Sindrome Genito-Urinaria. Terapie Ormonali Locali e Ospemifene punta di vista del Ginecologo

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Clinica Ostetrica e Ginecologia
Università degli Studi di Genova

DINOGMI 2018-2022 | DIPARTIMENTO DI ECCELLENZA MIUR

OSPEDALE POLICLINICO SAN MARTINO
Sistema Sanitario Regione Liguria
Istituto di Ricovero e Cura a Carattere Scientifico per l'Oncologia

Genito Urinary Syndrome of the Menopause (GSM) Consensus conference 2013

The syndrome may include but is not limited to:

Genital symptoms: dryness, burning, irritation

Sexual symptoms: lack of lubrication, discomfort or pain, and impaired sexual function.

Urinary symptoms: urgency, dysuria, and recurrent urinary tract infections.

Portman DJ et al. Menopause 2014

1. Sintomi e Segni di AVV

Sintomi	Segni	Indici oggettivi
ATROFIA VAGINALE		
Secchezza	Secchezza	Maturazione Epiteliale
Dispareunia	Pallore	pH
Bruciore	Appiattimento delle rughe	
Prurito	Perdita di elasticità	
Disuria	Fragilità	
	Petecchie	
ATROFIA VULVARE		
Secchezza	Assott. grandi e piccole labbra	
Dispareunia	Riduzione clitoride	
Bruciore	Alterazioni meato uretrale	
Prurito	Restringimento Introito	
	Pallore Mucosa	
	Petecchie, Escoriazioni, Ulcerazioni	

Diagnosi dell AVV

Indice di benessere vaginale

	Elasticità vaginale.	Secrezione Vaginale. e sua consistenza	pH.	Mucosa. Epiteliale.	Moisture Umidità
1	Assente.	Assente.	6.1.	Petecchie. senza trauma	Assente, Mucosa infiammata
2	Minima	Scarsa, sottile gialla	5.6-6.0.	Sanguina con lieve. con lieve contatto	Assente, mucosa non infiammata
3	Soddisfacente.	Superficiale, sottile biance.	5.1-5.5.	Sanguina con lo scraping	Minimal Minima
4	Buona	Moderata, sottile Bianca	4.7-5.0.	Non friabile mucosa sottile	Moderate Moderata
5	Eccellente	Normale (Bianca flocculenta).	$\leq$ 4.6.	Non friable mucosa normale	Normal Normale

Score più basso corrisponde ad una atrofia maggiore

Bachmann G, Maturitas 1995

Score <15
Sintomo soggettivo

AV (studio EVES)

The AGATA study

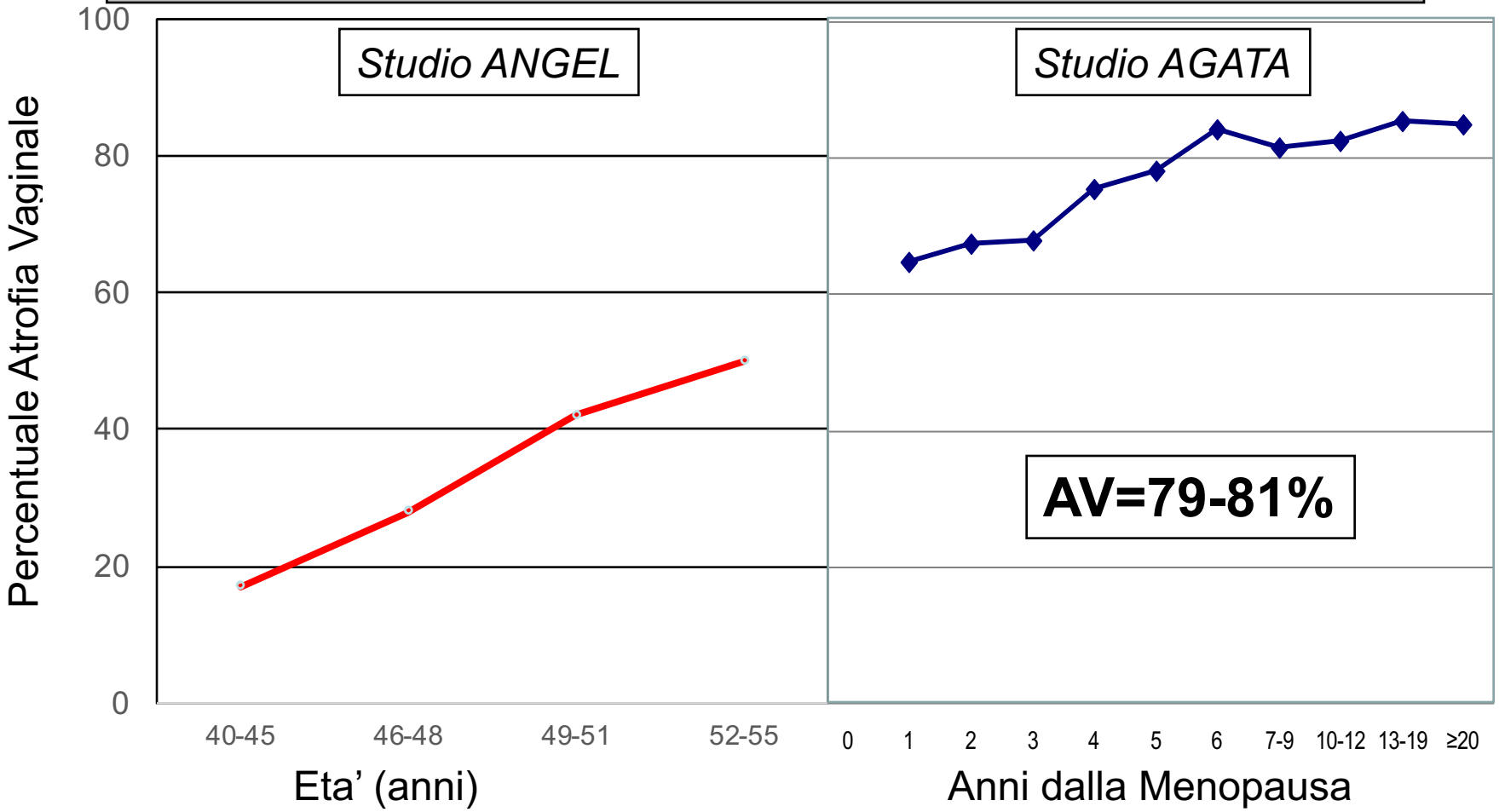
Epidemiology of VVA in postmenopause

VVA diagnosis was performed by the **co-presence** of

- pH >5
- Sensation of Vaginal Dryness
- An Objective Sign of VVA

The Study was performed on 913 women evaluated in 22 outpatient centers across the nation

2. Epidemiologia dell'Atrofia Vulvo-Vaginale



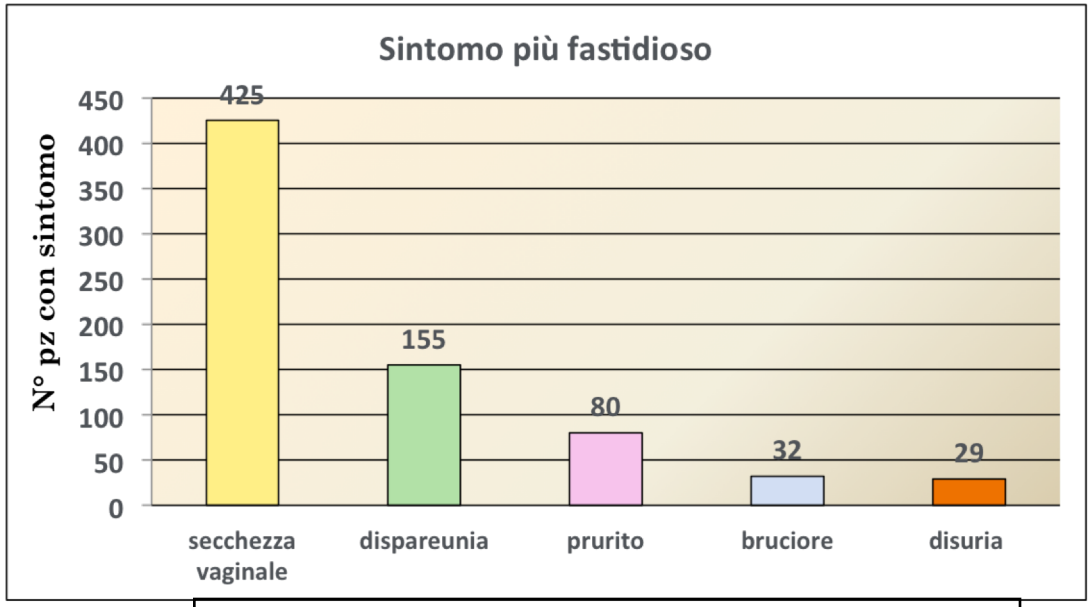
64% delle donne con AV hanno anche Atrofia Vulvare (Studio EVES)

Studio AGATA

Visione della donna

N=923

AV=722



secchezza vaginale	dispareunia	prurito	bruciore	disuria
58.8%	21.5%	11.0%	4.4%	4.0%

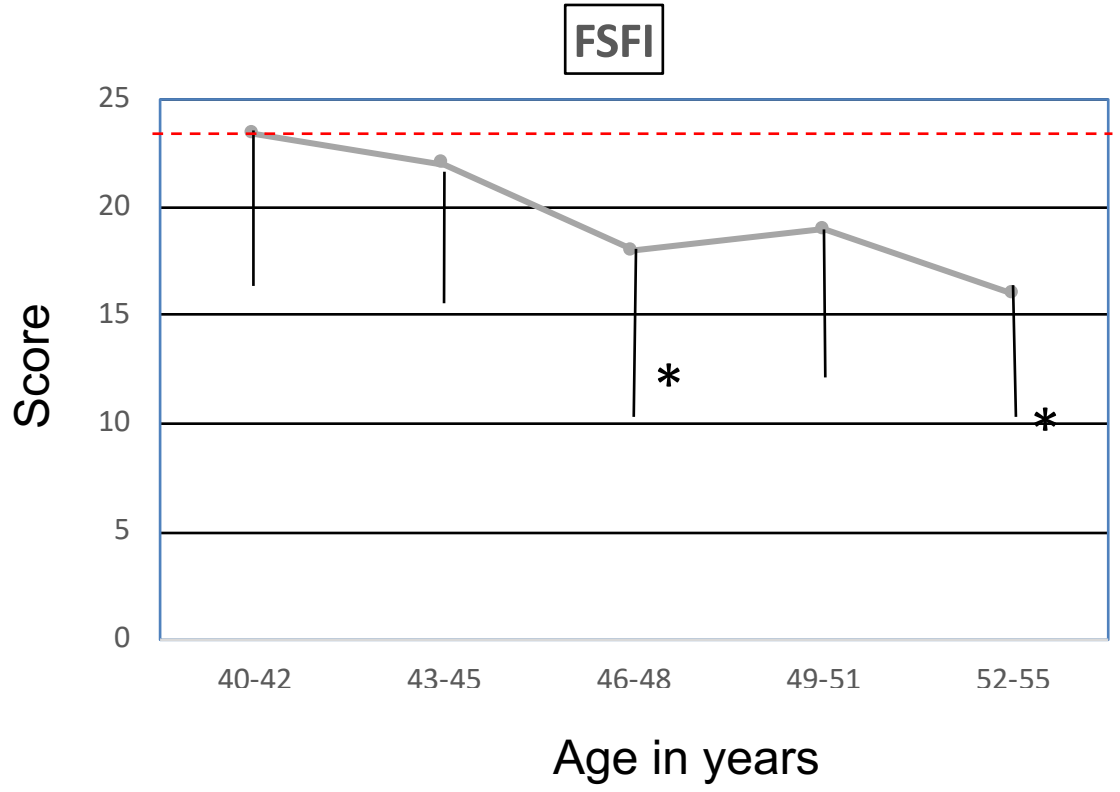
Palma et al., Maturitas 2017

Menopause: The Journal of The North American Menopause Society
Vol. 27, No. 1, pp. 14-19
DOI: 10.1097/GME.0000000000001427

ORIGINAL STUDY

Female sexuality and vaginal health across the menopausal age

Angelo Cagnacci, MD, PhD,[1] Martina Venier, MD,[1] Anjeza Xholli, MD,[1] Chiara Paglietti, MD,[1] Salvatore Caruso, MD,[2] for the ANGEL Study



Determinant of FSFI:

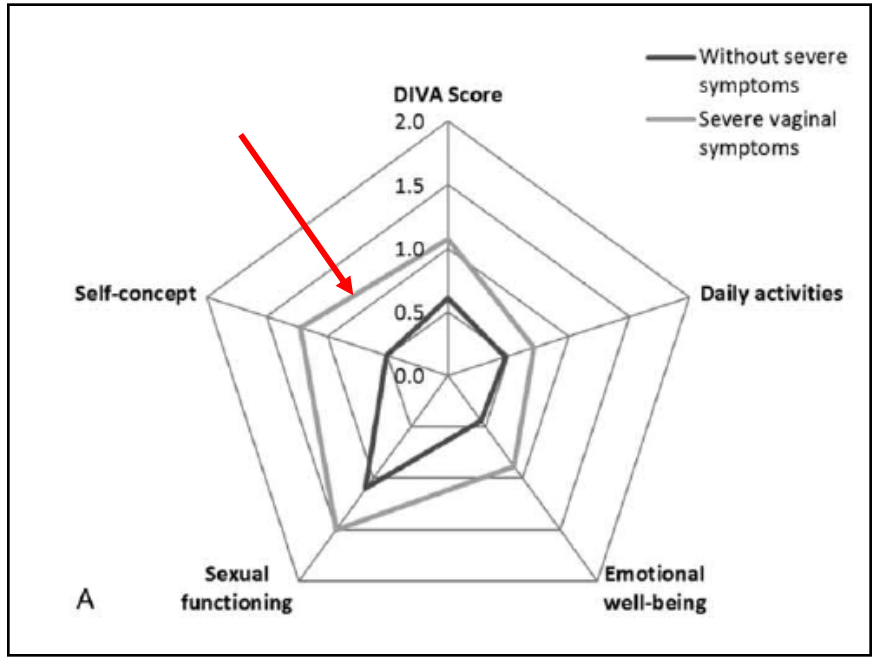
	Coefficent β
Age	**-0.67 per year**
Menopause	**-2.46 yes vs. no**
V. Dryness.	**-5.64 yes vs. no**

Menopause: The Journal of The North American Menopause Society
Vol. 26, No. 5, pp. 000-000
DOI: 10.1097/GME.0000000000001260

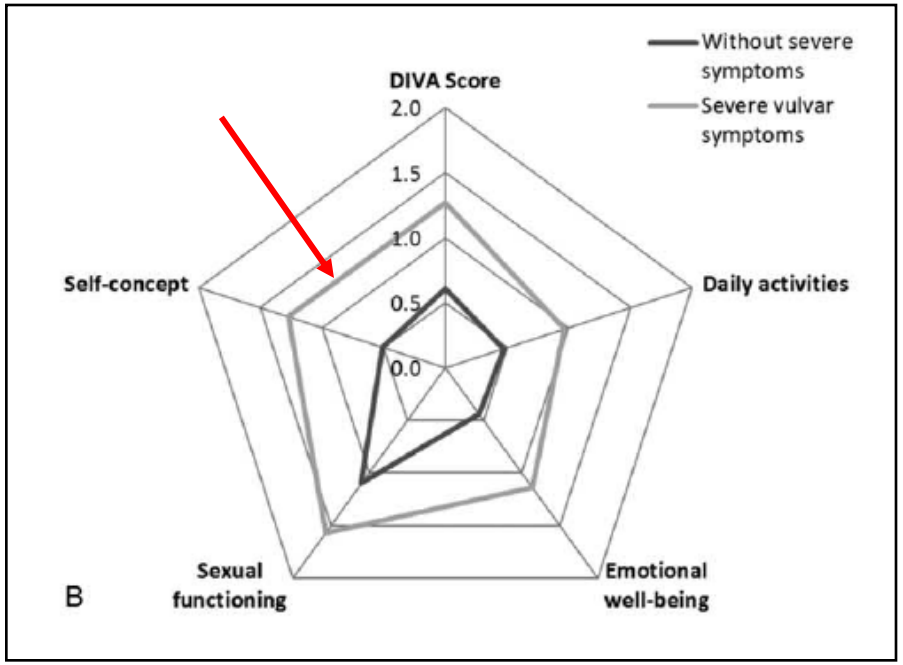
The burden of vulvovaginal atrophy on women's daily living: implications on quality of life from a face-to-face real-life survey

Rossella E. Nappi, MD, PhD,[1] Santiago Palacios, MD, PhD,[2] Nico Bruyniks, MD, MRCOG, MFSRH,[3] Martire Particco, MD,[4] Nick Panay, BSc, FRCOG, MFSRH,[5] and on behalf of the EVES Study investigators

Vaginal Symptoms



Vulvar Symptoms



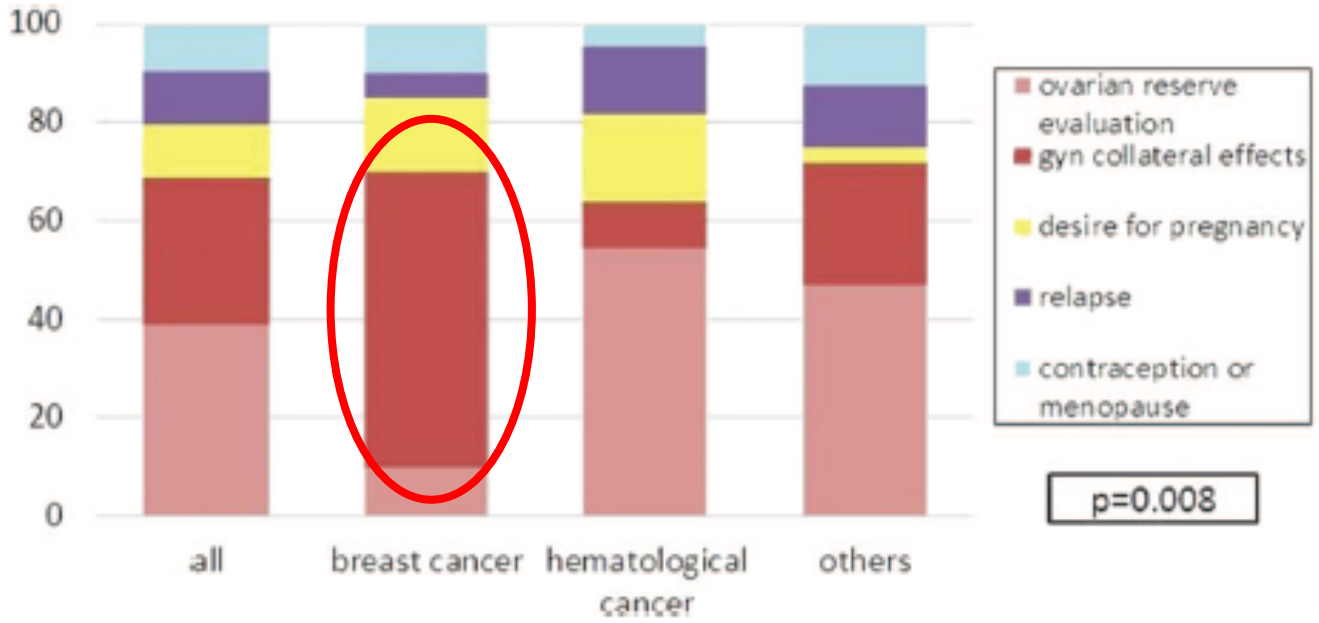
Human Reproduction, pp. 1–8, 2019
doi:10.1093/humrep/dez108

human reproduction
ORIGINAL ARTICLE *Gynaecology*

Beyond fertility preservation: role of the oncofertility unit in the reproductive and gynecological follow-up of young cancer patients

Claudia Massarotti[1,*], Paola Scaruffi[2], Matteo Lambertini[3,4], Fausta Sozzi[2], Valentino Remorgida[1], and Paola Anserini[2]

[1]Academic Unit of Obstetrics and Gynecology, DINOGMI Department, University of Genova, 16132, Genova, Italy [2]Physiopathology of Human Reproduction Unit, IRCCS Ospedale Policlinico San Martino, 16132, Genova, Italy [3]Department of Medical Oncology, U.O.C. Clinica di Oncologia Medica, IRCCS Ospedale Policlinico San Martino, 16132, Genova, Italy [4]Department of Internal Medicine and Medical Specialties (DIMI), School of Medicine, University of Genova, 16132, Genova, Italy



Massarotti et al, 2019

ACOG
The American College of Obstetricians and Gynecologists

CLINICAL CONSENSUS

NUMBER 2

DECEMBER 2021

(REPLACES COMMITTEE OPINION NO. 659, MARCH 2016)

Treatment of Urogenital Symptoms in Individuals With a History of Estrogen-dependent Breast Cancer

Committee on Clinical Consensus–Gynecology. This Committee Opinion was developed by the American College of Obstetricians and Gynecologists' Committee on Clinical Consensus – Gynecology in collaboration with committee member Betty Suh-Burgmann, MD, and liaison Elizabeth Evans, MD

Nonhormonal approaches

Vaginal Estrogens
After discussion of risks and benefits may be used also during Tamoxifen

Shared decision with oncologist if under Aromatase Inhibitors

DHEA and Testosterone
May help if vaginal estrogens are not an option

Ospemifene
No indication of higher recurrence. Long-term safety data are limited

British Menopause Society consensus statement on the management of estrogen deficiency symptoms, arthralgia and menopause diagnosis in women treated for early breast cancer

Post Reproductive Health
2019, Vol. 25(1) 21–32

DOI: 10.1177/2053369118824920
journals.sagepub.com/home/prh
SAGE

Nonhormonal approaches

Vaginal Estrogens
After discussion of risks and benefits may be used also during Tamoxifen

Should not be used under Aromatase Inhibitors

DHEA and Testosterone
May help but insufficient data

Ospemifene
Long-term safety data are limited. Not indicated. Approved by EMA at the end of adjuvant treatment. Not approved by FDA

Menopause: The Journal of The North American Menopause Society
Vol. 25, No. 6, pp. 596-608
DOI: 10.1097/GME.0000000000001121

CONSENSUS RECOMMENDATIONS

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

Nonhormonal approaches

Vaginal Estrogens
No clear indication
Use less potent estrogens: CEE>estradiol>estrone>estriol
Use less absorbable forms: Cream>Ring>Tablets Cream>Biohadesive Gel
Use lower third of vagina
Absorption decreases with time Atrophic> Estrogenized

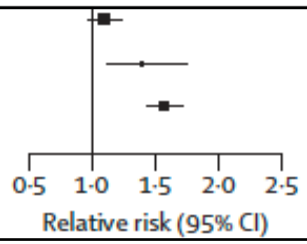
DHEA and Testosterone
Not more sicure than vaginal estrogens

Ospemifene
Long-term safety data are limited. Not indicated. Approved by EMA at the end of adjuvant treatment. Not approved by FDA

Type and timing of menopausal hormone therapy and breast cancer risk: individual participant meta-analysis of the worldwide epidemiological evidence

Collaborative Group on Hormonal Factors in Breast Cancer*

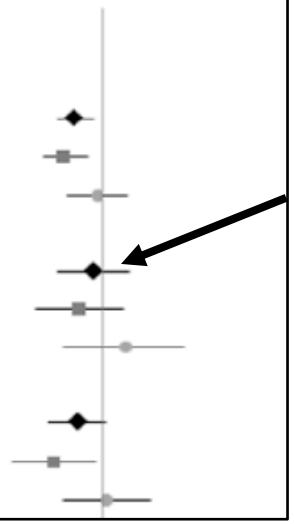
	Number of cases	Relative risk (95% CI) during years 5–14 of MHT use
Vaginal oestrogen	437	1·09 (0·97–1·23)
Progestagen only	112	1·39 (1·11–1·75)
Tibolone	680	1·57 (1·43–1·72)



Lancet 2019; 394: 1159–68

Breast Cancer, Endometrial Cancer, and Cardiovascular Events in Participants who used Vaginal Estrogen in the Women's Health Initiative Observational Study

End points	VE use N Events (rate)	No VE use N Events (rate)	HR (95% CI) Model 1	HR (95% CI) Model 2
GIE				
Overall	153 (14.0)	5906 (21.0)	0.69 (0.59, 0.81)	0.76 (0.64, 0.91)
Intact Uterus	96 (12.0)	4110 (19.9)	0.63 (0.51, 0.77)	0.68 (0.55, 0.86)
Hysterectomy	57 (19.7)	1796 (24.1)	0.83 (0.63, 1.08)	0.94 (0.70, 1.26)
Breast cancer				
Overall	40 (3.6)	1185 (4.1)	0.86 (0.62, 1.18)	0.91 (0.64, 1.29)
Intact Uterus	26 (3.2)	858 (4.0)	0.78 (0.53, 1.15)	0.79 (0.51, 1.22)
Hysterectomy	14 (4.7)	327 (4.2)	1.06 (0.61, 1.85)	1.23 (0.68, 2.21)
Death				
Overall	59 (5.3)	2592 (8.7)	0.67 (0.52, 0.87)	0.78 (0.58, 1.04)
Intact Uterus	32 (3.9)	1683 (7.7)	0.58 (0.41, 0.82)	0.62 (0.41, 0.93)
Hysterectomy	27 (9.0)	909 (11.3)	0.85 (0.58, 1.25)	1.04 (0.68, 1.58)



Menopause. 2018 January ; 25(1): 11–20.

Menopause: The Journal of The North American Menopause Society
Vol. 20, No. 9, pp. 888-902
DOI: 10.1097/gme.0b013e3182a122c2

POSITION STATEMENT

Management of symptomatic vulvovaginal atrophy: 2013 position statement of The North American Menopause Society

Circulating levels of E2 following vaginal estrogens

- Estradiol Ring 7.5 mc/day: 5-10pg/ml
- Estradiol Tablet 10 mcg: 5-11 pg/ml
- Estradiol Cream 200 mcg: 80 pg/ml
- CE 0.3 mg: no increase

JAMA Oncology | Original Investigation

Vaginal Testosterone Cream vs Estradiol Vaginal Ring for Vaginal Dryness or Decreased Libido in Women Receiving Aromatase Inhibitors for Early-Stage Breast Cancer

A Randomized Clinical Trial

Figure 3. Vaginal Atrophy Score Changes From Baseline to Week 12

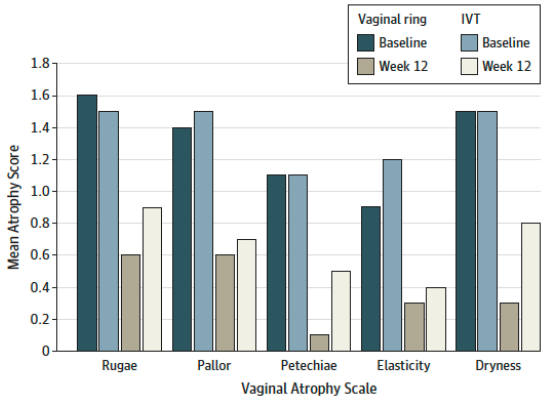
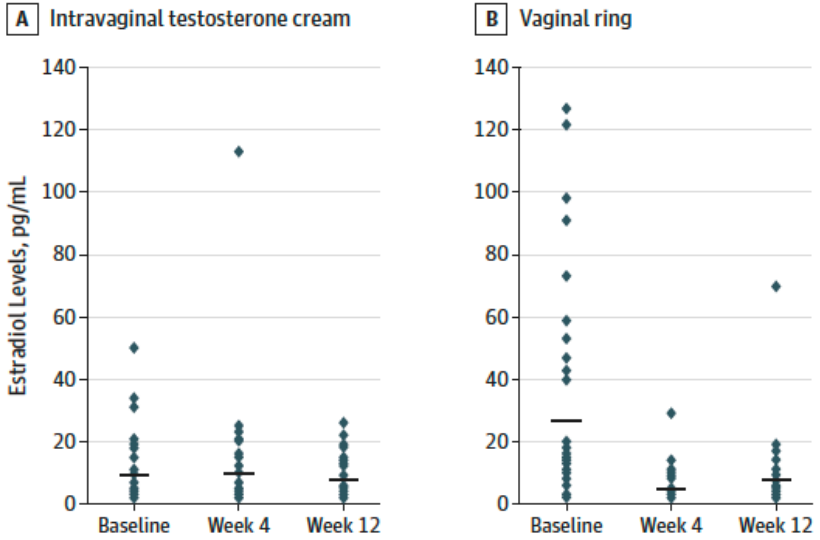


Figure 2. Estradiol Levels for Patients Who Completed 12 Weeks of Treatment



Findings In this randomized, noncomparative trial, persistent estradiol elevation was observed in no patients using a vaginal ring and in a small portion of IVT patients. Vaginal atrophy, sexual interest, and sexual dysfunction improved in both groups.

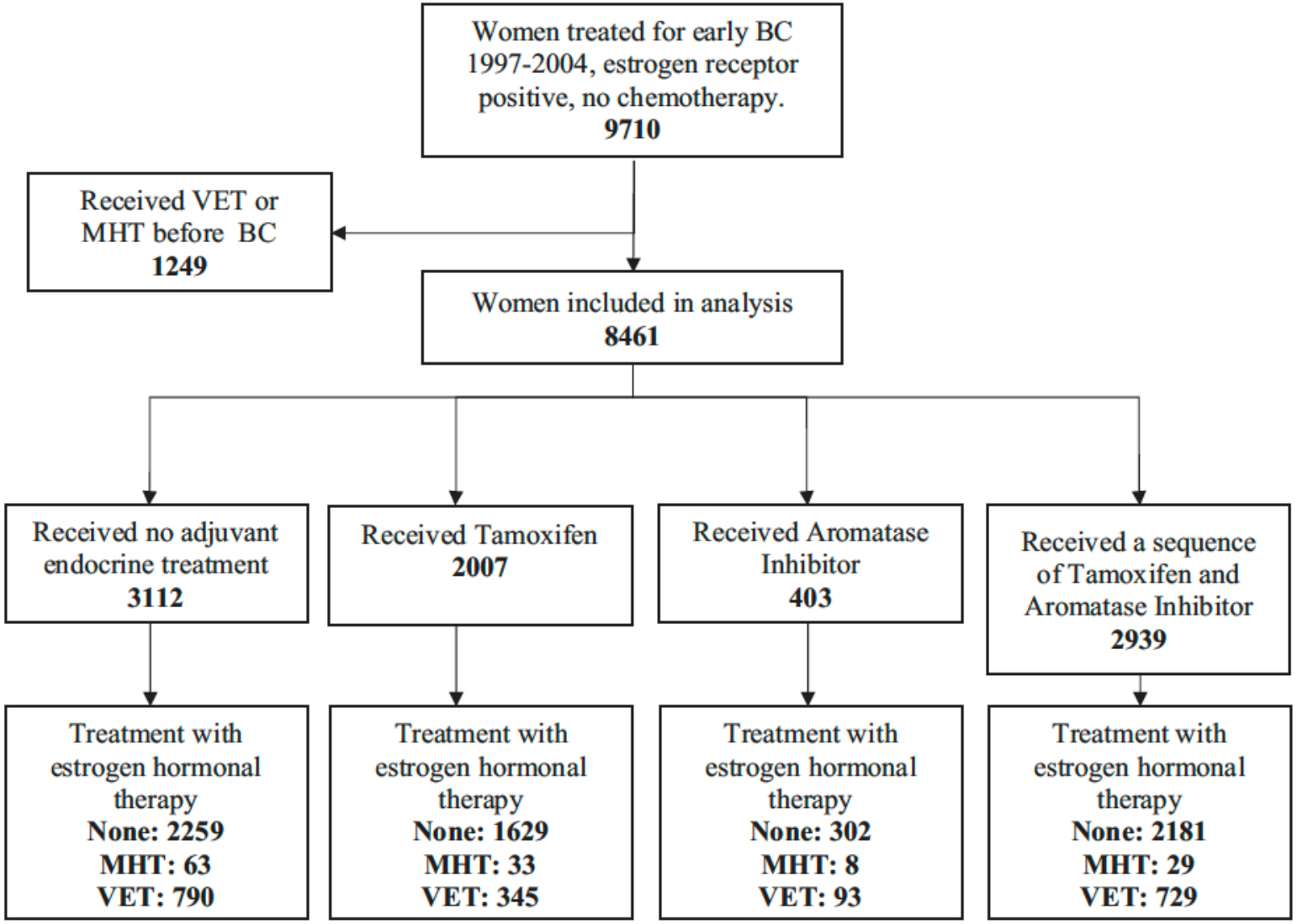
Meaning Persistent estradiol elevation was rare among patients with breast cancer on aromatase inhibitors using a vaginal ring or IVT, and use of these products is reasonable to consider for patients experiencing urogenital atrophy.

JAMA Oncol. doi:10.1001/jamaoncol.2016.3904

Systemic or Vaginal Hormone Therapy After Early Breast Cancer: A Danish Observational Cohort Study

Søren Cold, MD,[1,*] Frederik Cold, MD,[1] Maj-Britt Jensen, MSc,[2] Deirdre Cronin-Fenton, PhD,[3] Peer Christiansen, MD,[4] Bent Ejlertsen, MD[2,5]

Median follow-up period of 9.2 years for recurrence
Median follow-up period of 15.2 years for mortality



JNCI J Natl Cancer Inst (2022) 114(10): djac112

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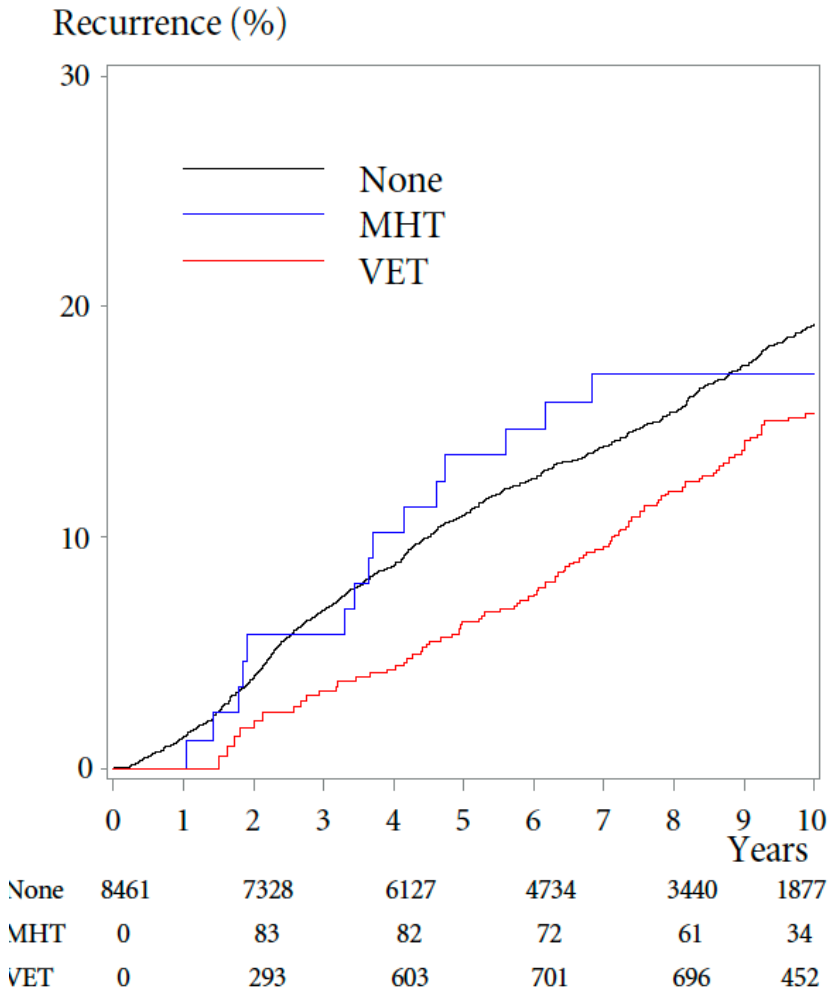
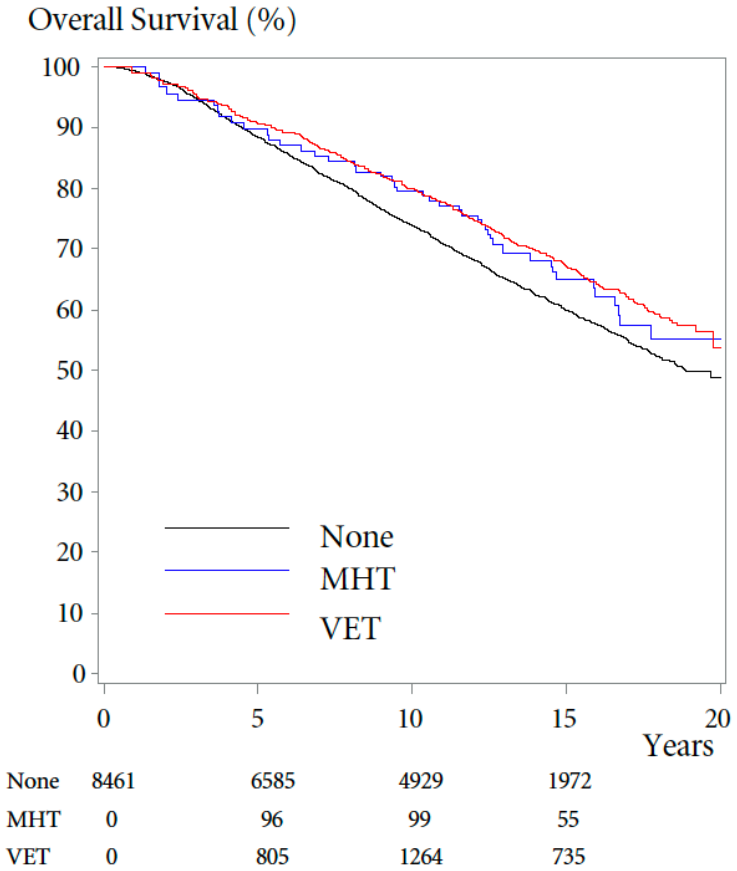




Vaginal Estrogens during Aromatase Inhibitors
Risk of Recurrence 1.39 (1.04-1.85)

Vaginal Estrogens during Aromatase Inhibitors
HR of Mortality 0.94 (0.70-1.26)

JNCI J Natl Cancer Inst (2022) 114(10): djac112

Climacteric

ISSN: 1369-7137 (Print) 1473-0804 (Online) Journal homepage: http://www.tandfonline.com/loi/icmt20

Pharmacokinetics and preliminary efficacy of two vaginal gel formulations of ultra-low-dose estriol in postmenopausal women

J. L. Delgado, J. Estevez, M. Radicioni, L. Loperete, J. Moscoso del Prado & C. Nieto Magro

Estriol 10% the Potency of Estradiol

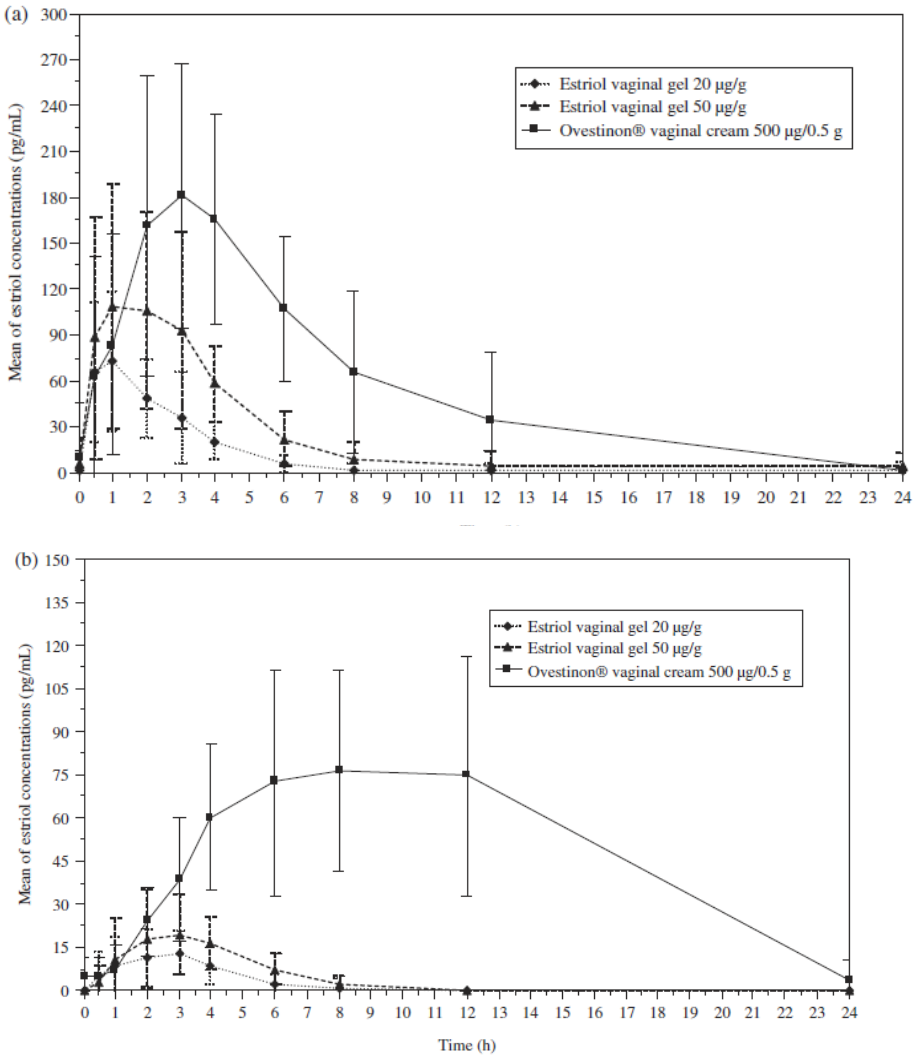
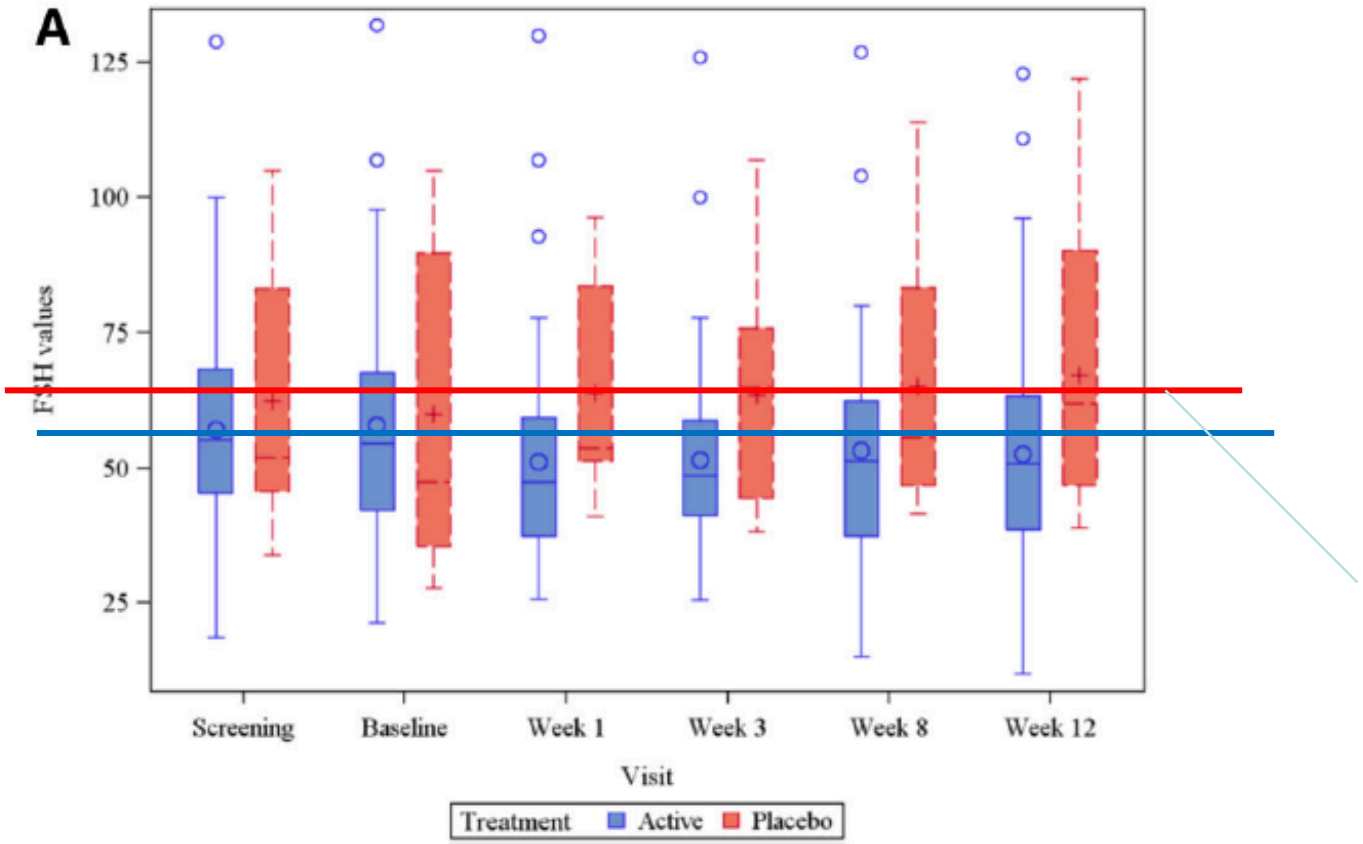


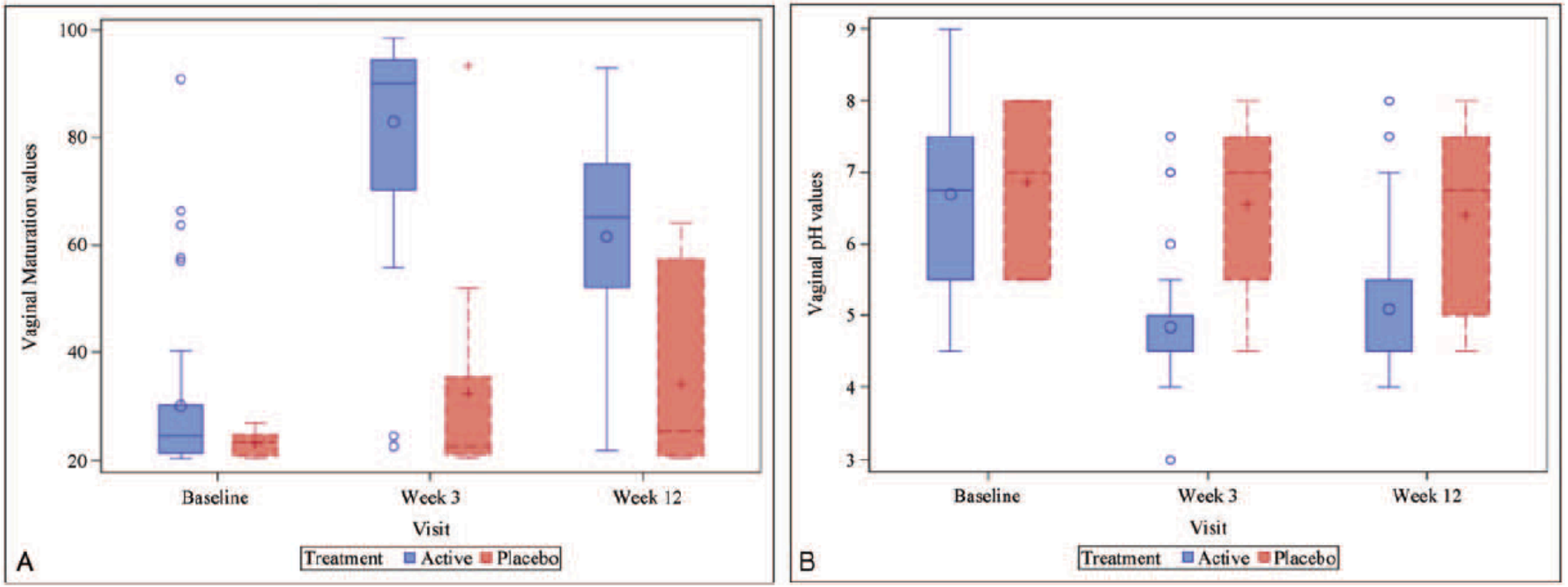
Figure 2. Mean (+ standard deviation) of plasma estriol concentrations (pg/ml) vs. time profile of estriol vaginal gel 20 µg/g (T1), estriol vaginal gel 50 µg/g (T2) and Ovestinon® vaginal cream (R) (linear scale) after (a) single administration (day 1) and (b) multiple administration (day 21).

A Phase II Prospective, Randomized, Double-Blind, Placebo-Controlled and Multicenter Clinical Trial to Assess the Safety of 0.005% Estriol Vaginal Gel in Hormone Receptor-Positive Postmenopausal Women with Early Stage Breast Cancer in Treatment with Aromatase Inhibitor in the Adjuvant Setting

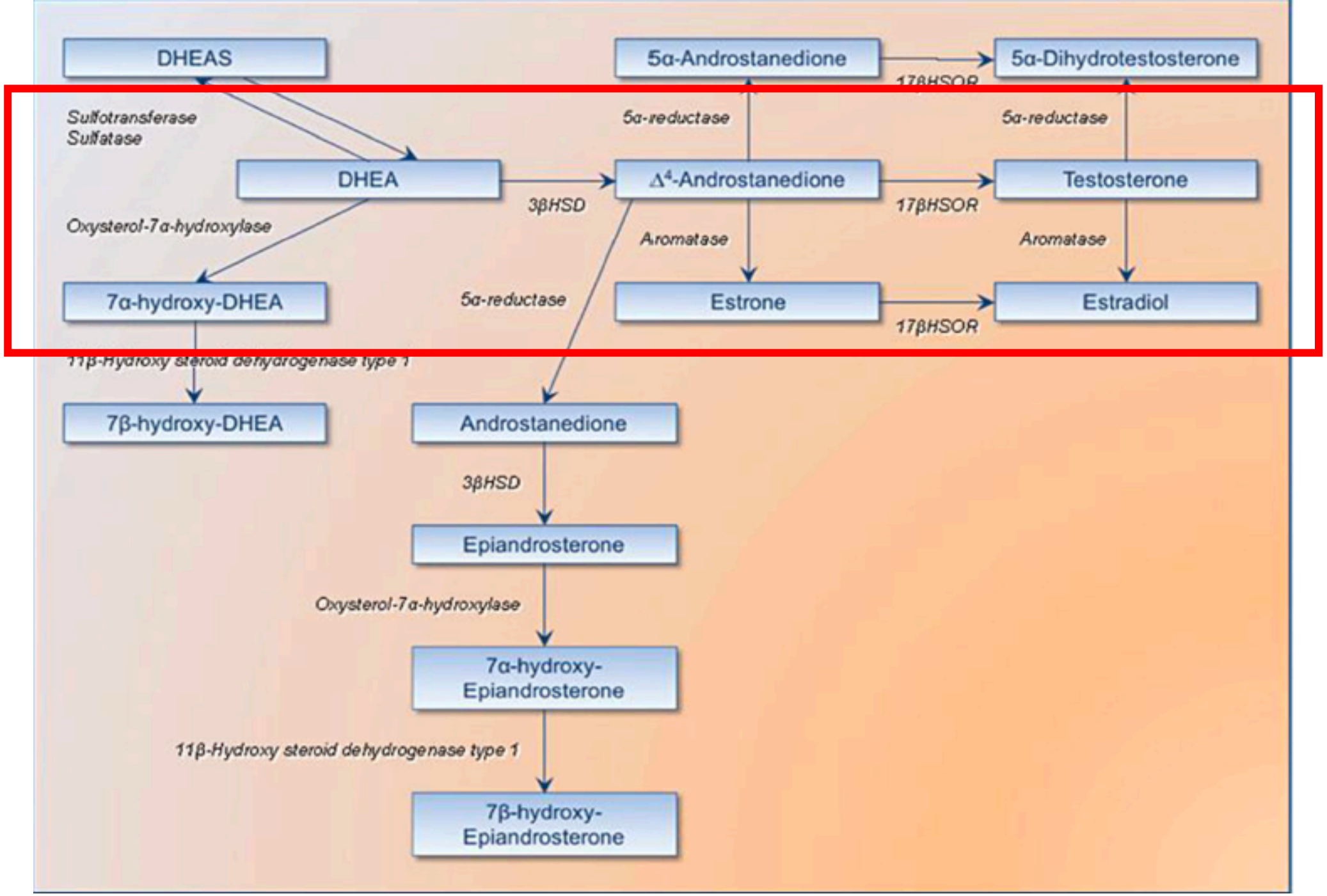


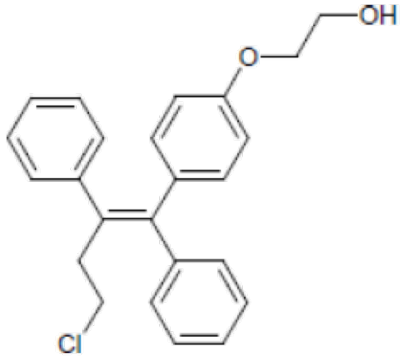
The Oncologist 2020;25:e1846–1854

Efficacy and safety of ultra-low dose 0.005% estriol vaginal gel for the treatment of vulvovaginal atrophy in postmenopausal women with early breast cancer treated with nonsteroidal aromatase inhibitors: a phase II, randomized, double-blind, placebo-controlled trial



Menopause, Vol. 27, No. 5, 2020


DHEAS
5α-Androstanedione
5α-Dihydrotestosterone
17βHSOR
Sulfotransferase
Sulfatase
5α-reductase
5α-reductase
DHEA
Δ4-Androstanedione
Testosterone
3βHSD
17βHSOR
Oxysterol-7α-hydroxylase
Aromatase
Aromatase
7α-hydroxy-DHEA
5α-reductase
Estrone
Estradiol
17βHSOR
11β-Hydroxy steroid dehydrogenase type 1
7β-hydroxy-DHEA
Androstanedione
3βHSD
Epiandrosterone
Oxysterol-7α-hydroxylase
7α-hydroxy-Epiandrosterone
11β-Hydroxy steroid dehydrogenase type 1
7β-hydroxy-Epiandrosterone



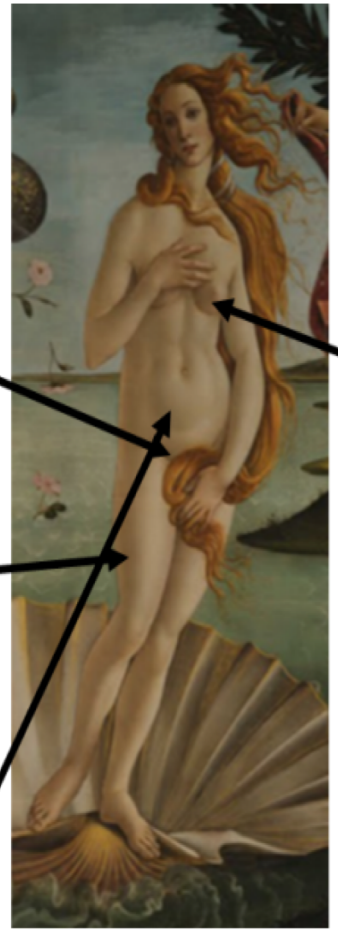
Ospemifene

Effetto **agonista** (estrogenico)

- **Epitelio vaginale**
- **Effetti Agonisti**/estrogenici

- **Osso**
- **Effetti Agonisti**/estrogenici osservati negli studi pre-clinici

- **Endometrio uterino**
- Effetti nell'insieme neutrali

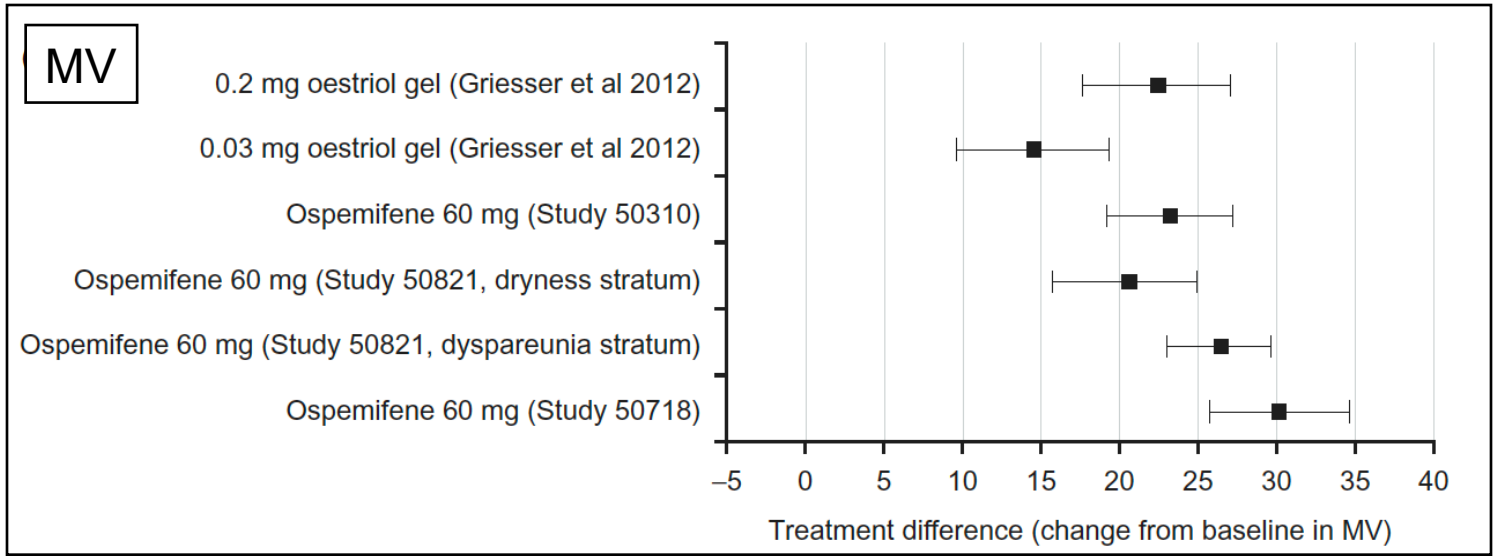


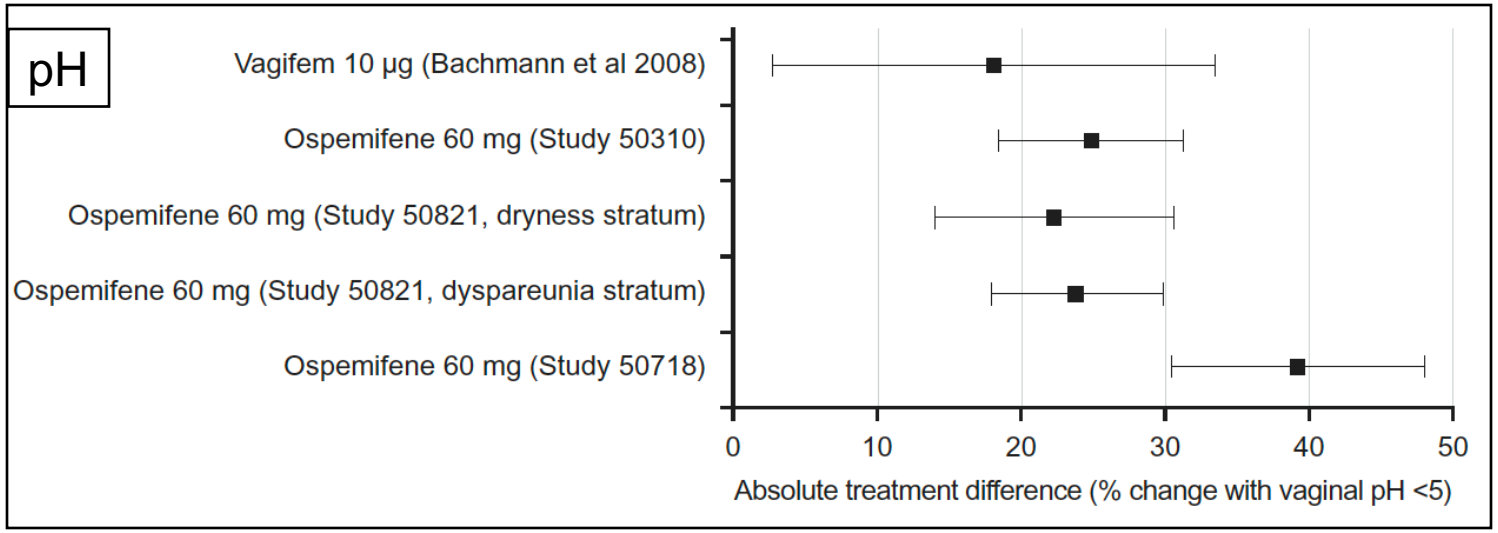
Effetto **antagonista** (antiestrogenico)

- **Mammella**
- **Effetti Antagonisti**/estrogenici osservati negli studi pre-clinici

La nascita di Venere- Botticelli

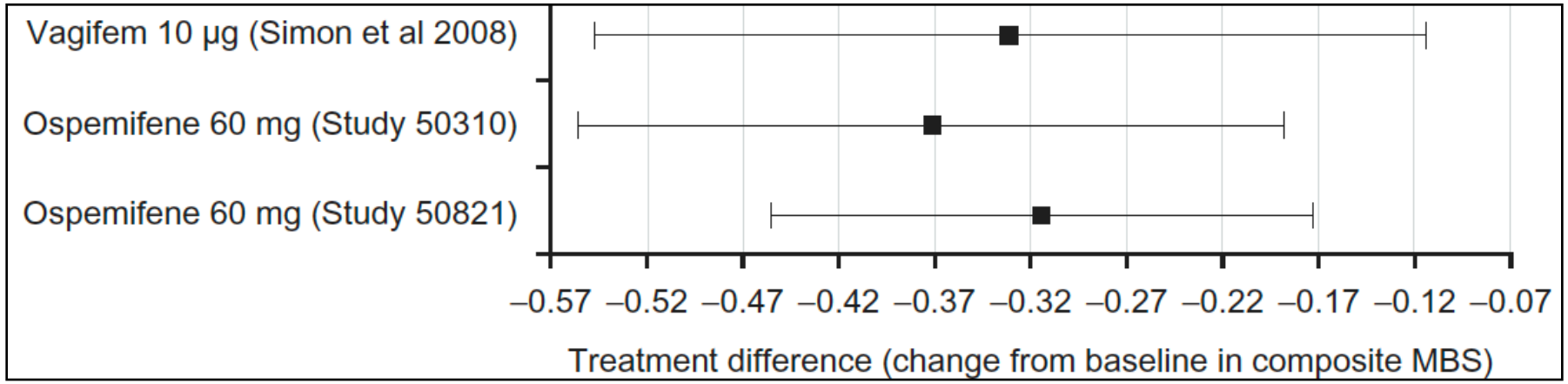
Ospemifene vs. Estrogens on epithelial maturation and pH





Brunicks et al, Climacteric 2017

Ospemifene vs. Estrogens on Most Bothersome Symptom



Brunicks et al, Climacteric 2017

Ospemifene versus local estrogen: adherence and costs in postmenopausal dyspareunia

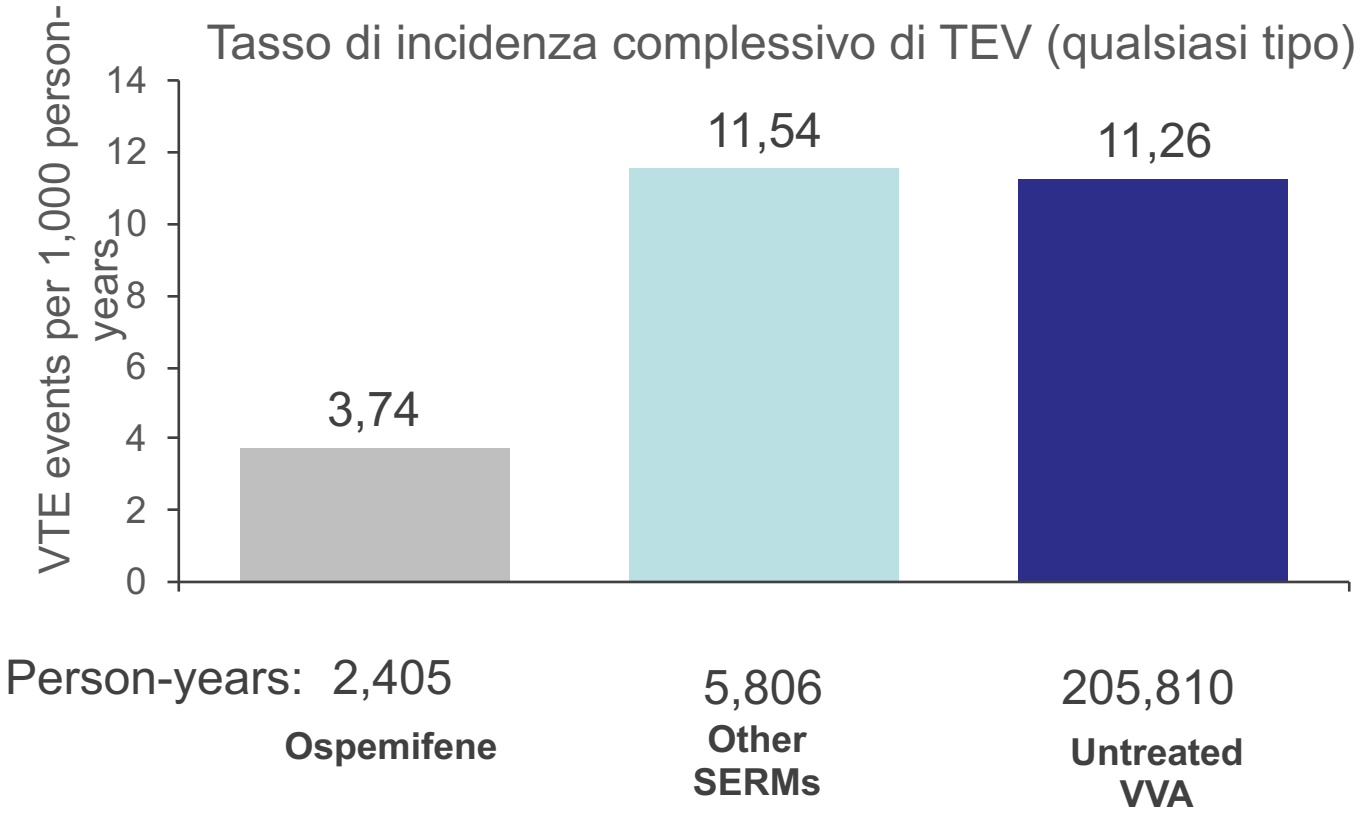
Brooke M Faught[1], Graziella Soulban[2], Jason Yeaw[3], Christiane Maroun[2], Katharine Coyle*[,4], Samuel Schaffer[2] & Mitch DeKoven[4]

Adherence

Ospemifene	1
CEE	0.07 (0.06-0.08)
E2 vaginal insert	0.46 (0.41-0.52)
E2 vaginal cream	0.11 (0.10-0.12)
E2 vaginal ring	1.71 (1.51-1.93)

J. Comp. Eff. Res. (2019) 8(13), 1111–1123

TEV 3 volte meno frequente nella coorte di ospemifene rispetto ad altri SERM e VVA non trattata

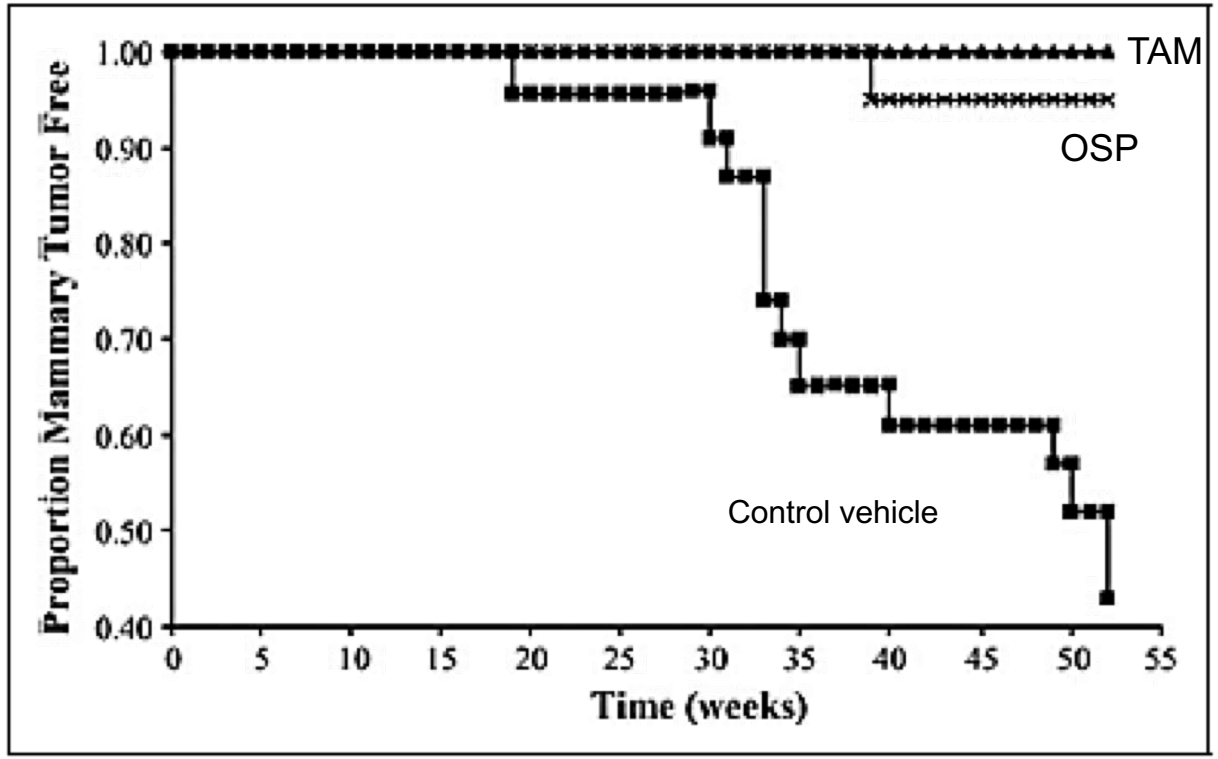


La coorte di Ospemifene ha avuto un'incidenza inferiore rispetto a entrambe le coorti di confronto, indipendentemente dalla durata del follow-up.

Nordstrom et al. Menopause 2020

Ospemifene e cancro alla mammella dati preclinici

Sia Ospemifene che tamoxifene riducono il numero di carcinomi mammari DMBA-indotti in modelli di topo femmine in confronto a topi non trattati



G.T. Wurz et al. Journal of Steroid Biochemistry & Molecular Biology 97 (2005) 230–240

No difference in mammography after 12 months of treatment

TABLE 5. NORMAL AND ABNORMAL BREAST MAMMOGRAM AND PALPATION FINDINGS

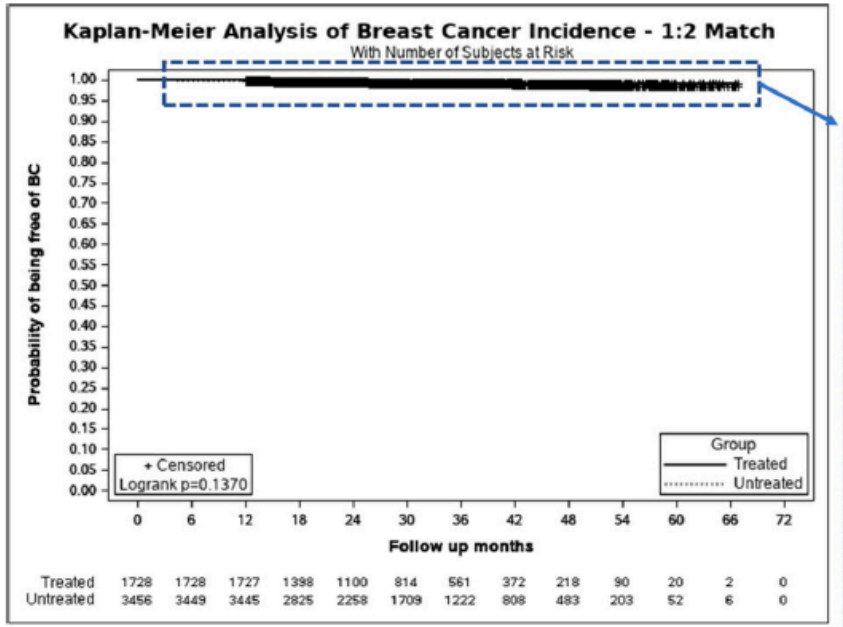
Characteristic,[a] n *(%)*	*Placebo*	*Ospemifene 60 mg*
Mammogram findings	$n = 63$	$n = 363$
Baseline (randomization), *n*	63	362
Normal	59 (93.7)	319 (88.1)
Abnormal-not clinically significant	4 (6.3)	43 (11.9)
Abnormal-clinical significant	0	0
12 months, *n*	47	269
Normal	43 (91.5)	248 (92.2)
Abnormal-not clinically significant	4 (8.5)	21 (7.8)
Abnormal-clinically significant	0	0

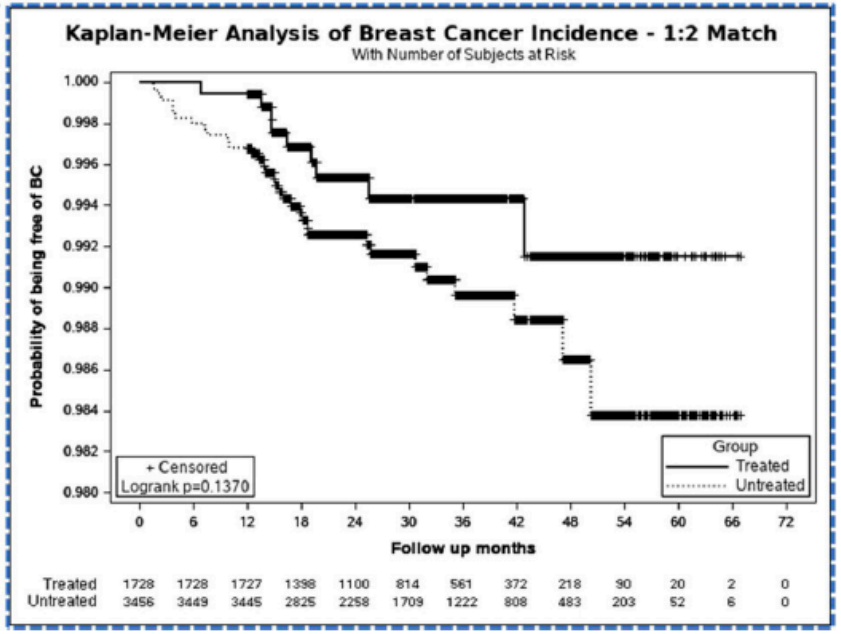
Simon et al. J of Women Health 2017

No increase in incidence or risk of recurrence of breast cancer in ospemifene-treated patients with vulvovaginal atrophy (VVA)

Bin Cai[a,*], James Simon[b], Paola Villa[c], Nicoletta Biglia[d], Nicholas Panay[e], Stora Djumaeva[f], Martire Particco[f], Hemanth Kanakamedala[g], Corrado Altomare[a]

1728 treated
3456 untreated





Median of treatment 313 days
Median of follow-up 970 days

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Table 3
: Recurrence of breast cancer in patients with VVA treated with ospemifene compared to untreated patients.

Matching (N cases, N controls)	Patients with Breast Cancer Diagnosis After Treatment Index Date		*p*-value[1]
	Ospemifene-Treated Group (N, %)	Untreated Group (N, %)	
1:1 (46, 46)	14 (30.43 %)	21 (45.65 %)	0.1328
1:2 (31, 62)	10 (32.26 %)	25 (40.32 %)	0.4492
1:3 (20, 60)	7 (35.00 %)	24 (40.00 %)	0.6910

[1] Chi-squared test was used to test for the association between breast cancer occurrence and treatment.

Conclusions

- VE are not associated with an increased risk of BC
- VE induce minimal increase in circulating estrogens
- No evidence of higher recurrence with VE (except in women with AI)
- Preferable to use weak estrogen (estriol) with bioadhesive formulation (polycarbophil gel)

Vaginal Estrogens can be used after BC
(after appropriate counselling)

- Ospemifene is a SERM that reduces breast tumor growth in vitro
- Ospemifene does not influence mammographic results after 1 year of tretament
- No evidence of increased risk of BC during Ospemifene
- No evidence of recurrence of BC during Ospemifene
- Approved by EMA but not FDA for women with BC at the end of adjuvant therapy

Ospemifene can be used at the end of BC treatment
(after appropriate counselling)

Grazie per l’Attenzione!!