et al., 2015; Christiansen et al, 2010; Grady et al 2004

Effetto di ospemifene sul rischio tromboembolico

Post-Authorization Safety Study (PASS STUDY)

frequenza e incidenza dell'outcome durante il trattamento

Journal of Gynecology and Women's Health
ISSN 2474-7602

Juniper Publishers
key to the Researchers

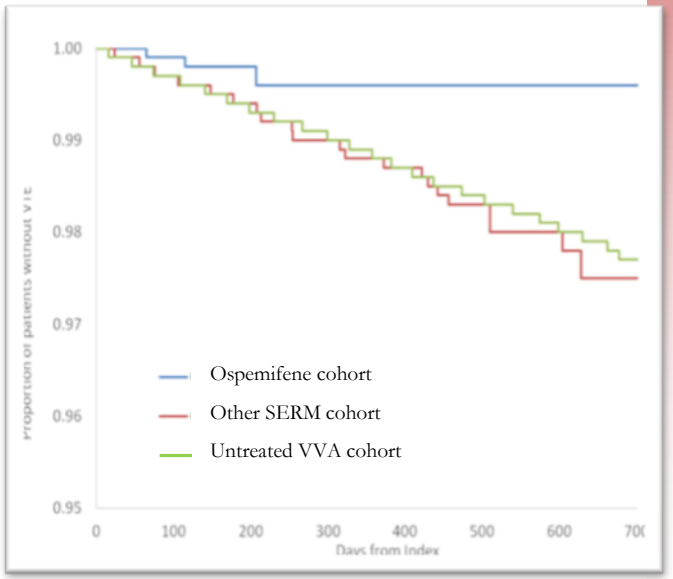
Research Article
Volume 9 Issue 3 - April 2018
DOI: 10.19080/JGWH.2018.09.555762

J Gynecol Women's Health

Safety of Ospemifene during Real-Life Use

Nico Bruyniks[1*], Fabio De Gregorio[2], Trevor Gibbs[2], Robert Carroll[3], Kathy H Fraeman[4] and Beth L Nordstrom[5]

	Ospemifene Cohort		Comparator SERM Cohort		Untreated VVA Cohort	
CI (Confidence Interval)	CI (Confidence Interval)		CI (Confidence Interval)		CI (Confidence Interval)	
	Incidence proportion	Incidence rate per 1,000 person-years (95% CI)	Incidence proportion	Incidence rate per 1,000 person-years (95% CI)	Incidence proportion	Incidence rate per 1,000 person-years (95% CI)
Any VTE	0.12%	4.02 (1.48 – 8.75)	0.64%	12.63 (9.49– 16.48)	1.23%	12.02 (11.50– 12.57)
Deep vein thrombosis	0.10%	3.35 (1.09 – 7.82)	0.55%	10.75 (7.87– 14.35)	1.01%	9.84 (9.37– 10.33)
Pulmonary embolism	0.04%	1.34 (0.16 – 4.84)	0.14%	2.8 (1.45– 4.89)	0.26%	2.56 (2.32– 2.81)
Retinal vein thrombosis	0.00%	0 (0.00 – 2.01)	0.02%	0.47 (0.06– 1.68)	0.05%	0.49 (0.39– 0.61)



Nel plot del Kaplan Meyer la coorte trattata con ospemifene si separa dalle altre due coorti molto precocemente dopo il primo episodio

PASS STUDY

*l'incidenza per 1000 anni-persona di **eventi cerebrovascolari** è inferiore nella coorte trattata con ospemifene rispetto alla coorte di donne non trattate e alla coorte trattata con altri SERM*

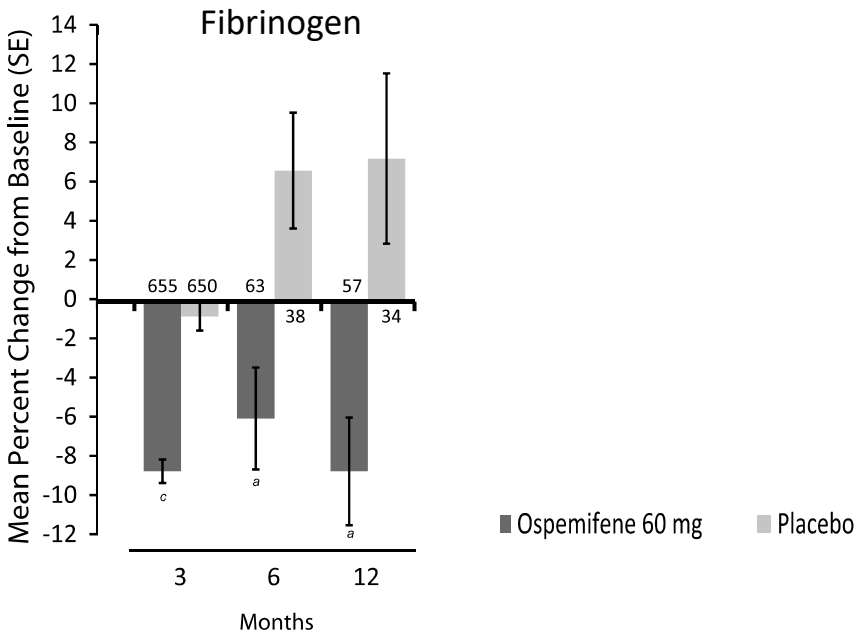
	Ospemifene Cohort		Comparator SERM Cohort		Untreated VVA Cohort	
	Incidence proportion	Incidence rate per 1,000 person-years (95% CI)	Incidence proportion	Incidence rate per 1,000 person-years (95% CI)	Incidence proportion	Incidence rate per 1,000 person-years (95% CI)
CVE	0.56%	19.5 (13.06- 28.00)	1.60%	31.97 (26.80 -37.84)	3.62%	36.09 (35.17- 37.03)

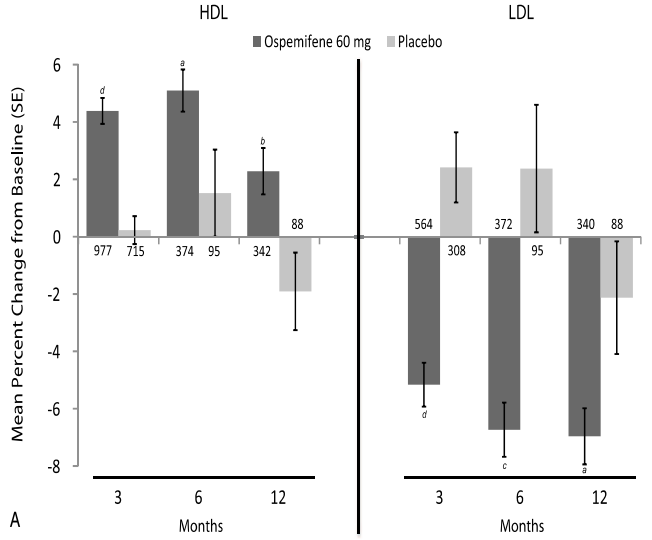
Menopause: The Journal of The North American Menopause Society
Vol. 24, No. 10, pp. 1167-1174
DOI: 10.1097/GME.0000000000000900

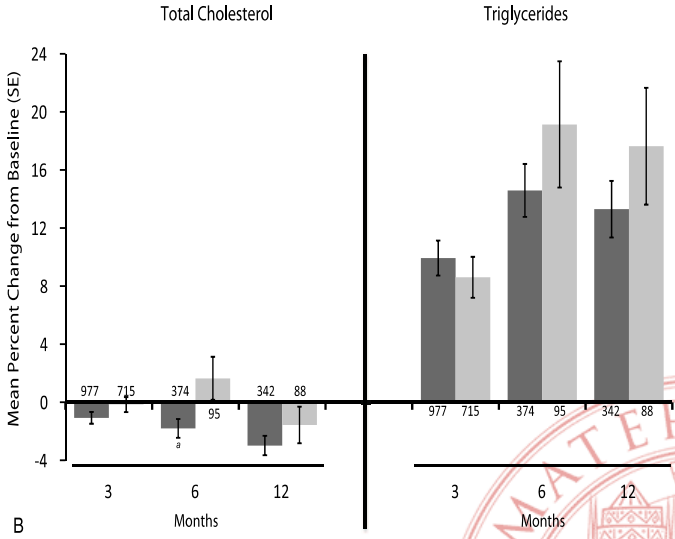
OPEN

Ospemifene's effects on lipids and coagulation factors: a post hoc analysis of phase 2 and 3 clinical trial data

David F. Archer, MD,[1] Corrado Altomare, MD,[2] Wei Jiang, PhD,[2] and Susannah Cort, MD[2]







- *aumento HDL e riduzione di LDL senza effetti negativi su colesterolo totale e trigliceridi*
- *riduzione dei livelli di fibrinogeno (fattore di rischio per malattia coronarica) dal basale, con una differenza significativa rispetto al placebo*

Effetto di ospemifene sul rischio di cancro alla mammella: dati preclinici

Studi su colture cellulari e modelli animali di cancro mammario

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[13]	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, 2013

Numero e percentuale di donne con eventi avversi transitori in relazione alla salute mammaria occorsi durante il trattamento con ospemifene 60 mg o placebo

nessuno degli eventi ha determinato la sospensione di ospemifene

Preferred term,[a] n *(%)*	*Placebo* (n = *958*)	*Ospemifene 60 mg* (n = *1242*)
Any breast-related TEAE	21 (2.2)	31 (2.5)
Breast tenderness	6 (0.6)	11 (0.9)
Breast mass	4 (0.4)	7 (0.6)
Breast pain	3 (0.3)	7 (0.6)
Breast enlargement[b]	0	2 (0.2)
Fibrocystic breast disease	1 (0.1)	1 (0.1)
Breast calcifications	0	1 (0.1)
Breast cyst	4 (0.4)	1 (0.1)
Breast discomfort	1 (0.1)	1 (0.1)
Breast disorder	0	1 (0.1)
Breast prosthesis implantation	0	1 (0.1)
Mammoplasty	0	1 (0.1)
Biopsy breast	1 (0.1)	0
Breast cancer	1 (0.1)	0
Breast cancer *in situ*	1 (0.1)	0
Breast discharge	1 (0.1)	0
Mammary duct ectasia	1 (0.1)	0

Simon JA, 2018

Journal of Gynecology and Women's Health
ISSN 2474-7602

Juniper Publishers
key to the Researchers

Research Article
Volume 13 Issue 5 - January 2019
DOI: 10.19080/JGWH.2019.13.555871

J Gynecol Women's Health

Safety and Efficacy of Ospemifene in Women with A History of Breast Cancer

Basale e variazione dal basale alla 12w di trattamento con ospemifene dei parametri fisiologici della VVA in donne con versus donne senza storia di k mammario

Donne trattate con ospemifene con:
- storia di ca mammario (≥10 anni prima dell'arruolamento; n=11)
versus
- nessuna storia di ca mammario (n=1091).

Event		*History of breast cancer*		*p-value*
		Yes (n = 11)	*No (n = 1091)*	
Treatment-emergent adverse event, n (%)	**Yes**	**7 (63.6%)**	752 (68.9%)	**0.7470**
	No	4 (36.4%)	339 (31.1%)	
Adverse drug reaction, n (%)	**Yes**	4 (36.4%)	510 (46.7%)	**0.5570**
	No	7 (63.6%)	581 (53.3%)	

Nessuna evento avverso è stato riportato più di una volta in donne trattate con ospemifene con storia di ca mammario.
Solo tre eventi avversi transitori sono stati riportati in questa popolazione (lieve secchezza nasale, un intervento al seno nasale in un soggetto e aumento di peso anomalo in un secondo soggetto).

N. Bruyniks, 2019

Effetti di ospemifene sull'endometrio

Menopause: The Journal of The North American Menopause Society
Vol. 22, No. 1, pp. 36-43
DOI: 10.1097/gme.0000000000000275

OPEN

Endometrial safety of ospemifene: results of the phase 2/3 clinical development program

Ginger D. Constantine, MD,[1] Steven R. Goldstein, MD,[2] and David F. Archer, MD[3]

- ***Nessuna evidenza di effetti negativi sull'endometrio***

U.S. Food and Drug Administration
Protecting and Promoting *Your* Health

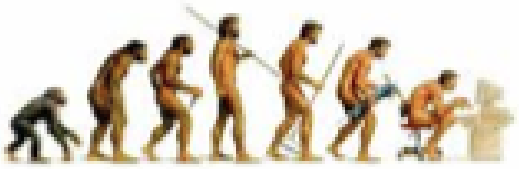
La Food and Drug Admnistration (FDA) in merito agli studi clinici sull'AVV raccomanda che a 12 mesi venga dimostrato un tasso di incidenza di iperplasia endometriale ≤ all'1% (CI 95%). Con un singolo caso di iperplasia semplice senza atipie (0,3%) riportato dopo 12 mesi di utilizzo di ospemifene, i risultati osservati rispondono al criterio dell'FDA per la sicurezza endometriale

Profilo di sicurezza di ospemifene

Il rischio ***cardiovascolare, mammario ed endometriale*** *non è aumentato in donne in post-menopausa con AVV trattate con ospemifene rispetto a donne non trattate*

Nuove opzioni terapeutiche

- *Uomini e donne, oltre al sistema endocrino, sono dotati di un importante formazione intracrina di steroidi nei tessuti periferici;*
- *Ogni cellula possiede un sofisticato sistema enzimatico per la formazione e inattivazione degli steroidi;*
- *L'intracrinologia iniziò con la scoperta di F. Labrie nel 1982 che la prostata umana sintetizza gli androgeni localmente dal precursore inattivo DHEA secreto dalle ghiandole surrenali;*
- *Questo sistema è presente sono nelle specie più evolute (primati);*
- *Dopo tre decenni di ricerche, è stata utilizzata la stessa intracrinologia per identificare la causa dell'atrofia vulvo-vaginale.*

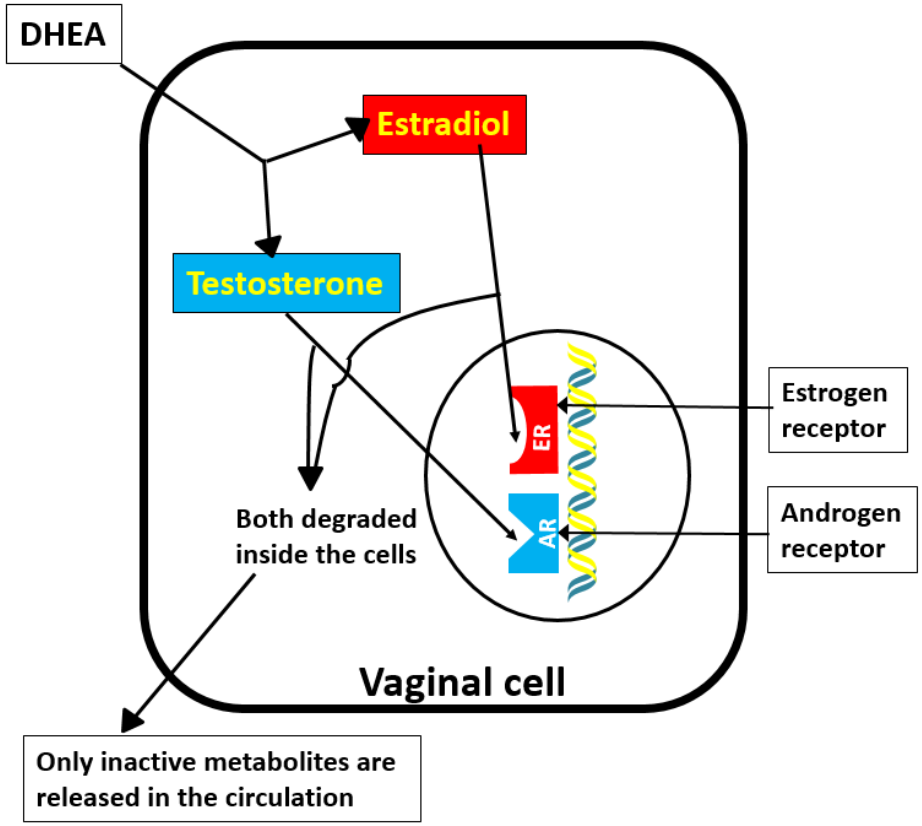


Meccanismo d'azione del DHEA

- ***DEFINITION: intracellular formation of estradiol and testosterone*** *from inactive DHEA followed by their local action and then, their intracellular inactivation by steroid inactivating enzymes*

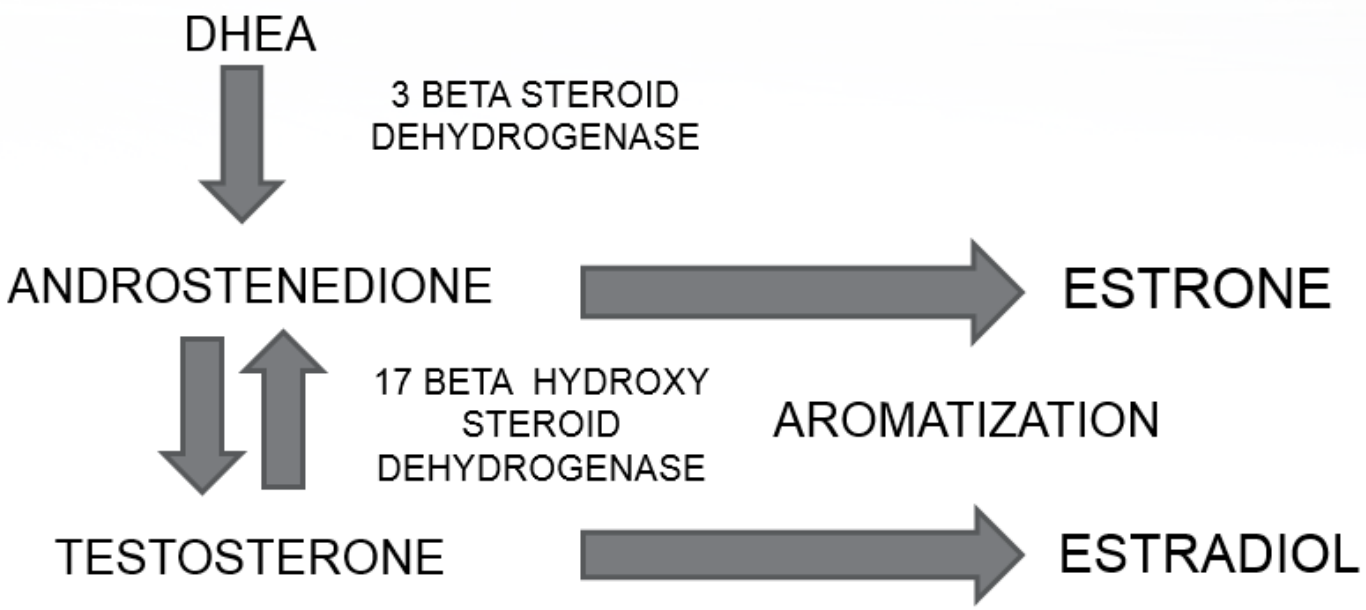
- ***Intracellular inactivating enzymes avoid biologically significant systemic exposure***

- *CONSEQUENCE: only inactive metabolites appear in the blood, thus avoiding action in other tissues*



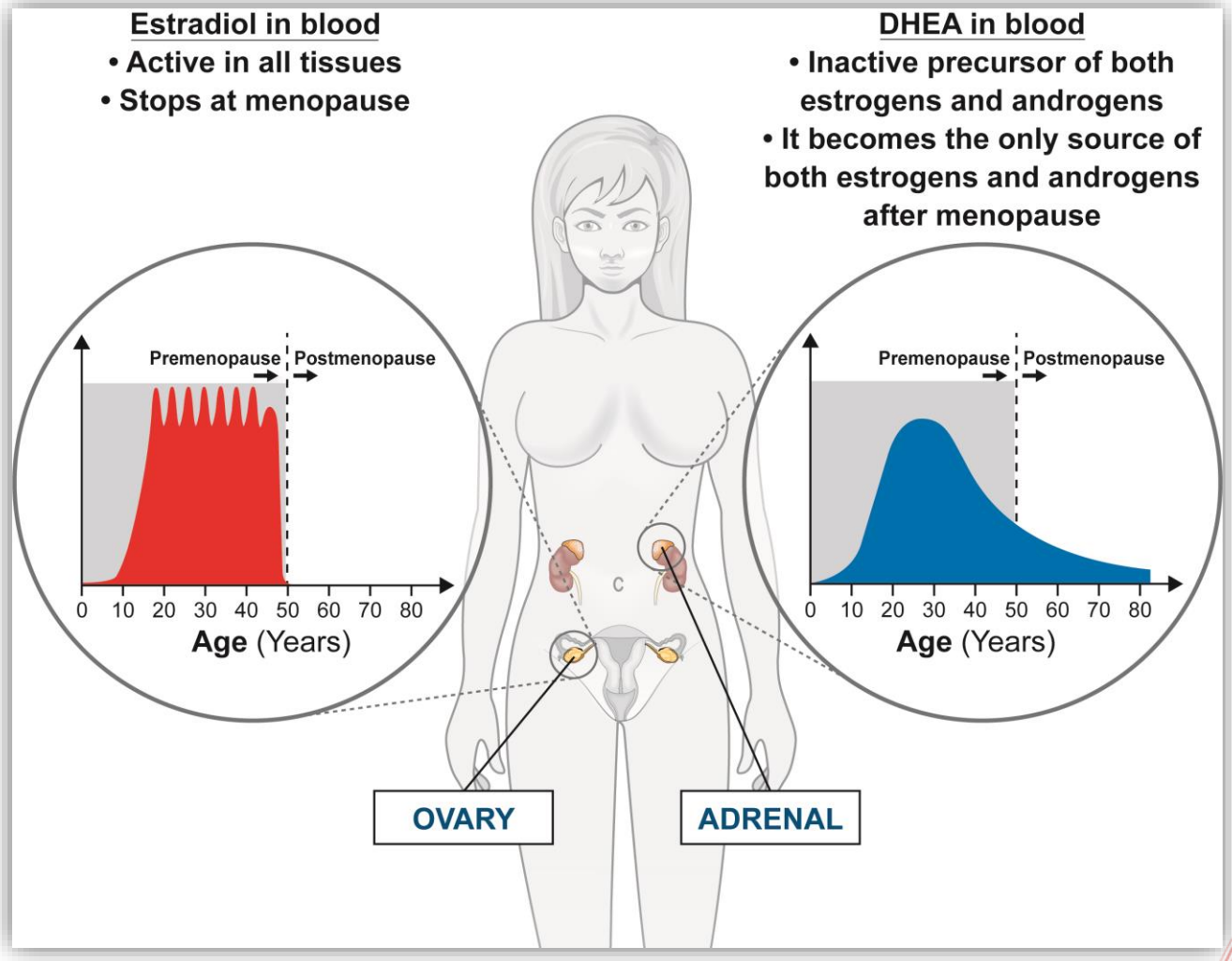
Labrie, Martel et al, Menopause, 2017

Three key steps in target cell DHEA metabolism



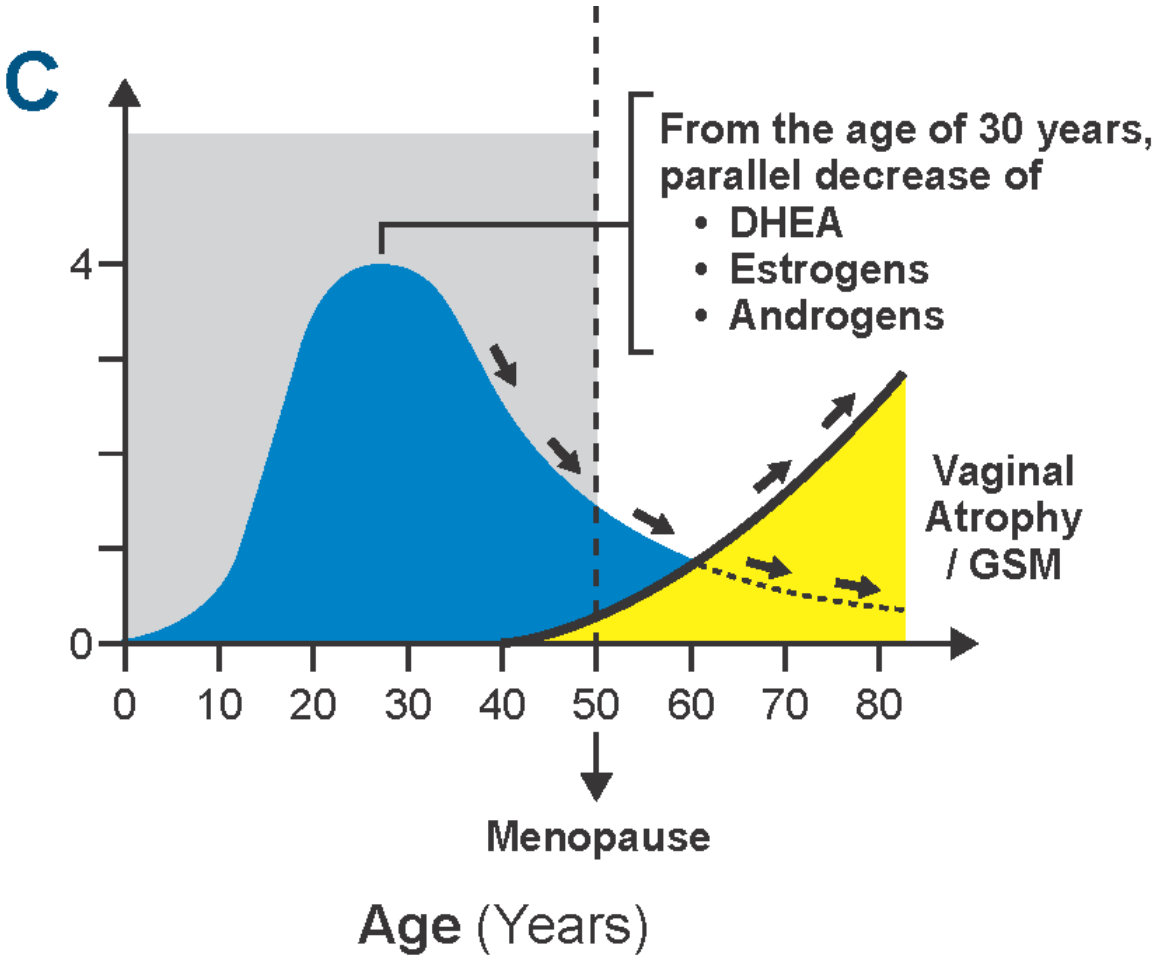
Modified from: Labrie, Martel et al, Menopause, 2017

Two source of sex steroids



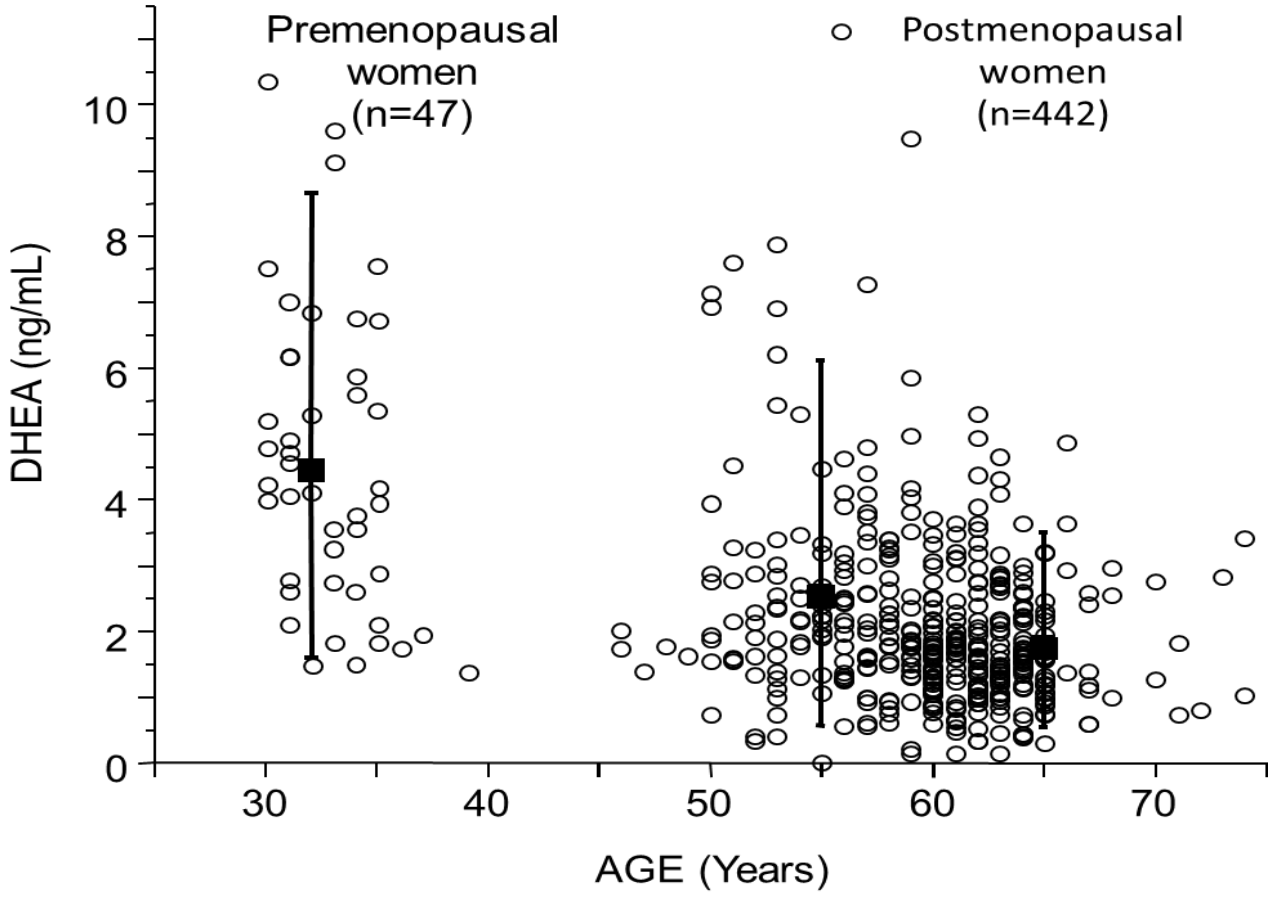
Labrie et Labrie, 2013; Labrie, Martel et al, 2011

Vaginal atrophy increases with the decrease of DHEA



Labrie et al, 2011; Labrie et al, 2017

Serum DHEA levels are highly variable between women



Role of both estrogens and androgens in vaginal health

As well demonstrated in preclinical studies, both estrogens and androgens play complementary roles for good vaginal health. Consequently, treatment with estrogens is only a partial treatment. DHEA makes estrogens and androgens in the three layers of the vagina with an exclusive androgenic action in the nerve endings possibly responsible for the benefits of intravaginal DHEA on sexual dysfunction.

Huggins, Jensen et al, 1954; Ladinsky, Gruchow et al,, 1968; Mehrotra and Karkun, 1973; Kennedy and Armstrong, 1976; Mori, Mills et al, 1992; Sourla, Flamand et al,, 1998; -Berger, El-Alfy et al, 2005; Berger, El-Alfy et al, 2008; Pelletier, Ouellet et al, 2012; Pelletier, Ouellet et al, 2013; Labrie, Martel et al, 2017

INTRAROSA acts like endogenous DHEA

INTRAROSA is «metabolized in the same manner as endogenous prasterone (DHEA)». Everything takes place inside the cells exactly as observed in normal postmenopausal women.

Treatment with INTRAROSA mimics the physiology or the intracrinology mechanisms observed in normal women.
Intravaginal natural prasterone replaces the missing DHEA in order to bring back normal function.

US Prescribing information, Intrarosa (Prasterone) vaginal insert; Labrie,,1991; Labrie, Bélanger et al, 2017; Labrie, Martel et al, 2017.

Effect of dehydroepiandrosterone on VVA

Approved for use in Postmenopausal Vaginal Atrophy

- *Improves objective signs:*

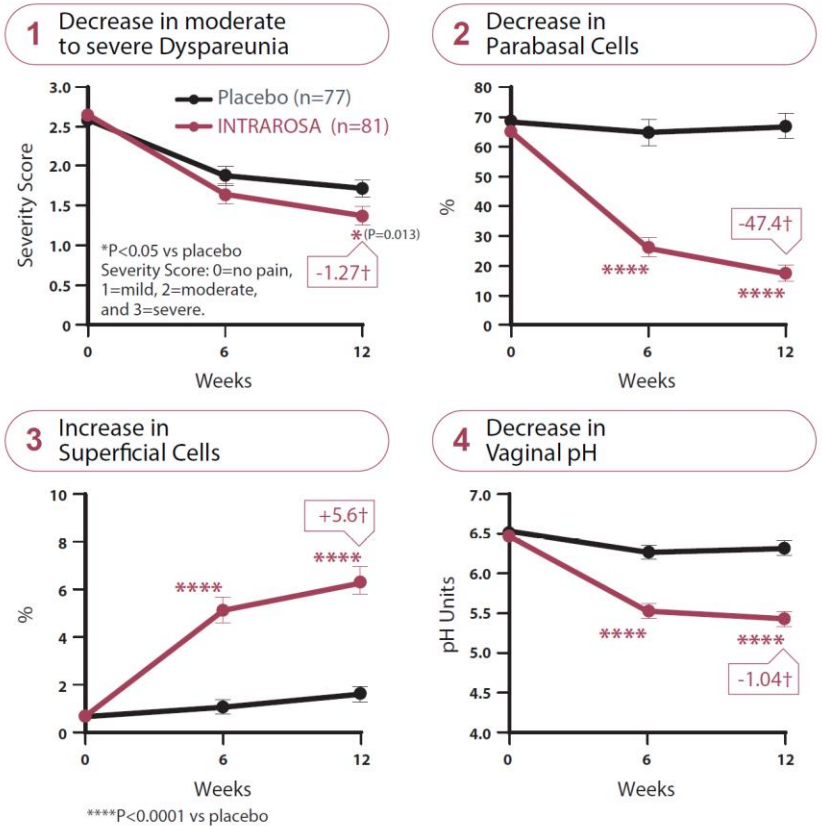
– *Decrease vaginal pH*
– *Increases percent superficial cells*
– *Reduces percentage of basal cells*
– *Improves vaginal color (pink), thickness, moisture and integrity*

- *Improves subjective symptoms:*

- Dyspareunia
- Itching
- Dryness

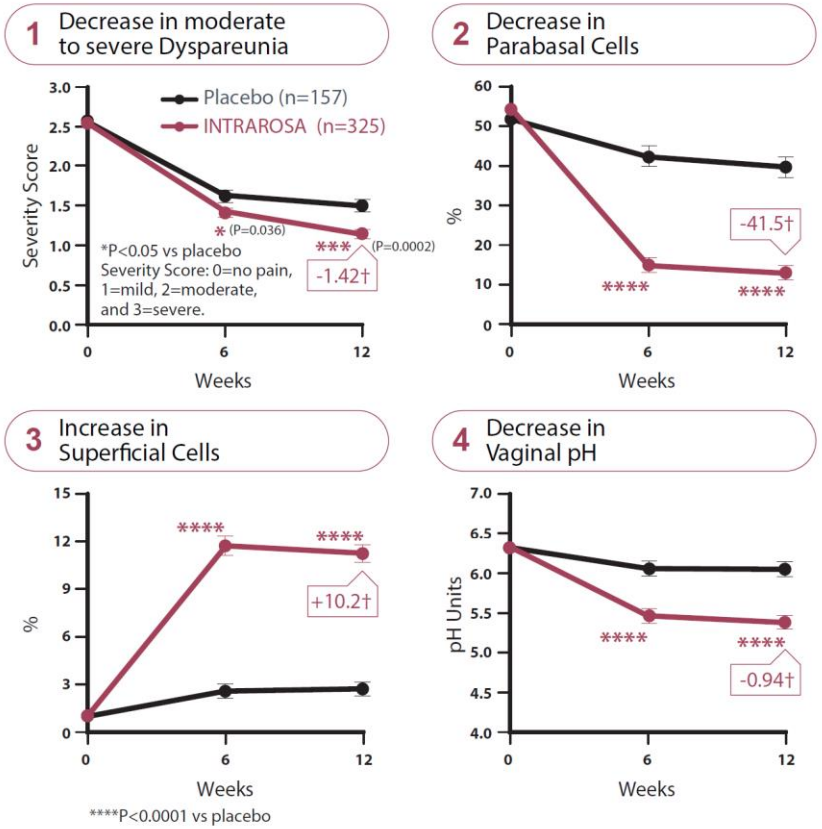
TRIAL 1

STATISTICALLY SIGNIFICANT EFFICACY ON ALL FOUR FDA-DESIGNATED CO-PRIMARY ENDPOINTS



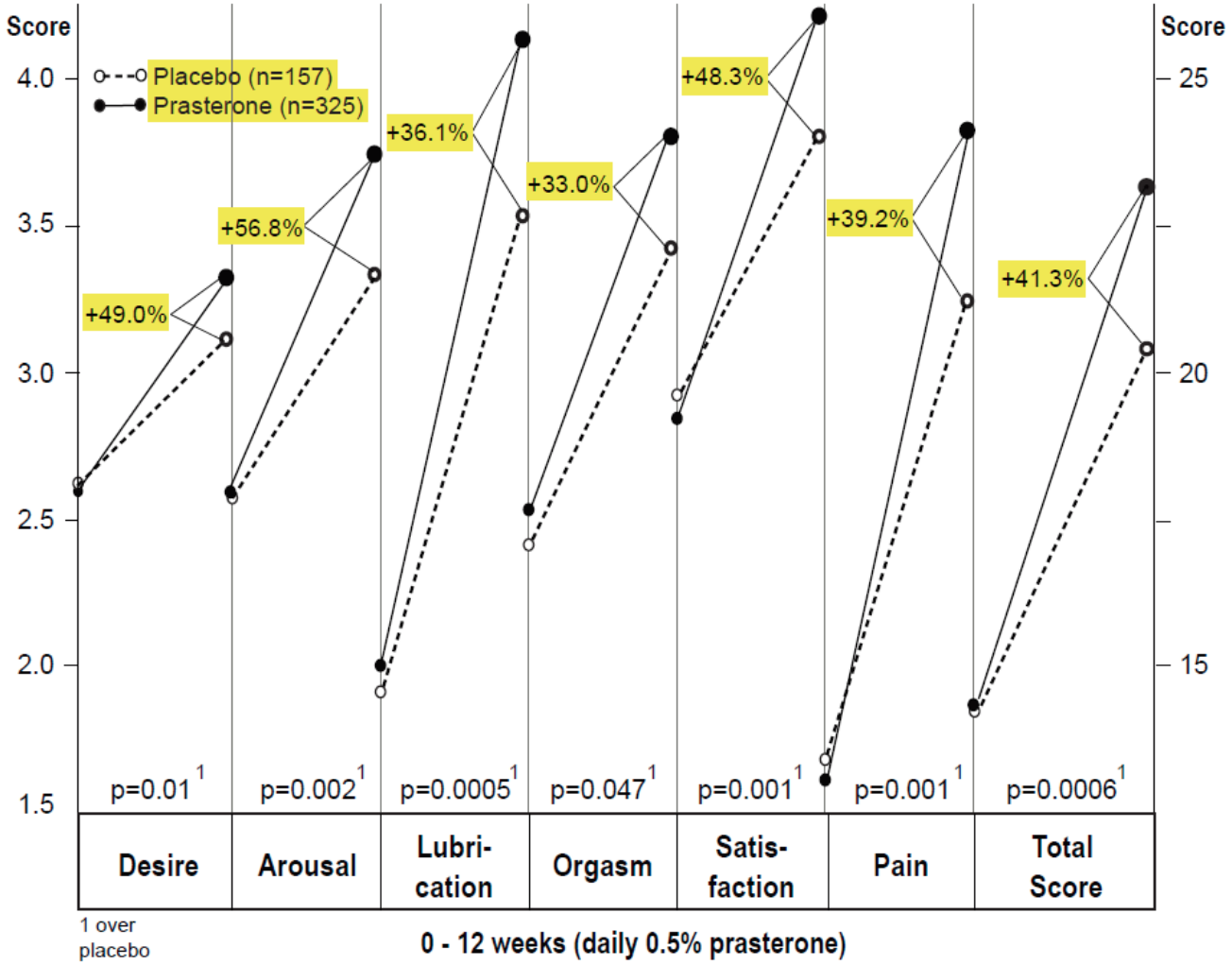
TRIAL 2

STATISTICALLY SIGNIFICANT EFFICACY ON ALL FOUR FDA-DESIGNATED CO-PRIMARY ENDPOINTS

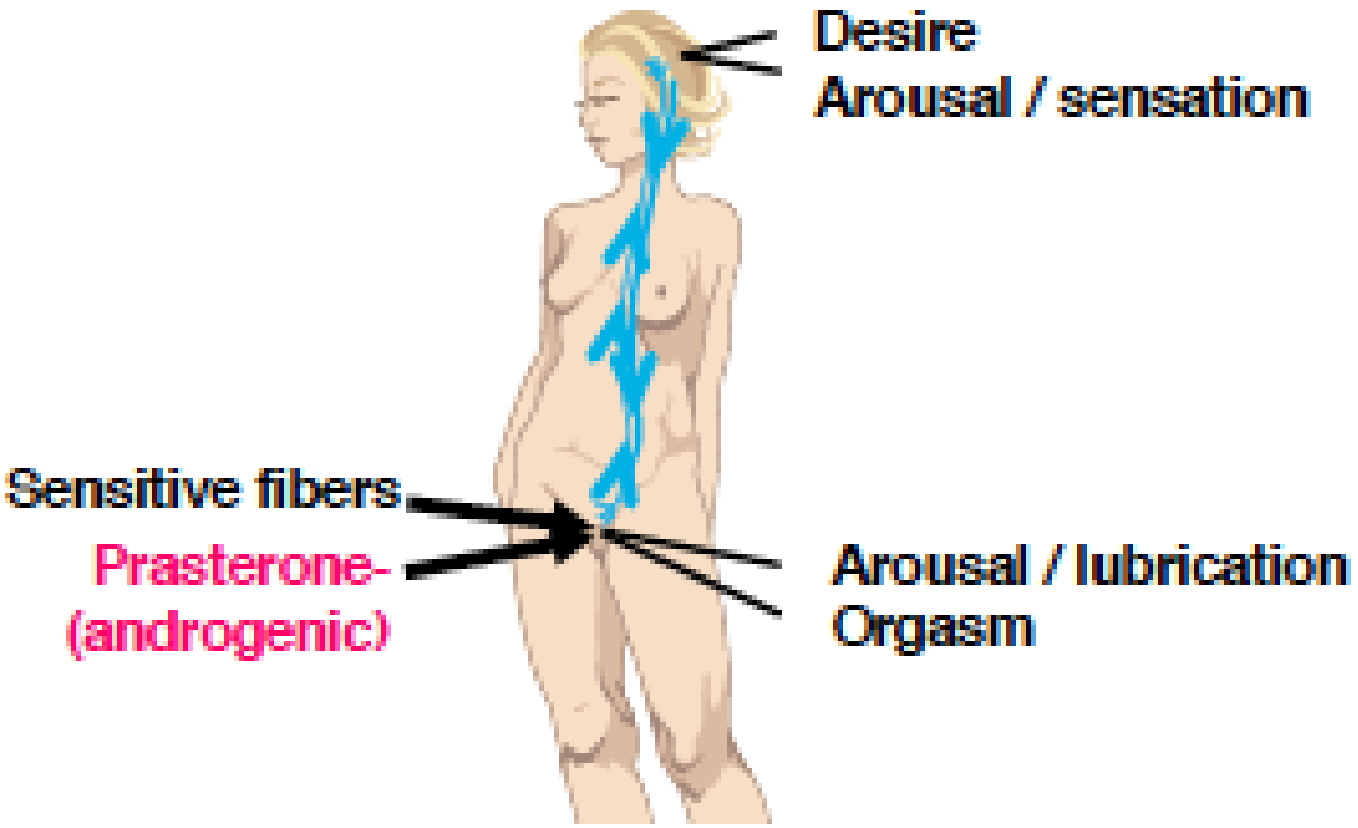


Archer, Labrie et al, Menopause, 2015

FSFI Domains : VVA Population

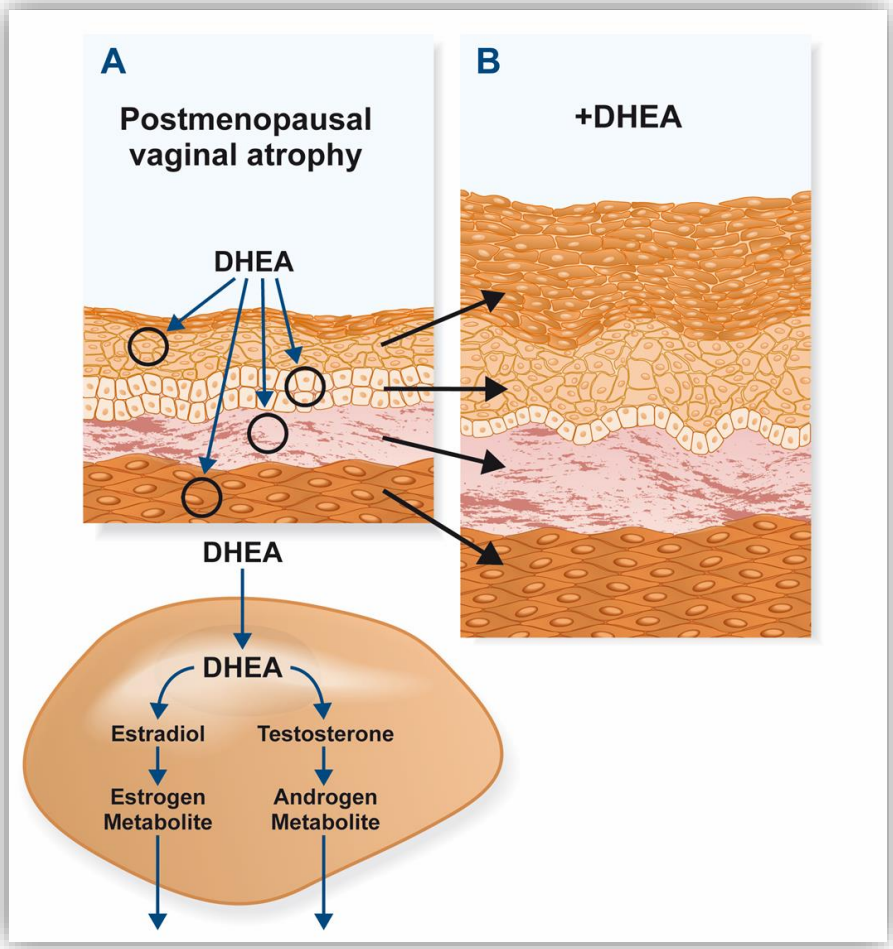


Labrie, Derogatis et al, J. Sex. Med. 2015



Pelletier, Ouellet et al, J. Sex. Med., 2013; Labrie, Derogatis et al, J. Sex. Med, 2015

Profilo di sicurezza



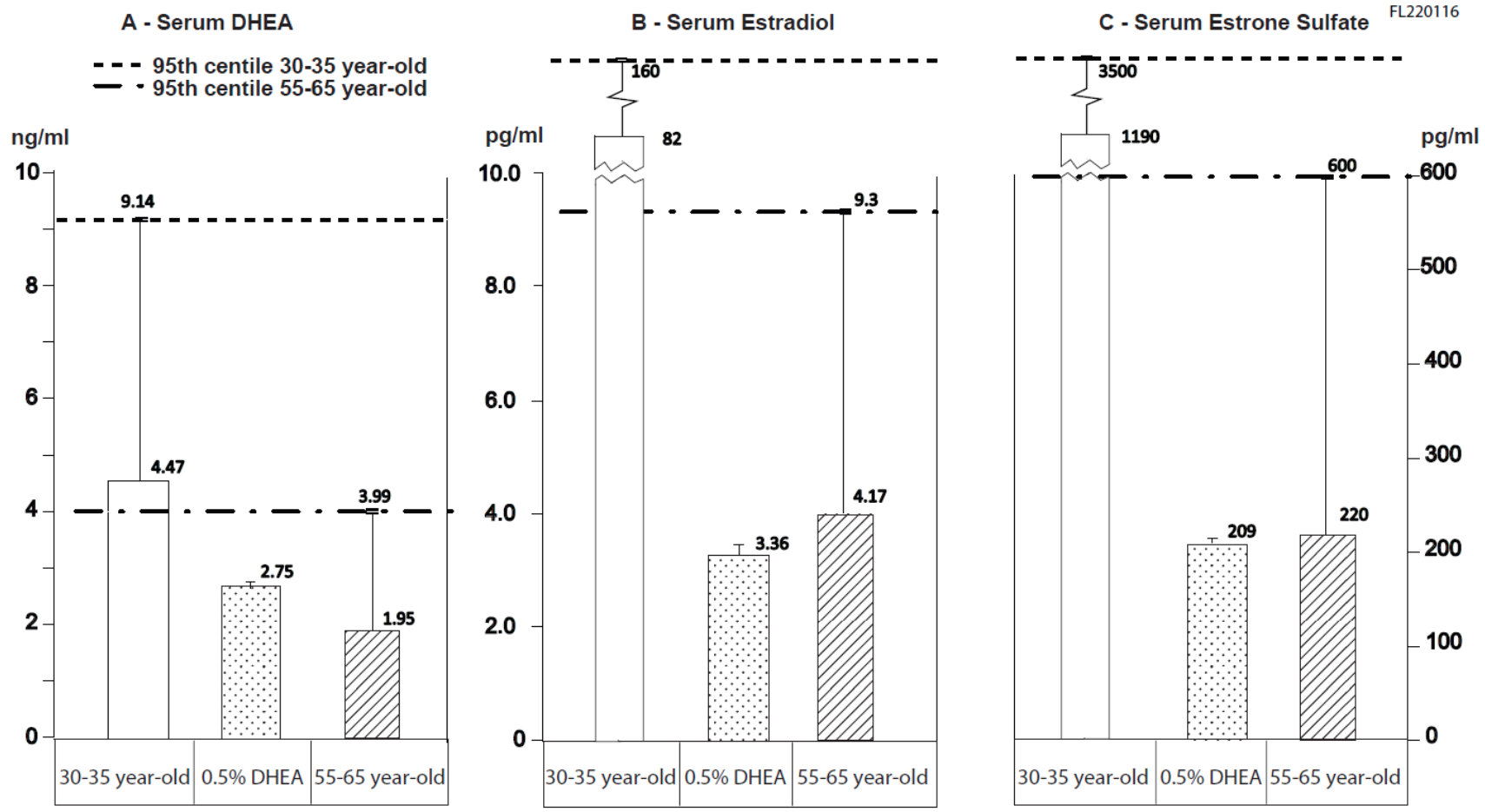
WITH DHEA, ALL SERUM STEROIDS REMAIN WITHIN NORMAL VALUES AND PRACTICALLY ONLY THE INACTIVE ESTROGEN AND ANDROGEN METABOLITES APPEAR IN THE BLOOD

After menopause, all estrogens are synthesized in peripheral tissues from DHEA. Serum estradiol, however, must remain below 10pg/ml.

INTRAROSA is the only treatment of vulvovaginal atrophy that maintains serum estradiol within normal values, thus avoiding the risk of systemic effects

Jameson JL ET AL., 2010; Mayo Medical Laboratories, 2017; Cusan et al, 2009

All steroids (LC-MS/MS assays) well within the normal postmenopausal values



Martel, Labrie et al, J. Ster. Biochem. Mol. Biol., 2016

Endometrium: not affected by DHEA

Endometrial biopsy

- 389 women who received 6.5 mg prasterone had sufficient tissue for histopathological evaluation
- **385 (99%) had atrophic endometrium**
- **4 (1%) had an inactive endometrium**

Endometrial thickness

- **Transvaginal ultrasonography performed at week 52 in 43 participants showed no clinically significant change in endometrial thickness**

The enzymes required to transform DHEA (prasterone) into estrogens are absent in the endometrium *– an organ with no physiological role after menopause*

No black box warning with Intrarosa

INCREASED RISK OF:

- Breast cancer
- Cardiovascular events
- Cerebrovascular events
- Memory and cognition problems, and dementia
- Thromboembolism
- Uterine cancer

FDA Black Box Warning for Estrogens [1]

WARNINGS

ESTROGENS INCREASE THE RISK OF ENDOMETRIAL CANCER

Close clinical surveillance of all women taking estrogens is important. Adequate diagnostic measures, including endometrial sampling when indicated, should be undertaken to rule out malignancy in all cases of undiagnosed persistent or recurring abnormal vaginal bleeding. There is no evidence that the use of "natural" estrogens results in a different endometrial risk profile than synthetic estrogens at equivalent estrogen doses.

CARDIOVASCULAR AND OTHER RISKS

Estrogens with or without progestins should not be used for the prevention of cardiovascular disease or dementia.

The Women's Health Initiative (WHI) study reported increased risks of stroke and deep vein thrombosis in postmenopausal women (50 to 79 years of age) during 6.8 years of treatment with oral conjugated estrogens (CE 0.625 mg) alone per day, relative to placebo.

The WHI study reported increased risk of myocardial infarction, stroke, invasive breast cancer, pulmonary emboli, and deep vein thrombosis in postmenopausal women (50 to 79 years of age) during 5 years of treatment with oral conjugated estrogens (CE 0.625 mg) combined with medroxyprogesterone acetate (MPA 2.5 mg) per day, relative to placebo.

The Women's Health Initiative Memory Study (WHIMS), a substudy of the WHI study, reported increased risk of developing probable dementia in postmenopausal women 65 years of age or older during 5.2 years of treatment with CE 0.625 mg alone and during 4 years of treatment with CE 0.625 mg combined with MPA 2.5 mg, relative to placebo. It is unknown whether this finding applies to younger postmenopausal women.

Other doses of oral conjugated estrogens with medroxyprogesterone acetate, and other combinations and dosage forms of estrogens and progestins were not studied in the WHI clinical trials and, in the absence of comparable data, these risks should be assumed to be similar. Because of these risks, estrogens with or without progestins should be prescribed at the lowest effective doses and for the shortest duration consistent with treatment goals and risks for the individual woman.

Profilo di sicurezza del prasterone

- *All serum steroids remain within normal postmenopausal values;*

- *No serious adverse events with DHEA in our as well as other studies and public databases;*

- ***ENDOMETRIUM:*** *not affected by DHEA****;***

- ***NO BLACK BOX WARNINGS.***

INTRAROSA: posology and method of administration

- *Recommended dose is one 6.5 mg pessary at bedtime per day*
- *Vaginal use (finger/applicator)*
- *Should only be initiated for symptoms that adversely affect quality of life*
- *Careful appraisal of the risks and benefits should be reassessed at least every 6 months*
- ***Continue as long as the benefit outweighs the risk***

INTRAROSA: controindications

- *Hypersensitivity to prasterone*
- *Undiagnosed genital bleeding*
- ***Known, past or suspected breast cancer***
- ***Known or suspected oestrogen-dependent malignant tumours** (e.g endometrial cancer)*
- *Untreated endometrial hyperplasia*
- *Acute liver disease, or a history of liver disease as long as liver function tests have failed to return to normal*
- *Previous or current venous thromboembolism (deep vein thrombosis, pulmonary embolism)*
- ***Known thrombophilic disorders** (e.g. protein C, protein S, or antithrombin deficiency)*
- *Active or recent arterial thromboembolic disease (e.g. angina, myocardial infarction)*
- *Porphyria*

Intrarosa® 6.5 mg

Prasterone

Vaginal use

Indications and Usage

- *INTRAROSA is a steroid indicated for the treatment of moderate to severe dyspareunia, a symptom of vulvar and vaginal atrophy, due to menopause* ***(FDA)***
- *INTRAROSA is approved for the treatment of vulvar and vaginal atrophy in postmenopausal women having moderate to severe symptoms* ***(EMA)***

Dosage and Administration

One INTRAROSA vaginal pessary (6.5 mg of prasterone) is inserted once daily at bedtime, with the applicator provided within the pack or with the finger

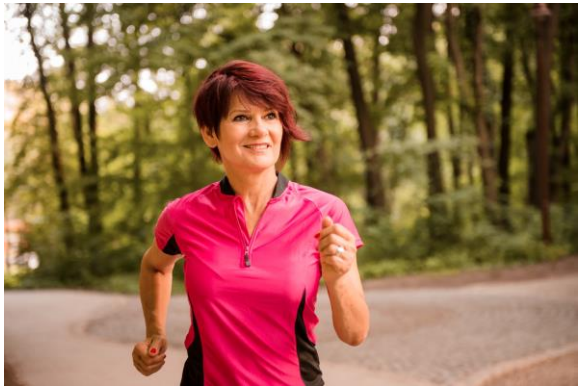
Conclusioni

- *La AVV è una condizione che ha un elevata prevalenza in peri- e postmenopausa che peggiora la qualità di vita della donna ma rimane sottostimata;*

- *Gli estrogeni vaginali sono efficaci e sicuri;*

- *Ospemifene ripristina le caratteristiche istologiche dell'epitelio vaginale e vulvare già dopo 4 settimane, mostrando un buon profilo di sicurezza;*

- *Il prasterone, agendo come deidroepiandrosterone (DHEA), mediante un'azione intracrina, rappresenta una promettente opzione per il trattamento della VVA, in assenza del black box warning.*



«Intracrinology
it's a revolutionary way of thinking
which is now confirmed at all levels,
there is no question about it»

Roger Guillemin , MD, PhD
Nobel Laureate

…grazie per l'attenzione!

stefania.alvisi2@unibo.it