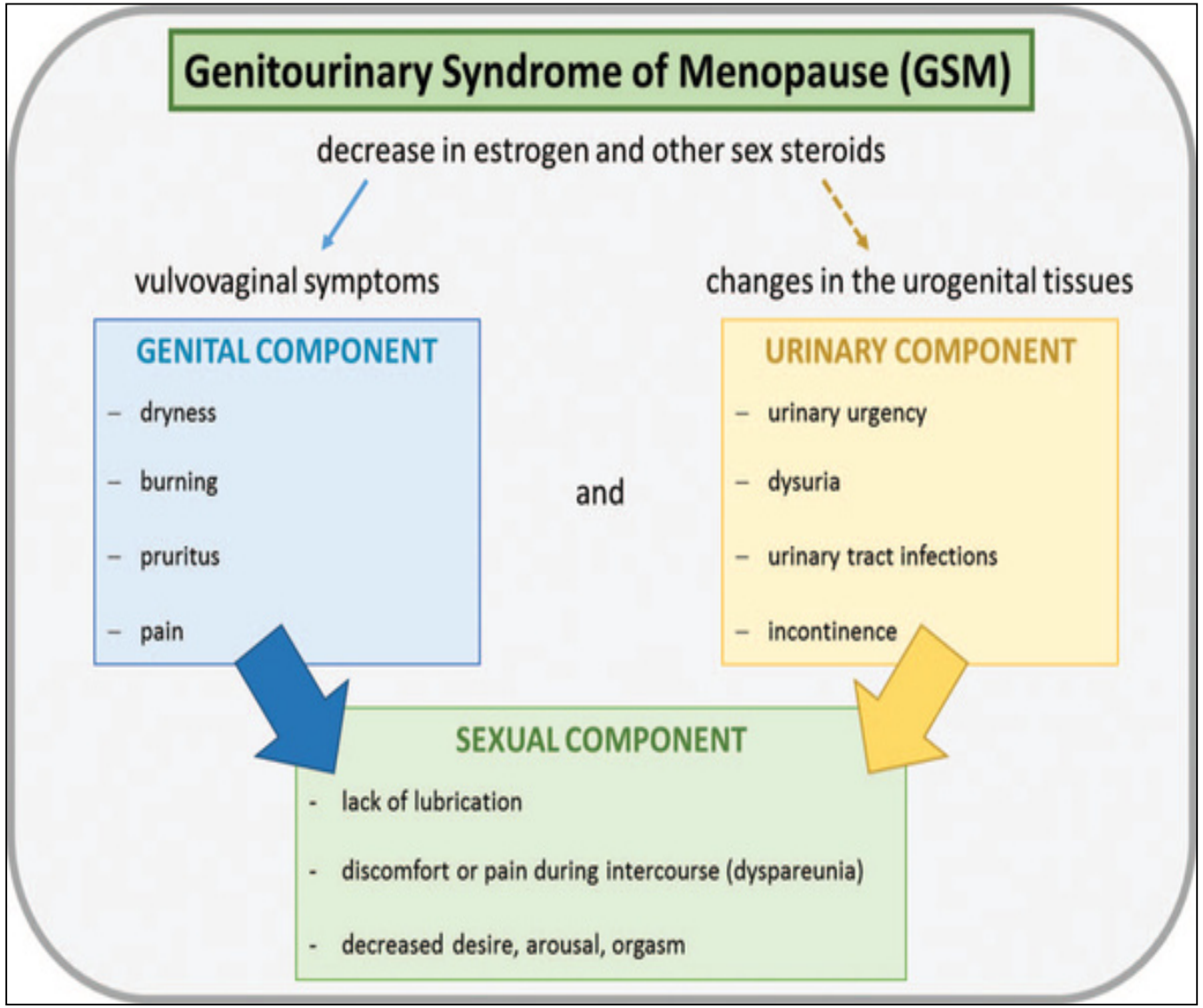


Genitourinary syndrome of menopause: new terminology for vulvovaginal atrophy

from the International Society for the Study of Women's Sexual Health and The North American Menopause Society.

Portman, David; Gass, Margery

Menopause 21:1063-8, 2014.

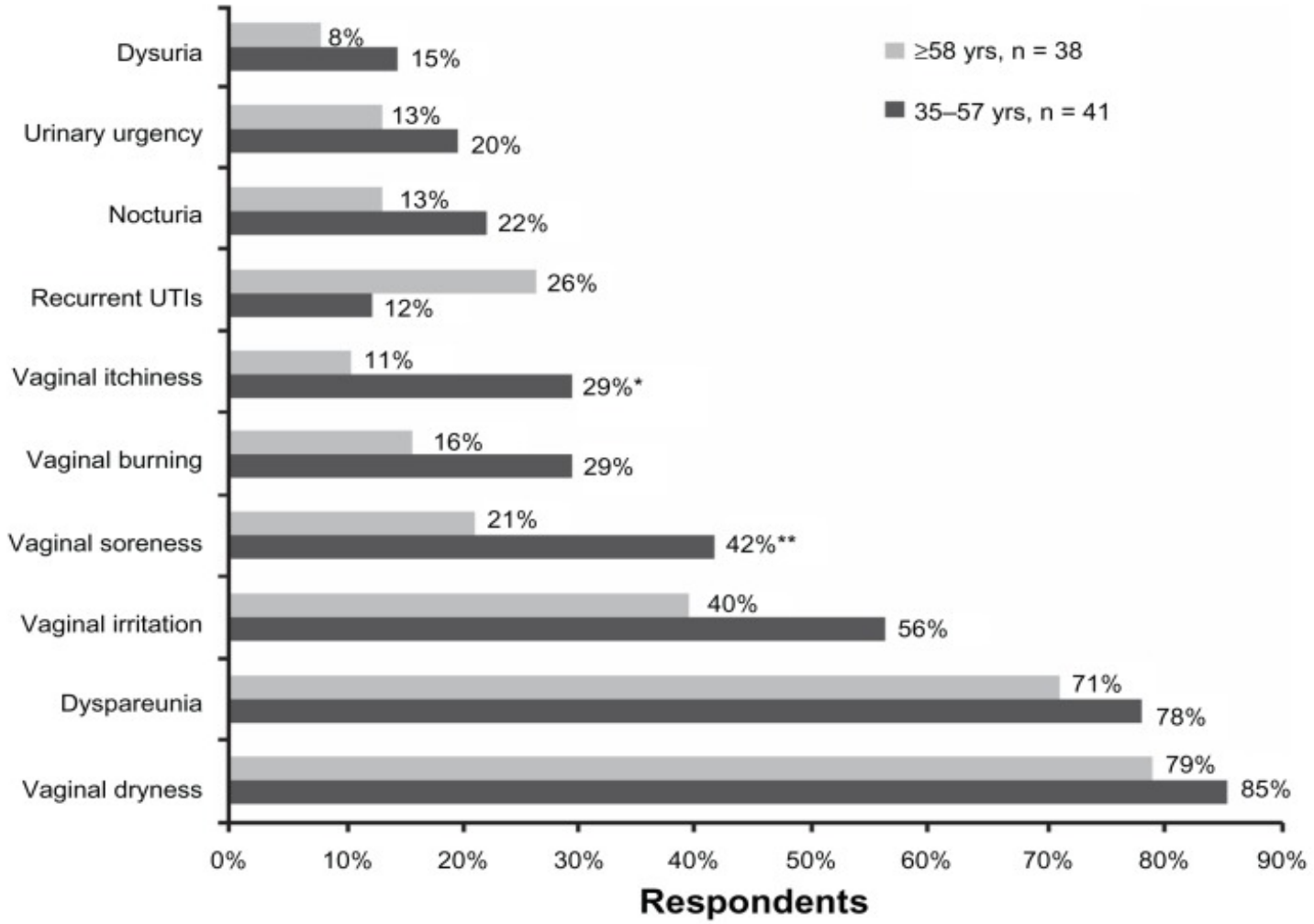
Treft tot 84% van de vrouwen 6 jaar na de menopauze

(Maturitas 2016; 83: 40-4)

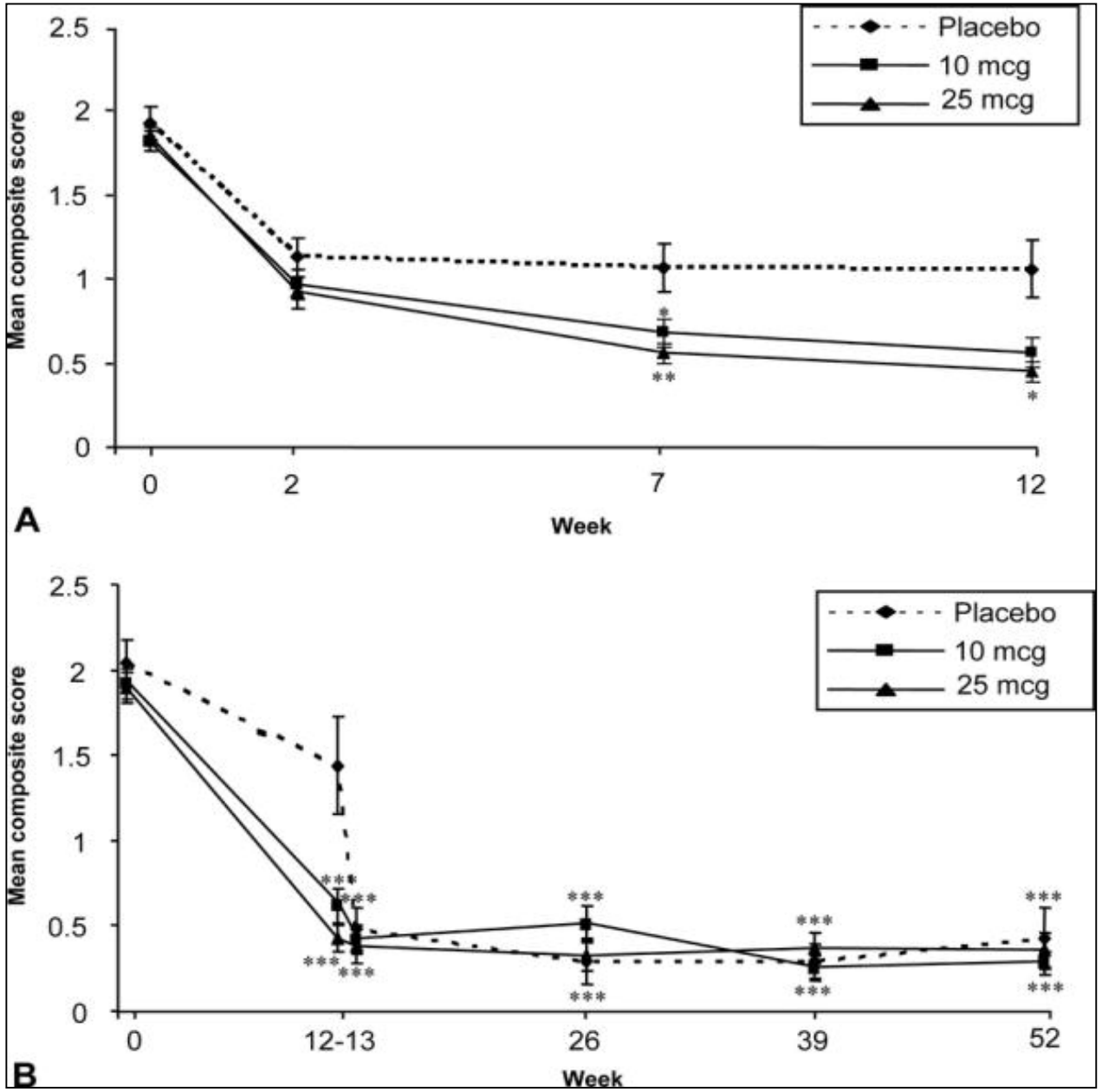
Gabes et al.

Menopause 26(11):1342-1353, 2019.

Genito-urinary syndrome of menopause: genital and sexual symptoms prevail

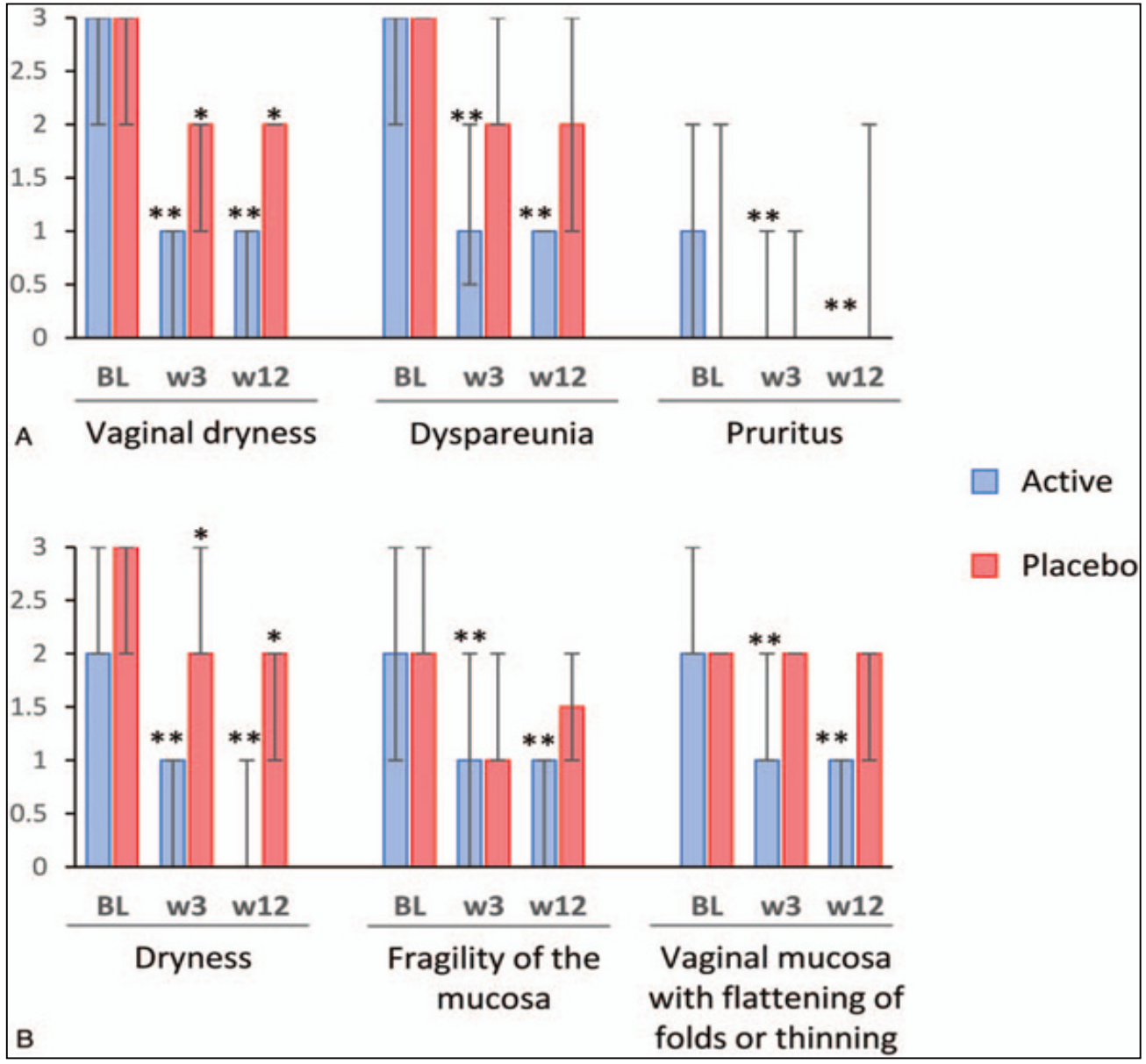


Int J Womens Health 2013; 5: 133-9



Efficacy of low-dose estradiol vaginal tablets in the treatment of atrophic vaginitis: a randomized controlled trial.
Bachmann et al. Obstetrics & Gynecology. 111:67-76, 2008.

Relief of vaginal symptoms. Mean score of **three symptoms (vaginal dryness, soreness, and irritation)**, as assessed by participants, over time. A. Twelve-week randomized study (N=230 participants). * PPP values describe changes from placebo. B. Fifty-two-week extension study (N=102 participants after switch to 25 mcg estradiol). *** PP values describe changes from baseline.

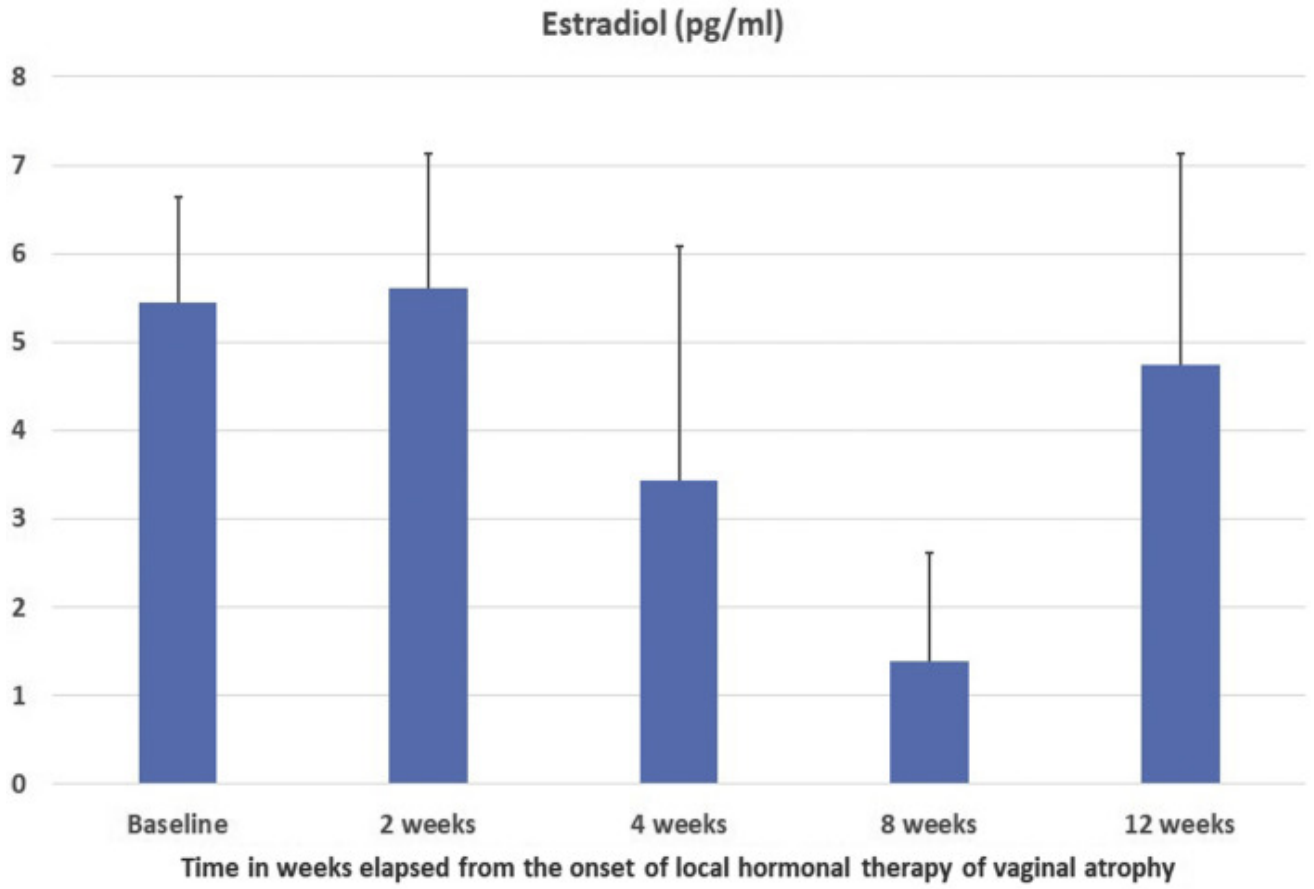


Efficacy and safety of **ultra-low dose 0.005% estriol vaginal gel** for the treatment of vulvovaginal atrophy **in postmenopausal women with early breast cancer treated with nonsteroidal aromatase inhibitors**: a phase II, randomized, double-blind, placebo-controlled trial. Hirschberg et al, Menopause 27:526-34, 2020.

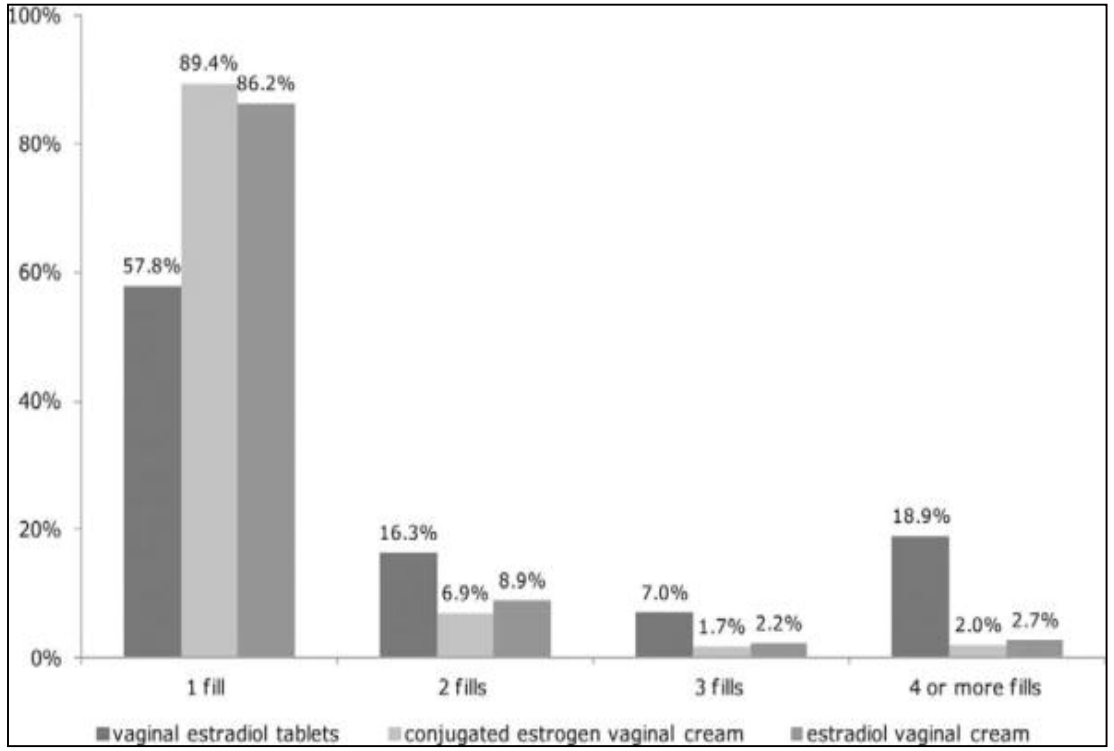
Columns and error bars represent median and IQR, respectively. Symptoms/signs severity are presented on a 0-3 scale: 0 = lack of symptoms/signs, 1 = mild, 2 = moderate, and 3 = severe.
BL, baseline; IQR, interquartile range; w, week. **P 0.001, *P 0.05 for differences between baseline and the given visit.

Safety of local hormonal treatment in women with ER-positive breast cancer who are on adjuvant aromatase inhibitor therapy: meta-analysis.

(Clin Breast Cancer 2019; 19: e731-40)



- No increased risk of endometrial hyperplasia after 52 weeks (clinical trials)
- No increased risk of endometrial or breast carcinoma (observational studies)

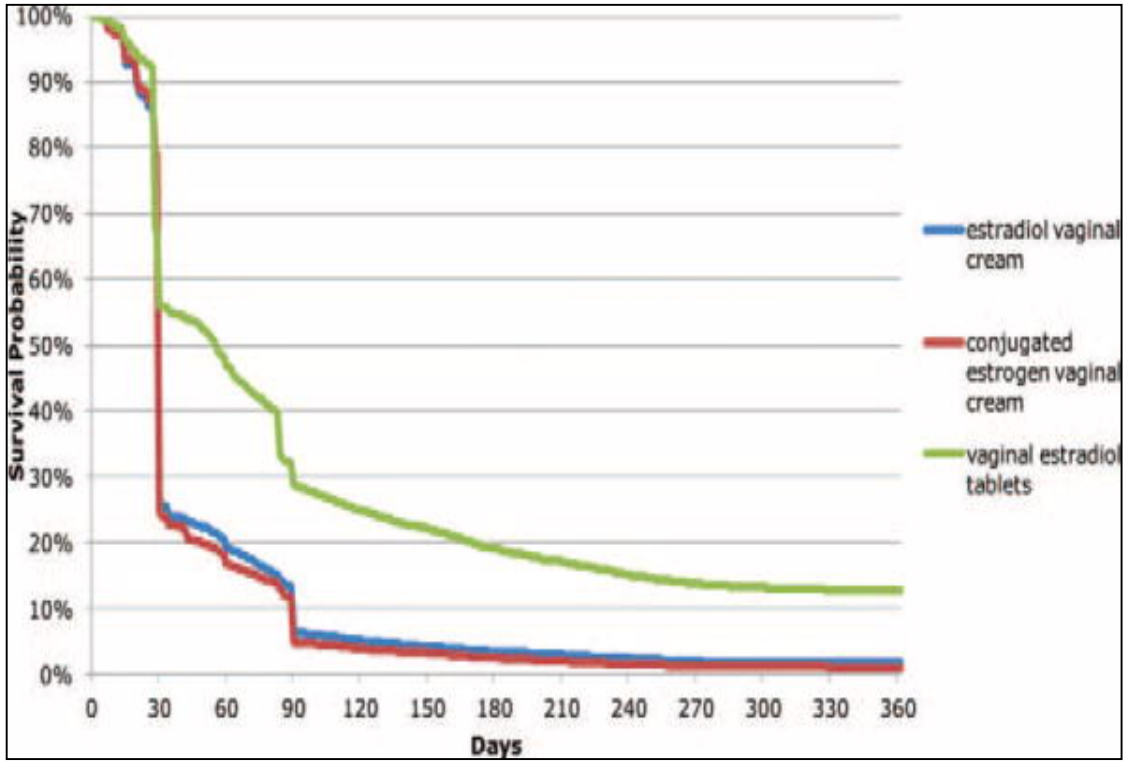


▲ Number of prescriptions filled for local estrogen therapy during the 12-month follow-up period

►Kaplan-Meier analysis of discontinuation with local estrogen therapy

Overall 12-month compliance: 12.9% vaginal estradiol tablets; 1.1% conjugated estrogens cream; 1.8% estradiol vaginal cream

One-year treatment persistence with local estrogen therapy in postmenopausal women diagnosed as having vaginal atrophy.
Portman et al. Menopause 22:1197-1203, 2015.



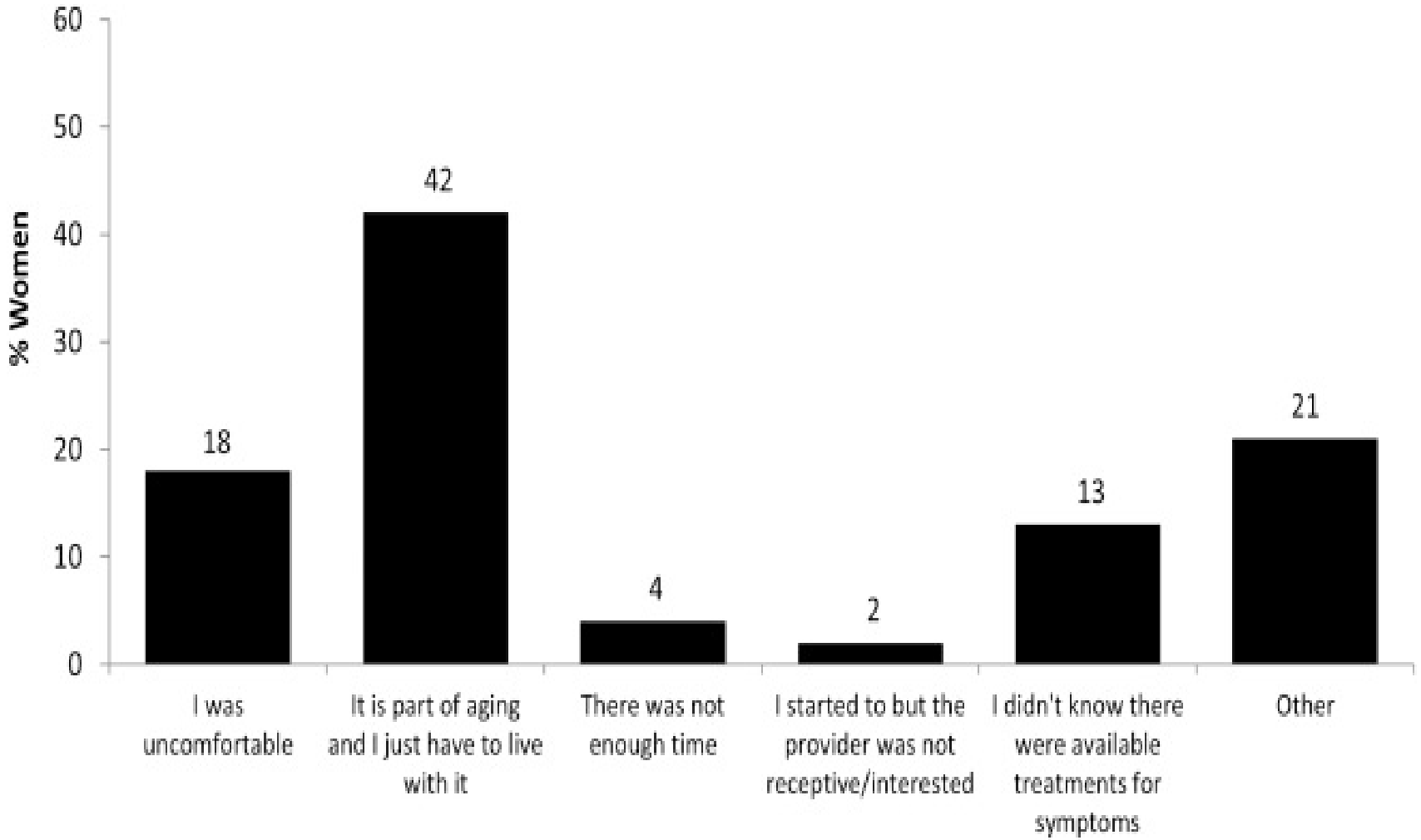
►Goudenstandaardbehandeling is topische oestrogeentherapie: waarom is het gebruik ondermaats??

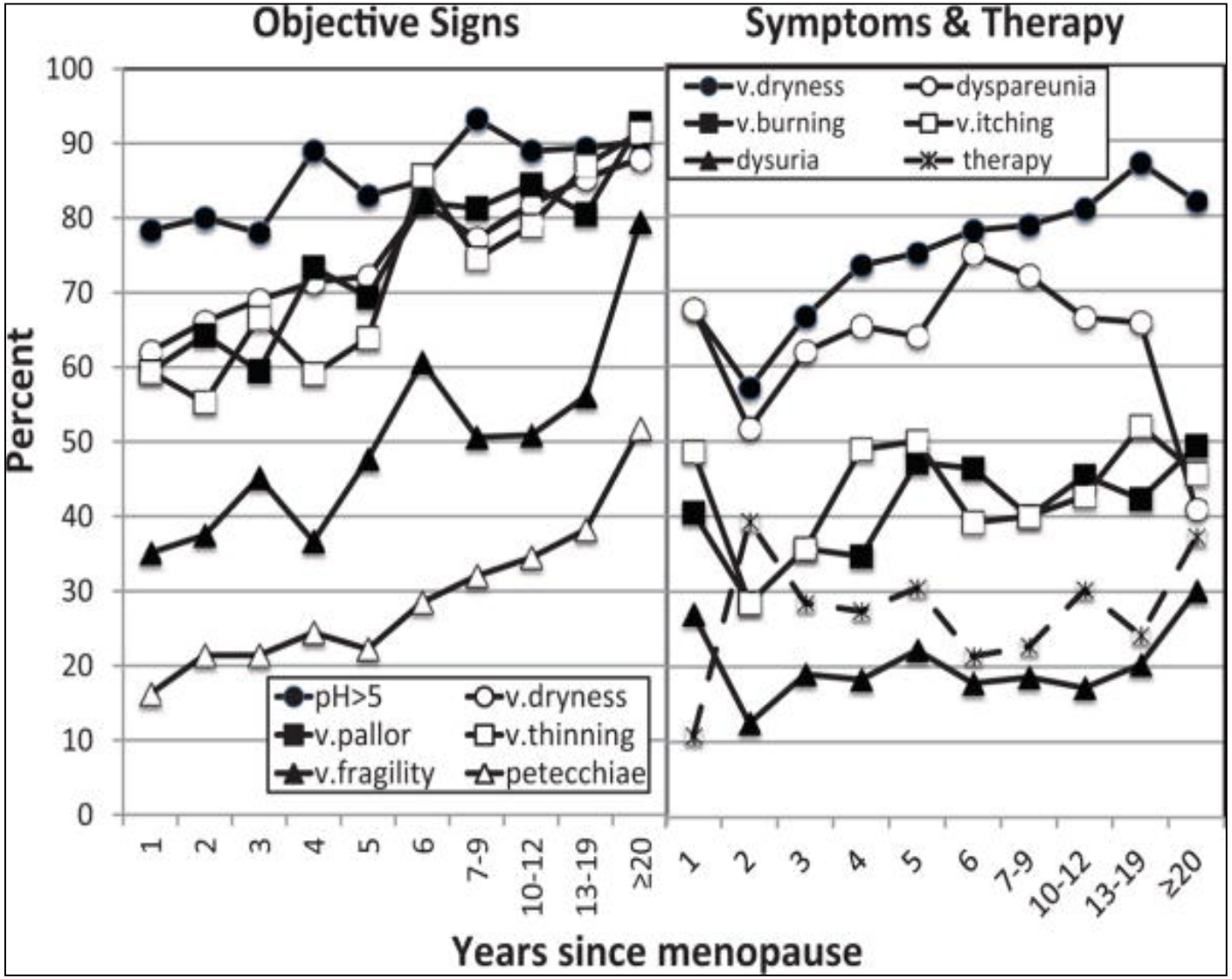
- GSM assessment:
  - drempels vanwege de patiënt/ zorgverlener/ interactie
  - subjectieve symptomen correleren slecht met ‘objectieve’ tekens
  - dyspareünie is een paraplu-term voor seksuele disfunctie, relatieproblemen, hormonale disfunctie
- Behandeling

Drempels bij het bespreken van de vulvovaginale gezondheid: Women's EMPOWER Survey

(1858 vrouwen met symptomen in USA, 45-90 jaar, "representatief" monster van bevolking)
(J Sex Med 2017; 14: 413-24)

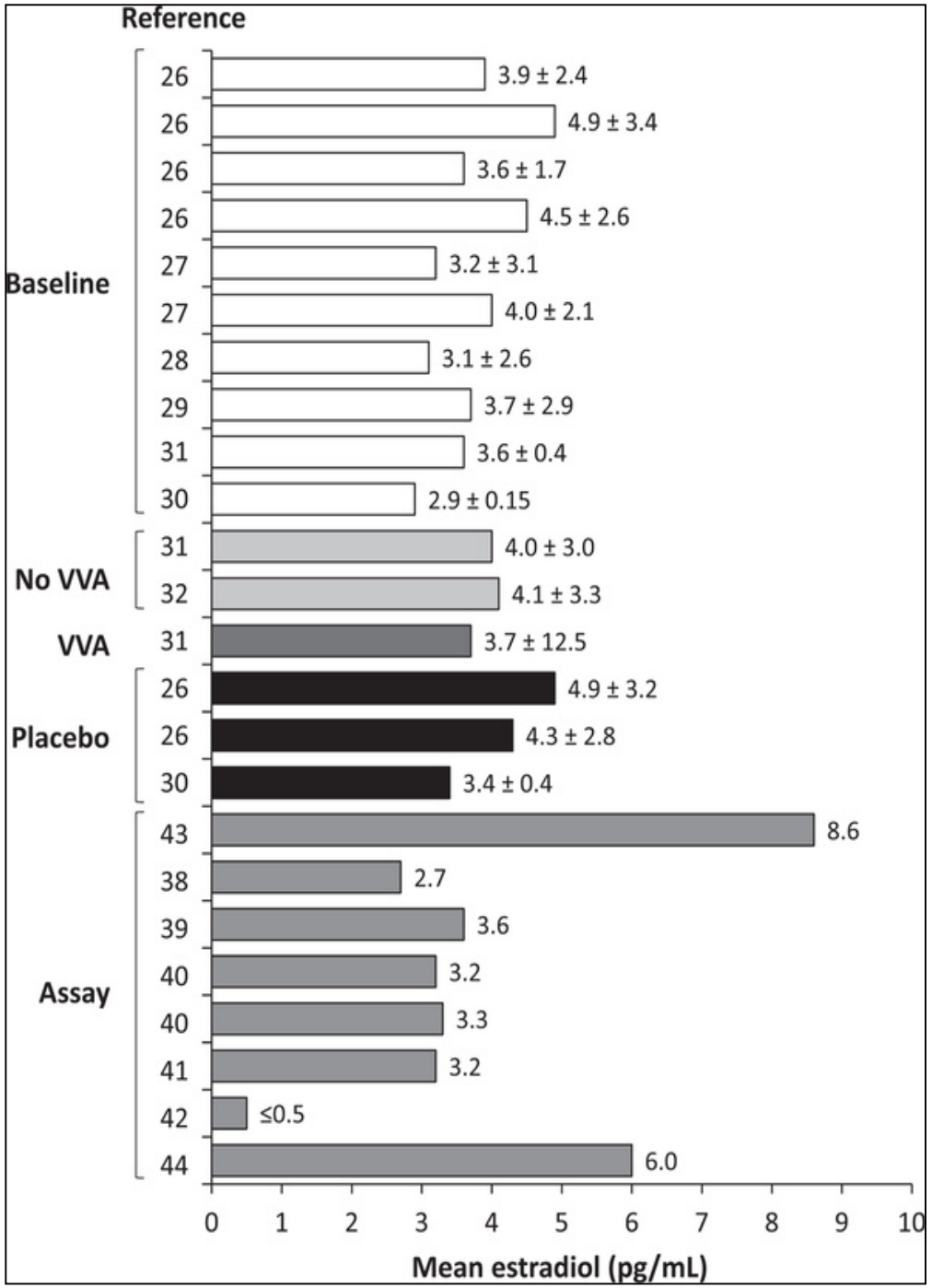
Redenen om vaginale gezondheid niet te bespreken met hulpverlener (n = 1046 = 56%)





Prevalence and association between objective signs and subjective symptoms of vaginal atrophy: the AGATA study.
Cagnacci et al, Menopause 23: 1139-45, 2016.

Poor concordance between objective signs and patient-reported symptoms!



Santen et al.
Menopause. 27: 361-70, 2020

Serum estradiol levels (mean +/- SD) in postmenopausal women before vaginal therapy administration or with placebo, or untreated used as a control (without or without VVA), or those from assay validation studies; only studies using MS-based assays were included.
VVA, vulvar and vaginal atrophy.

Dyspareünie als paraplu-term voor seksuele-responsdisfunctie (SRD) in de algemene praktijk
SRD bij vrouwen vs. mannen: populatiestudies

- SRD neemt toe met de leeftijd zowel bij vrouwen als bij mannen
- 1992 US probability sample[1] 1749 ♀ en 1410 ♂ van 18-59 jaar

  - SRD bij 43% van ♀ vs. 31% van ♂
- 2004 US probability sample[2] 1550 ♀ en 1455 ♂ van 57-85 jaar

    - % seksueel actief over ganse lijn lager bij ♀ dan ♂
    - % seksueel actief daalt sneller bij ♀ (ten dele door leeftijdsverschil)
    - 35% van ♀ vindt seks “totaal niet belangrijk” vs. 13% van ♂
    - maar evenveel ♂ als ♀ (~50%) rapporteert 1 of meerdere “problemen”

1 Laumann et al., JAMA 1999; 281: 537-44
2 Lindau et al., N Engl J Med 2007; 357: 762-74

Mogelijke oplossingen 1
Assessment van GSM

- Speciale GSM/WHS raadplegingen, patient education tools: “alles is bespreekbaar”

  cf. ervaring van menopauzeconsultaties: “women seek care for a broad range of concerns that are not typically in gynecologists’ scope of practice” (J Womens Health 2014; 23: 513-8)
- Algemene seksuele disfunctie screening is nuttig, ihb naar HSDD (hypoactive sexual desire disorder)
- Hormonale evaluatie kan nuttig zijn, ihb diagnose van female androgen insufficiency

Decreased sexual desire screener (DSDS)

Clayton et al, J Sex Med 2009; 6: 730-8

1. Was u vroeger tevreden over uw gehalte van seksuele zin en interesse? Ja/Nee
2. Is uw gehalte van seksuele zin en interesse gedaald? Ja/Nee
3. Vindt u dat erg? Ja/Nee
4. Zou u graag een hoger gehalte van seksuele zin en interesse hebben? Ja/nee
5. Zijn er factoren die hiertoe zouden kunnen bijdragen, zoals
    - een operatie, een ziekte, een ongeval, een depressie
    - medicatie, alcohol, andere drugs
    - (zwangerschap, bevalling), menopauzale klachten
    - pijn, verminderde opwinding of orgasme
    - seksuele problemen bij uw partner
    - ontevredenheid over uw relatie
    - stress of vermoeidheid

1-4 Ja, 5 negatief: veralgemeende verworven HSDD (hypoactive sexual desire disorder)

1-4 Ja, 5 positief: sluit andere oorzaak uit

Female androgen insufficiency: Princeton consensus

(Fertil Steril 2002; 77: 660-5)

- Symptomen:

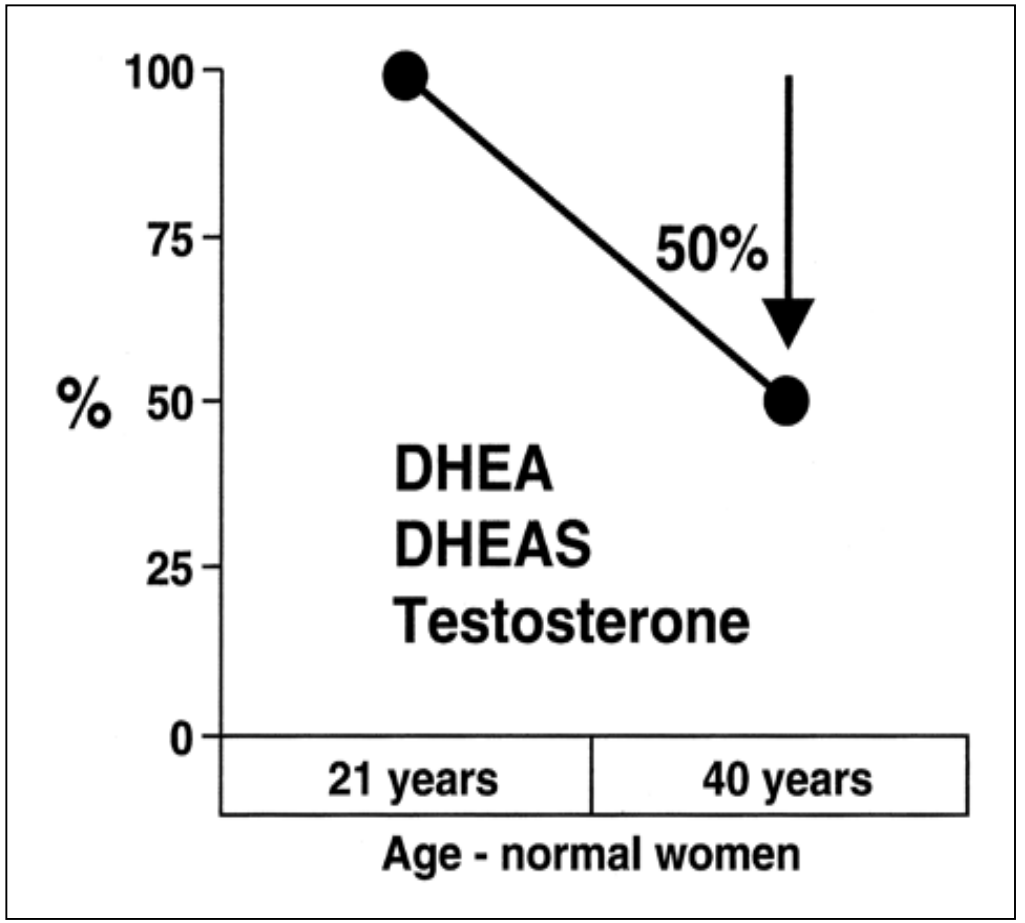
- verminderd welbevinden en neerslachtige stemming

- blijvende onverklaarde vermoeidheid

- verminderde seksuele interesse

- Omdat oestrogenen ook een invloed hebben op stemming en seksuele respons, kan de diagnose alleen gesteld worden bij vrouwen met adequate oestrogenisatie

- Vrije testosteronwaarde ≤ 25ste percentiel van normale waarden bij vrouwen tussen 20 en 40 jaar



Waarom is GSM onderbehandeld?

- Assessment
- Behandeling:

  - onaangepaste bijsluiter → ‘vlucht’ naar compounded creams (US) en zeer lage persistence
  - vaginale toediening → lagere adherence, persistence en tevredenheid
  - nevenwerkingen, kost → lagere persistence en tevredenheid
  - onduidelijk eindpunten: wat willen we behandelen?
  - vulva en vagina hebben verschillende hormonale regulatie en mogelijke behandeling:

    androgenen zijn belangrijker voor de vulva

Waarom is GSM onderbehandeld?

- Behandeling:

SLECHT AANPASBAAR	AANPASBAAR
- bijsluiter	- beperking op magistrale bereidingen zonder bijsluiter
- vaginale toediening	- betere eindpunten in klinische studies
- duur en kost van de behandeling	- breder scala aan agentia: androgene metabolieten

NAMS Working Group on Women's Health and Well-Being in Menopause:
"Why the product labeling for low-dose vaginal estrogen should be changed."
Menopause 2014; 21: 911-6

North American Menopause Society (Menopause 2020; 27: 611-3):

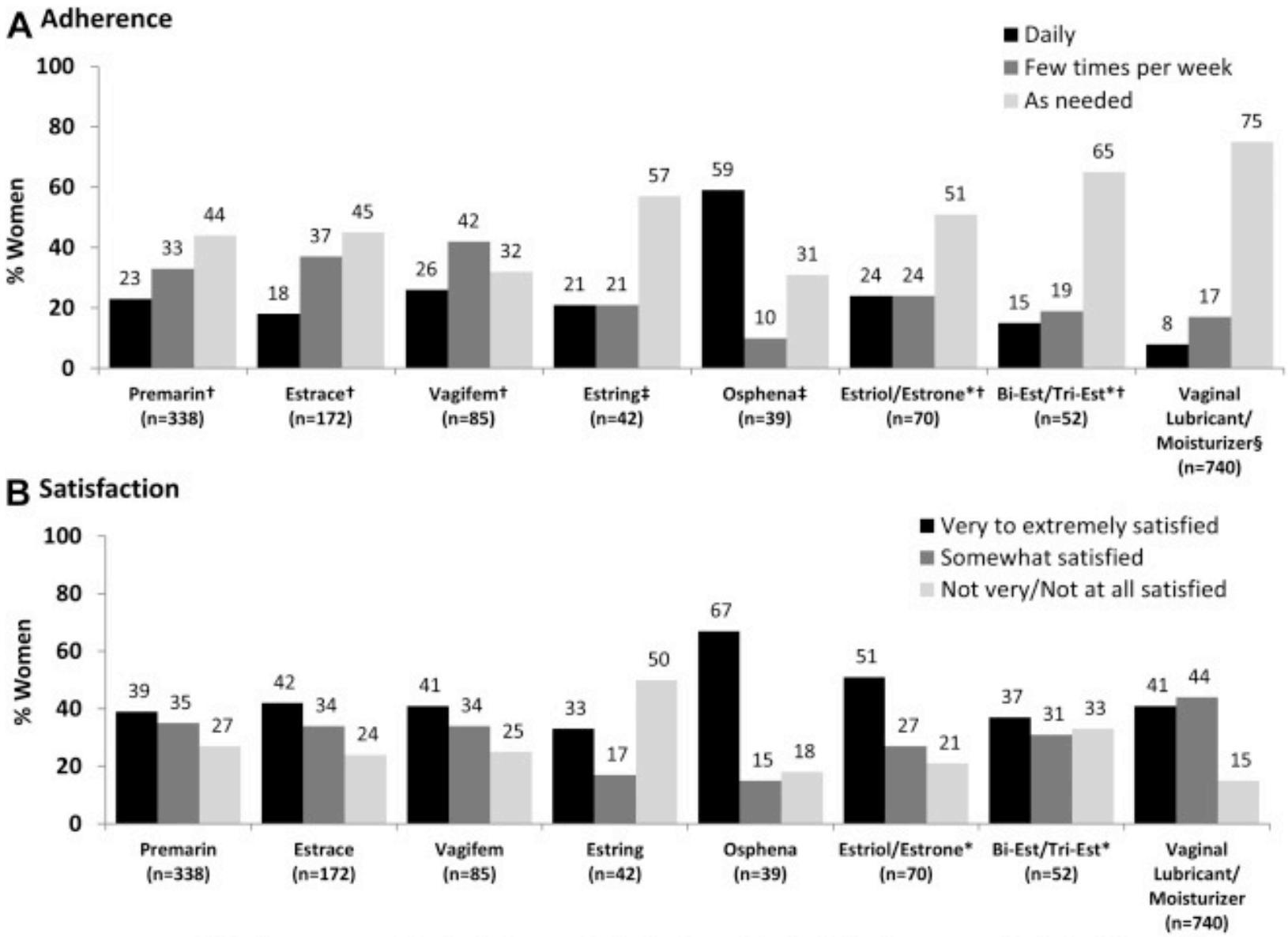
"…. many women have reported being frightened to use safe-and-effective methods to treat GSM because of fear that vaginal estradiol is unsafe, based on "black box warning" …. They are often confused about the difference between systemic HT risks and the distinctly different risks associated with low-dose vaginal therapies".

NAMS recommendations:

- ►Remove the black box warning in the Warnings and Precautions section
- ►Women must be prepared for the boxed warning

NAMS Applauds NASEM Efforts on Compounded Bioidentical Hormone Therapy

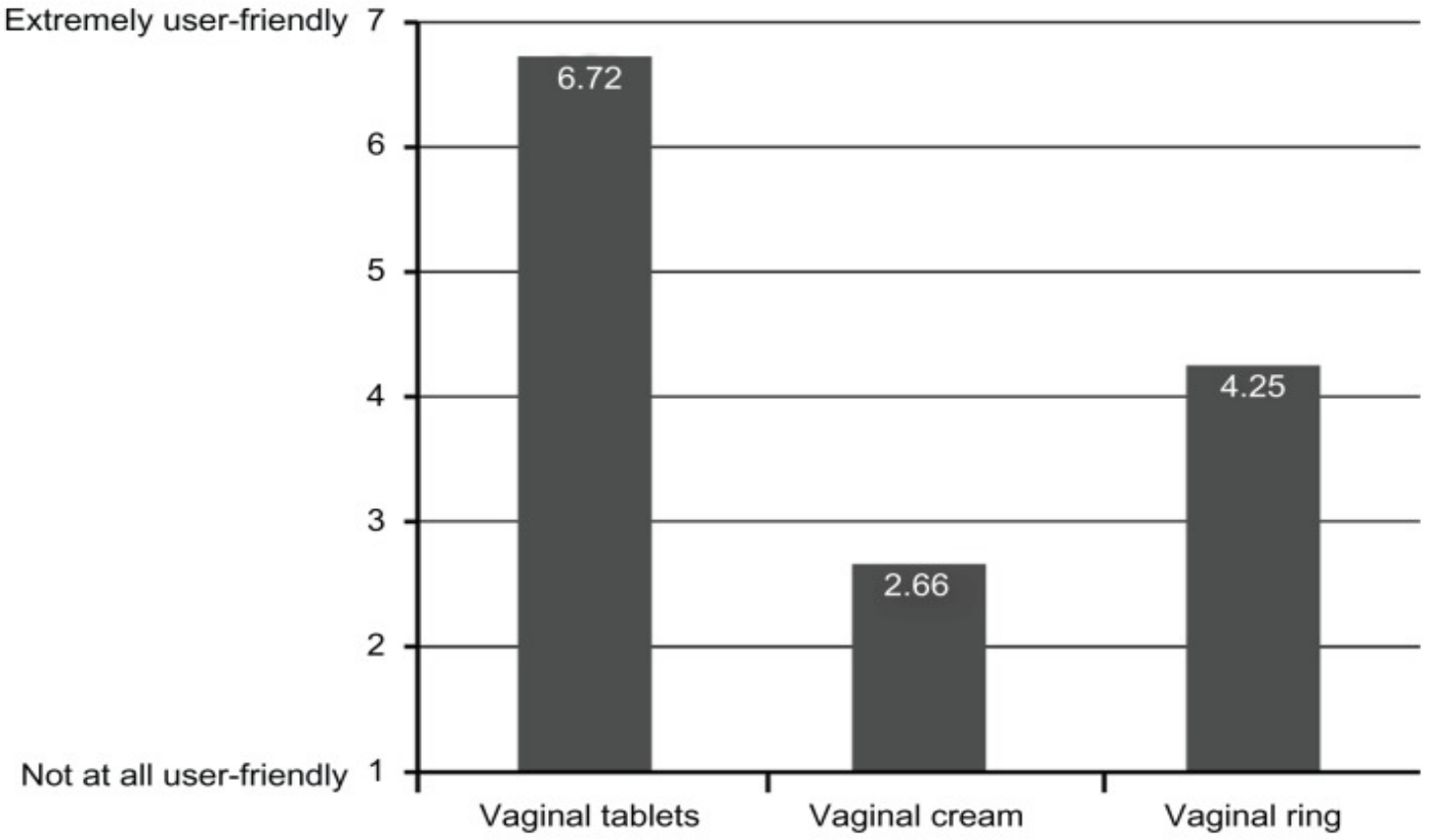
Women's EMPOWER Survey: better adherence and satisfaction with ospemifene (=oral agent)



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

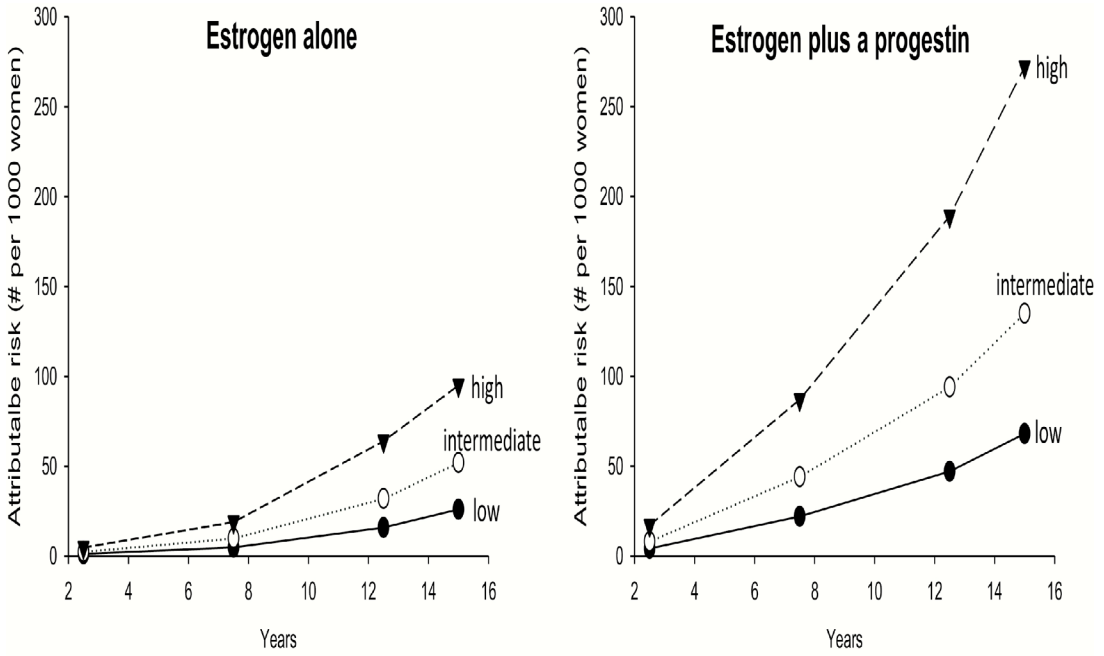
User-friendliness ratings of vaginal estrogen formulations: women don’t like creams

Int J Womens Health 2013; 5: 133-9



Cave alternatief van ORALE oestrogeen-alleen therapie indien uterus in situ, ook met ‘veilige’ oestrogenen als oestriol (E3) of estetrol (E4): risico’s van systeemtherapie blijven

- Met oraal oestriol 2 mg:
  - Risico van bloeding 14%*
  - Risico van endometriumpoliepen 14%**
- Risico’s op trombose (korte termijn) en borstcarcinoma (>10 jaar, afhankelijk van basaal risico)



*Takahashi et al, Maturitas 2000; 34: 169-77

**Granberg et al, Maturitas 2002; 42: 149-56

Ongoing discussie over zinvolle eindpunten in GSM/HSDD klinische studies

- GSM:

Traditioneel (FDA, 2003): verandering in “most bothersome symptom” +

2 objectieve parameters: vaginale pH, verandering in cytologische maturatie index

Meer zinvol: patient-reported outcomes (PRO), vooral seksueel functioneren en ‘zelf-concept’/lichaamsbeeld*

- Hypoactive sexual desire disorder (HSDD):

Traditioneel (FDA, EMA): aantal “satisfying sexual events”, dagboek

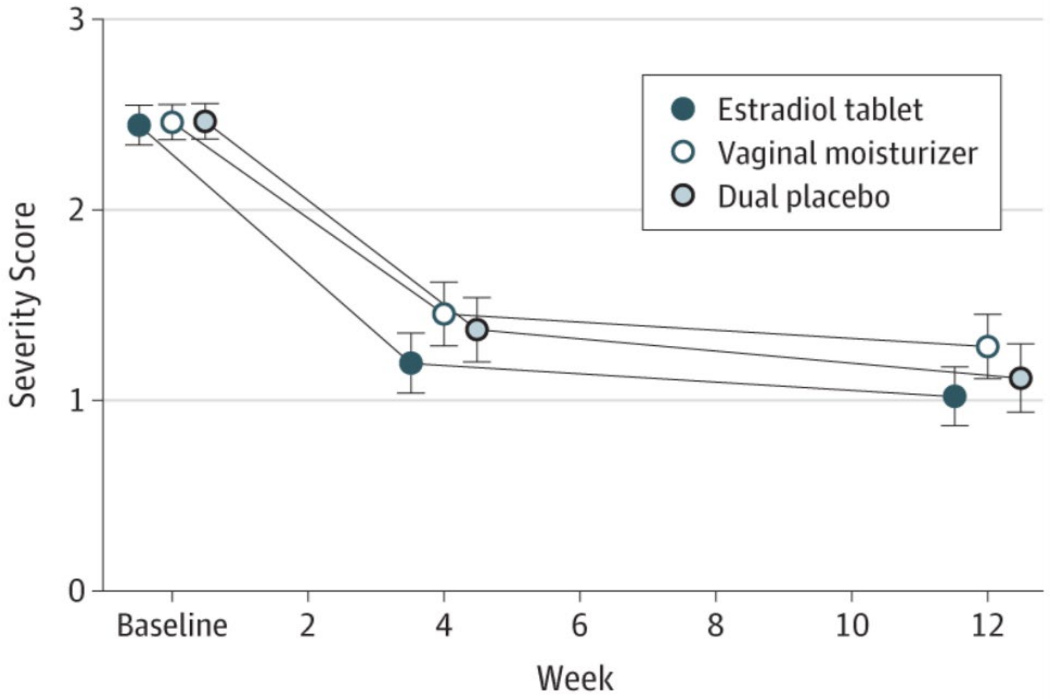
Meer zinvol (FDA): PRO, vooral distress veroorzaakt door HSDD

*Gibson et al, Am J Obstet Gynecol 2020; 99.e7; Christmas et al, Menopause 2020; 27: 1070-80

Efficacy of vaginal estradiol or vaginal moisturizer vs placebo for treating postmenopausal vulvovaginal symptoms and menopause-specific quality of life (MENQOL): a randomized clinical trial (MsFLASH GSM Study)

JAMA Intern Med. 2018; 178: 681-90

Menopause 2018; 25: 1086-93



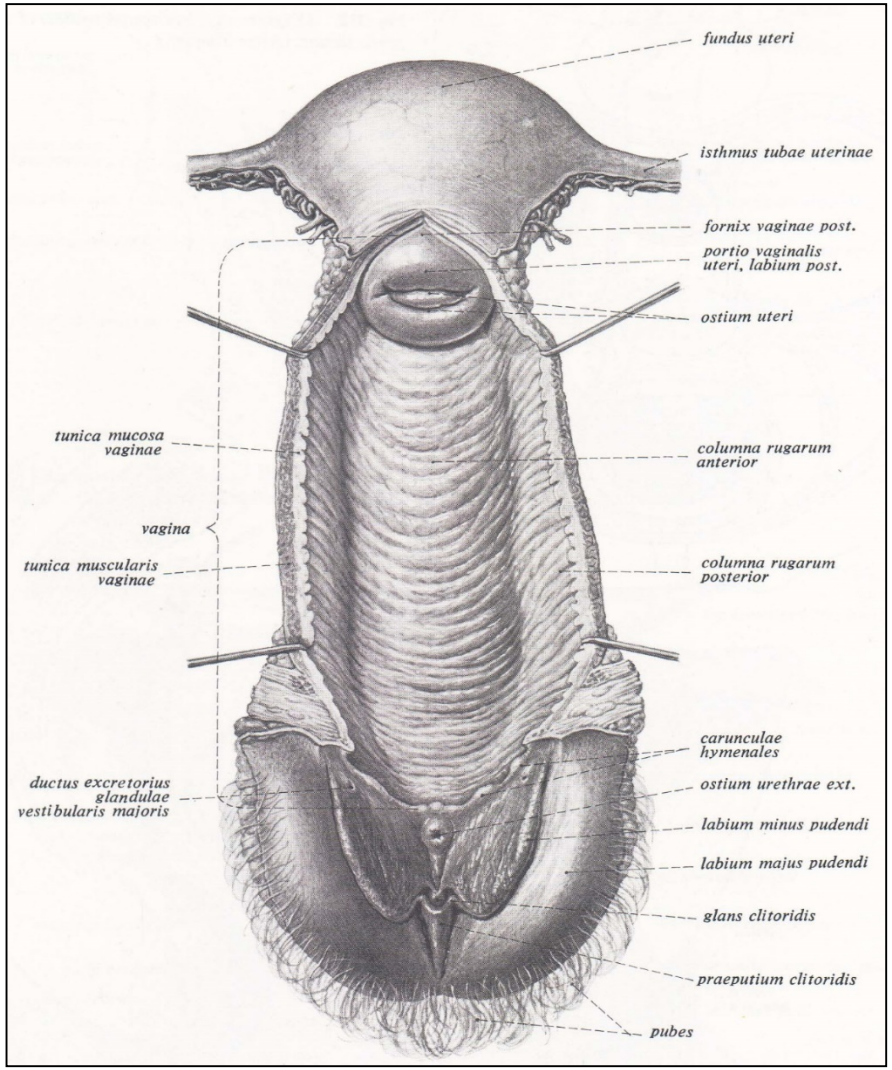
No. at risk			
Estradiol tablet	99	97	96
Vaginal moisturizer	100	97	99
Dual placebo	99	97	95

Most Bothersome Symptom Severity Score Change Over 12 Weeks. There was no significant difference in the change from baseline in severity scores between treatment groups at 4 or 12 weeks (estradiol vs dual placebo, P = .25; moisturizer vs dual placebo, P = .31). Moisturizer = Replens. Placebo = hydroxyethylcellulose gel

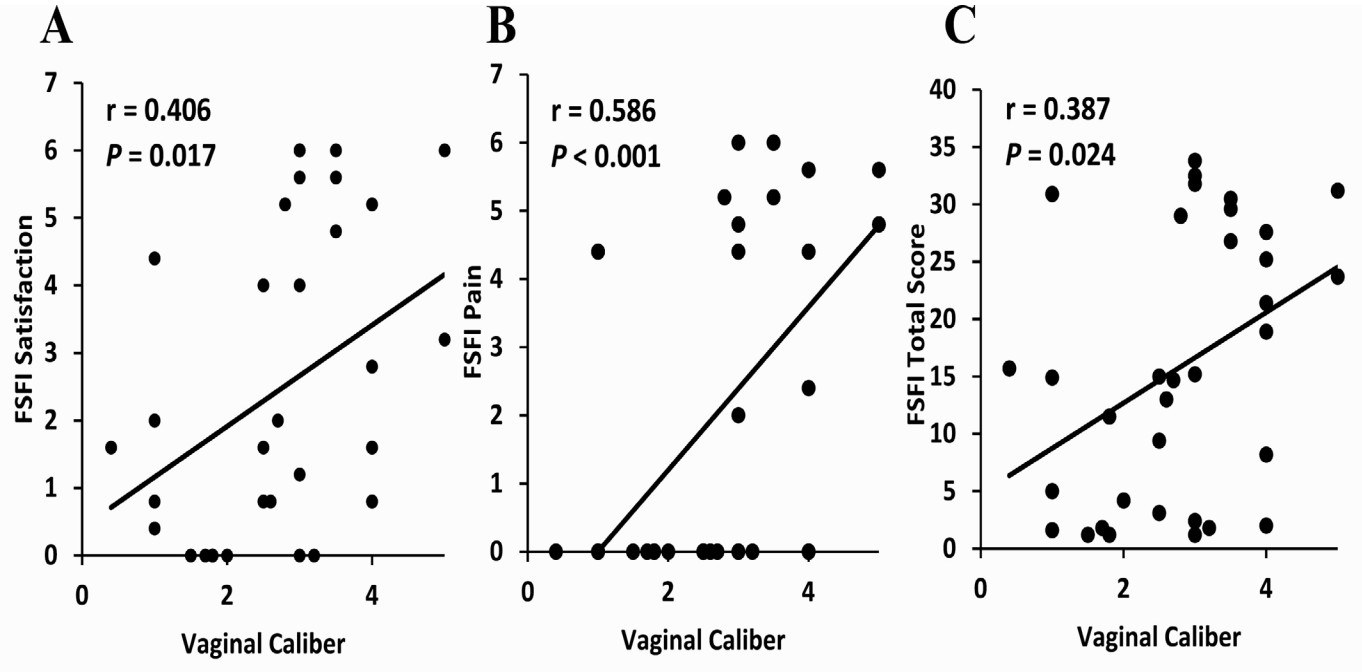
Estradiol tablet improved overall menopause-related quality of life vs. placebo (P = 0.01)

Estradiol tablet improved sexual function domain-related quality of life vs. placebo (P = 0.005)

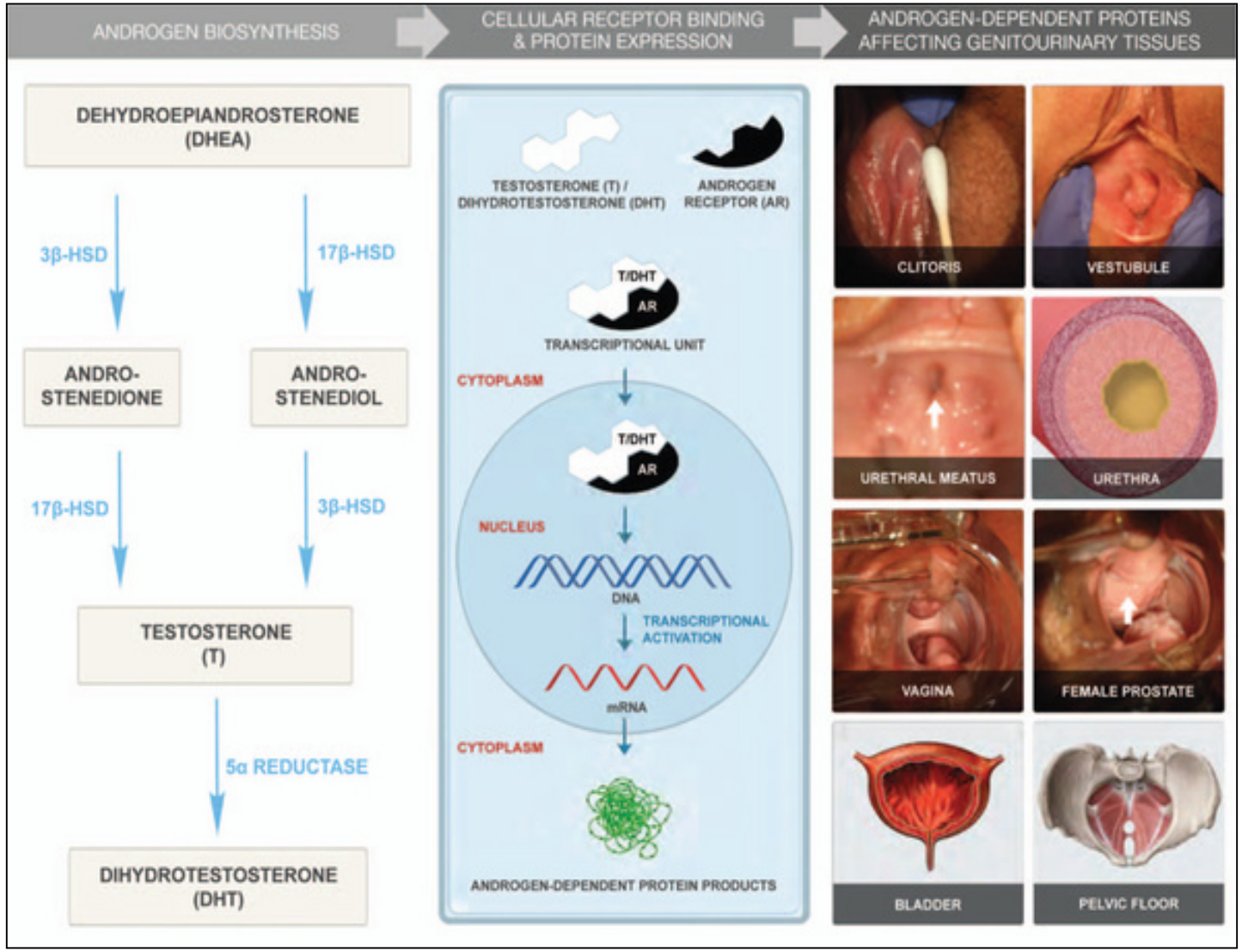
The prime characteristic of the vagina is its elasticity



Relationship between parameters of sexual function and vaginal caliber in women with congenital adrenal hyperplasia who have undergone genital surgery



J. Endocr. Soc., Volume 4, Issue 11, November 2020,



The role of androgens in the treatment of genitourinary syndrome of menopause (GSM):

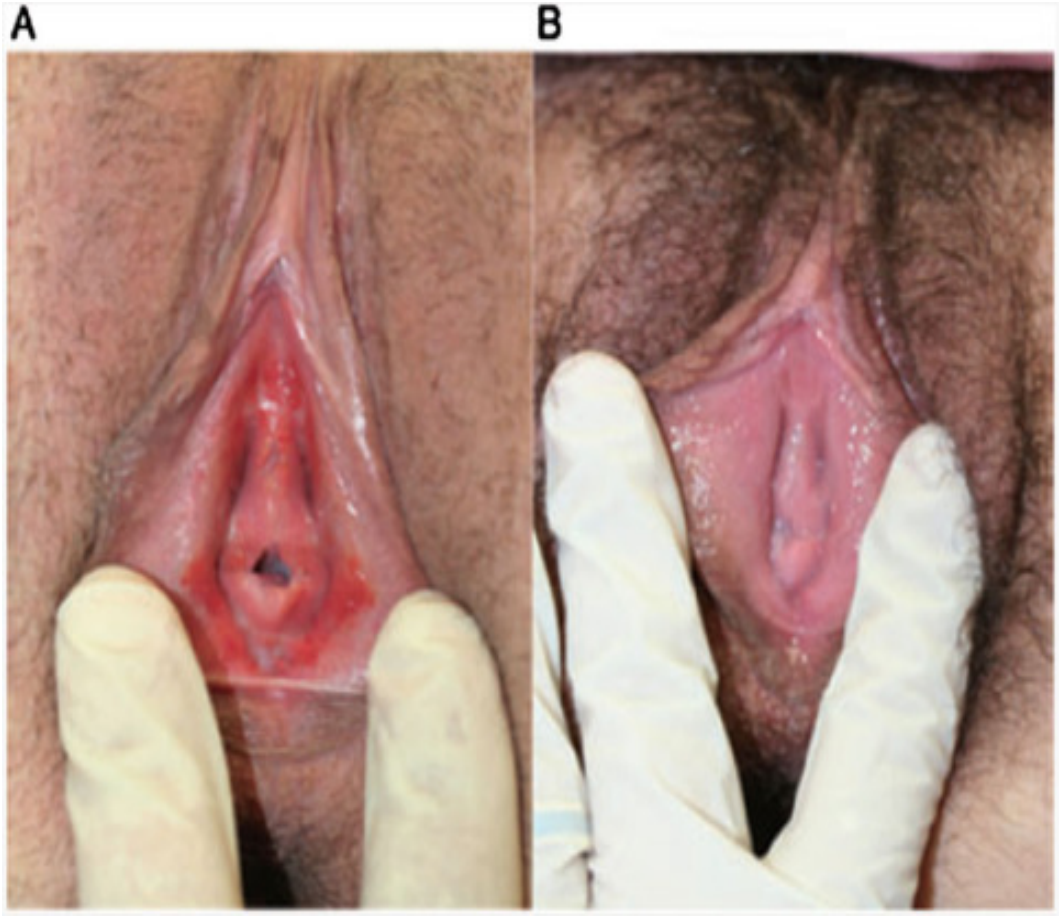
International Society for the Study of Women's Sexual Health (ISSWSH) expert consensus panel review.
Simon et al., Menopause 25: 837-47, 2018.

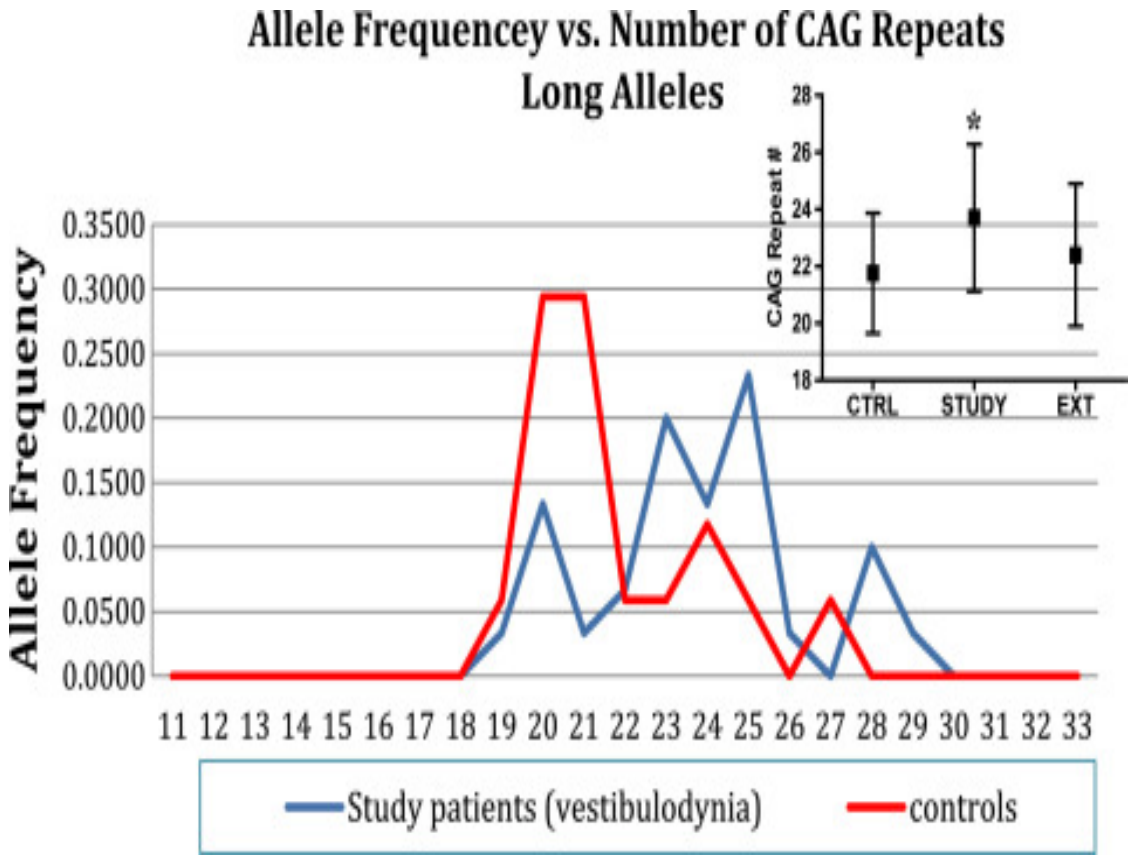
Androgen biosynthesis is depicted in the left panel; cellular receptor binding and protein expression is depicted in the center panel; photographs and illustrations of androgen dependent genitourinary tissues of menopausal women with GSM after both systemic and local testosterone treatment are depicted in the right panel.
HSD, hydroxysteroid dehydrogenase.

Vulvodynia and androgens:

effect of testosterone (A, B), androgen receptor CAG repeats (right)

Goldstein et al, J Sex Med 2014; 11: 2764-71



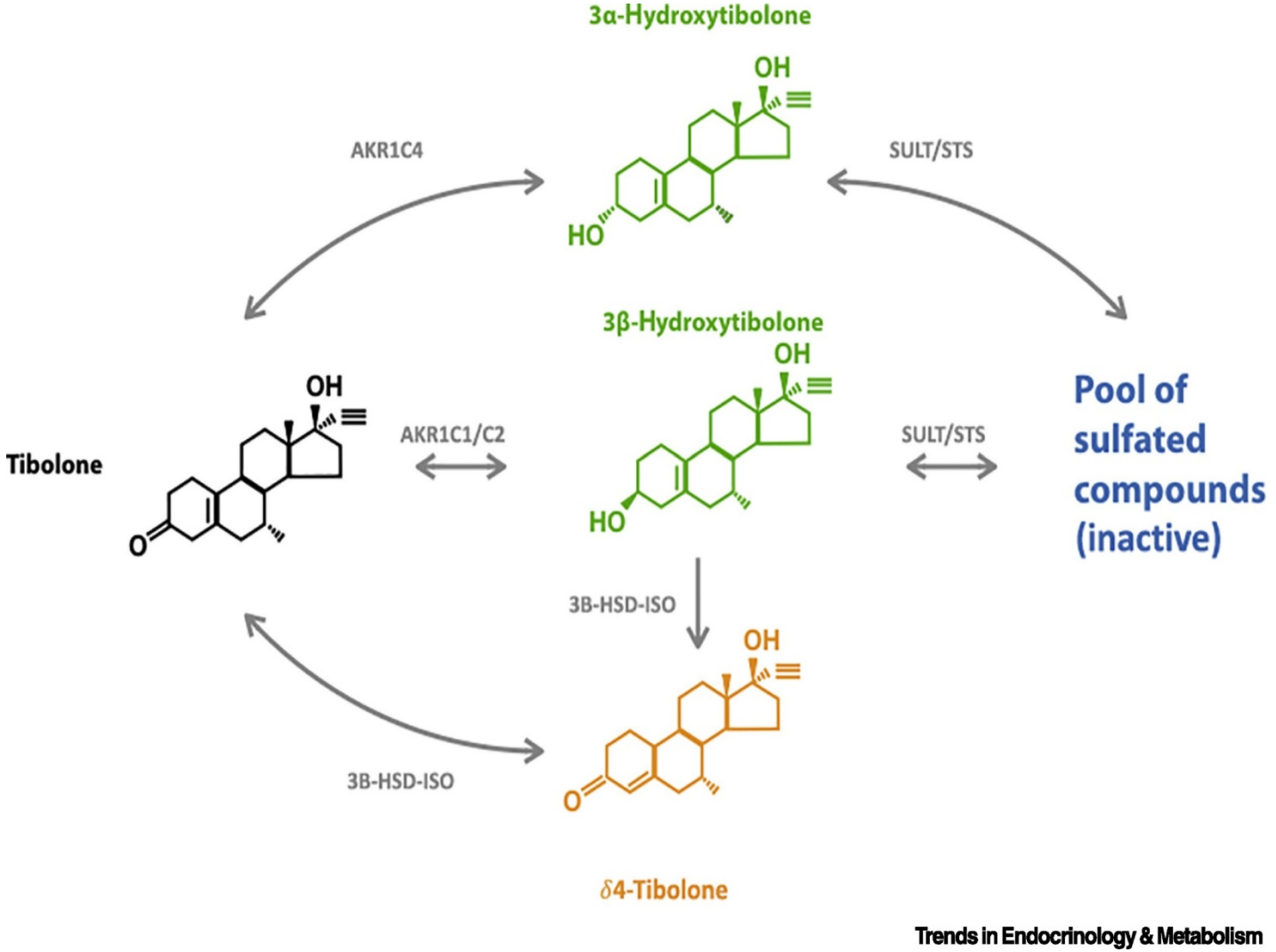


Androgenen als behandeling voor GSM in België: weinig opties

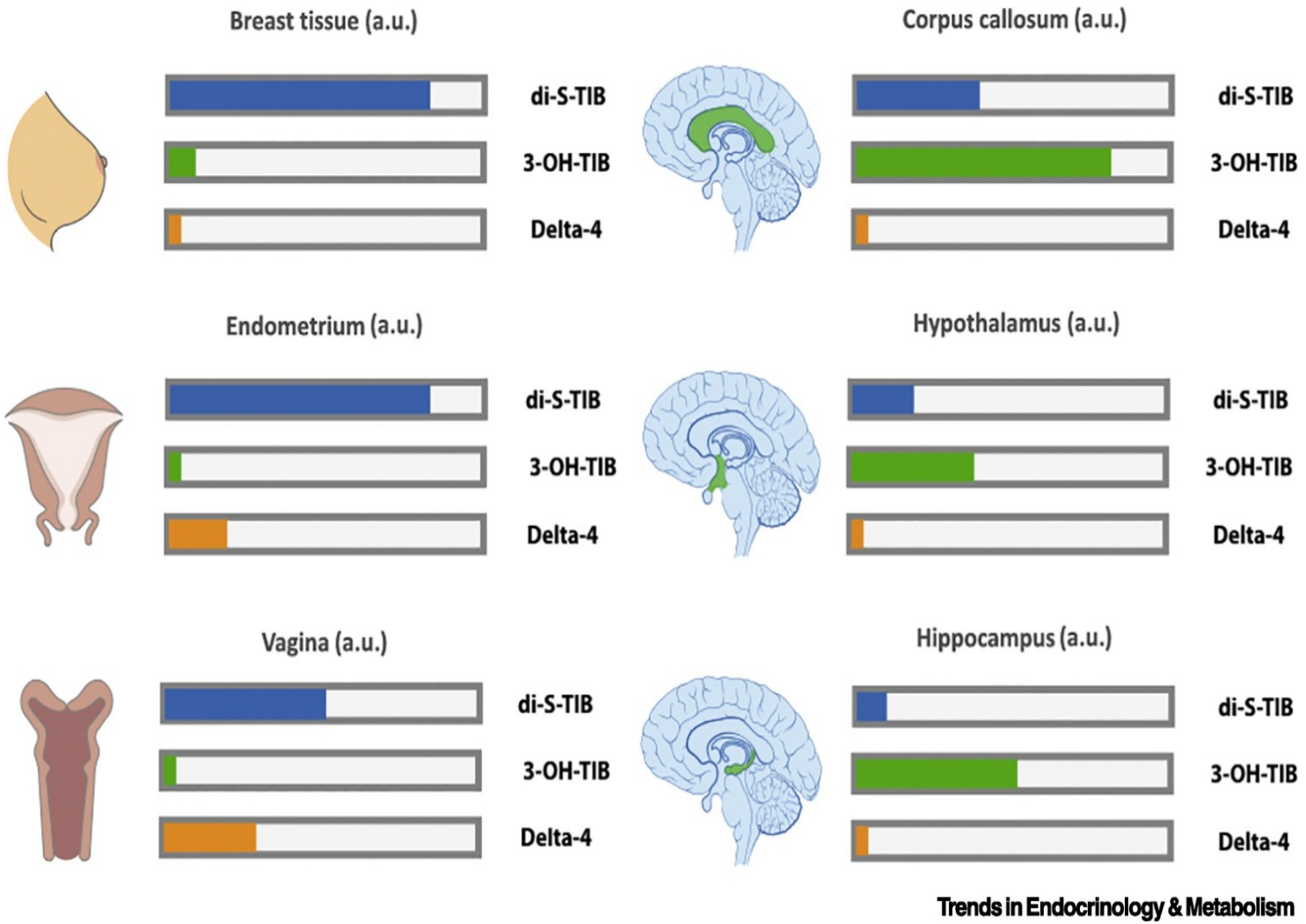
Systemisch:
- tibolon ►►►
- DHEA magistrale gelules*
- testosteron magistrale crème* (1%, 0,5 g/dag op abdomen/dij/billen)

Locaal:
- DHEA ovules

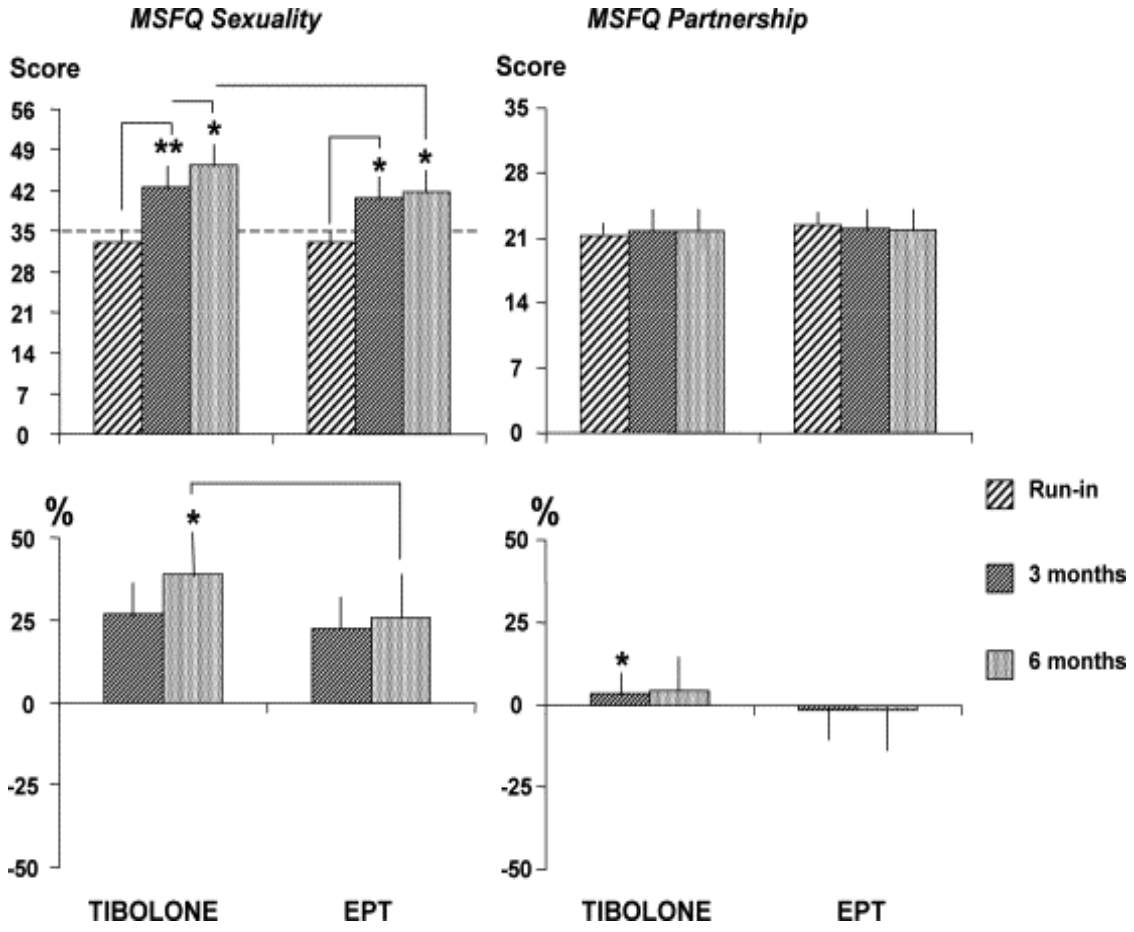
*: geen bijsluiter!



Tissue-specific effect of tibolone: highest androgenic + progestogenic effect (delta-4) in vagina
highest estrogenic effect in brain (3-OH-TIB)
inactive disulfated metabolite (di-S-TIB) highest in breast and endometrium

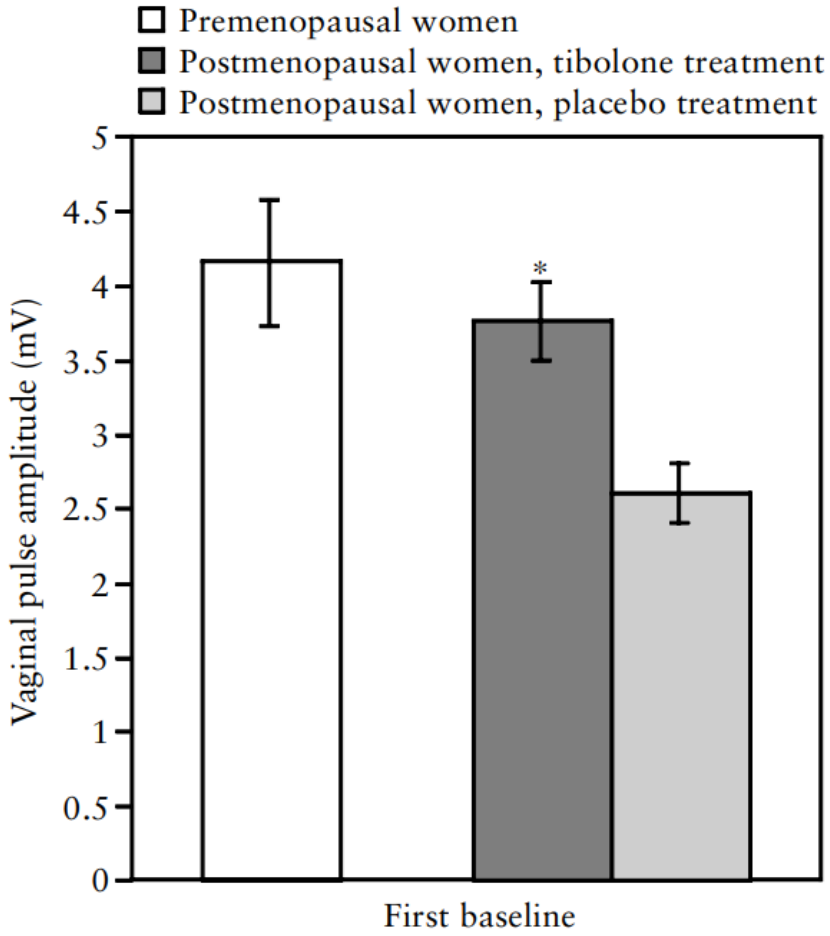


Tibolone: generally positive effects on sexual life



Nappi et al, Maturitas 2006; 55: 288-95

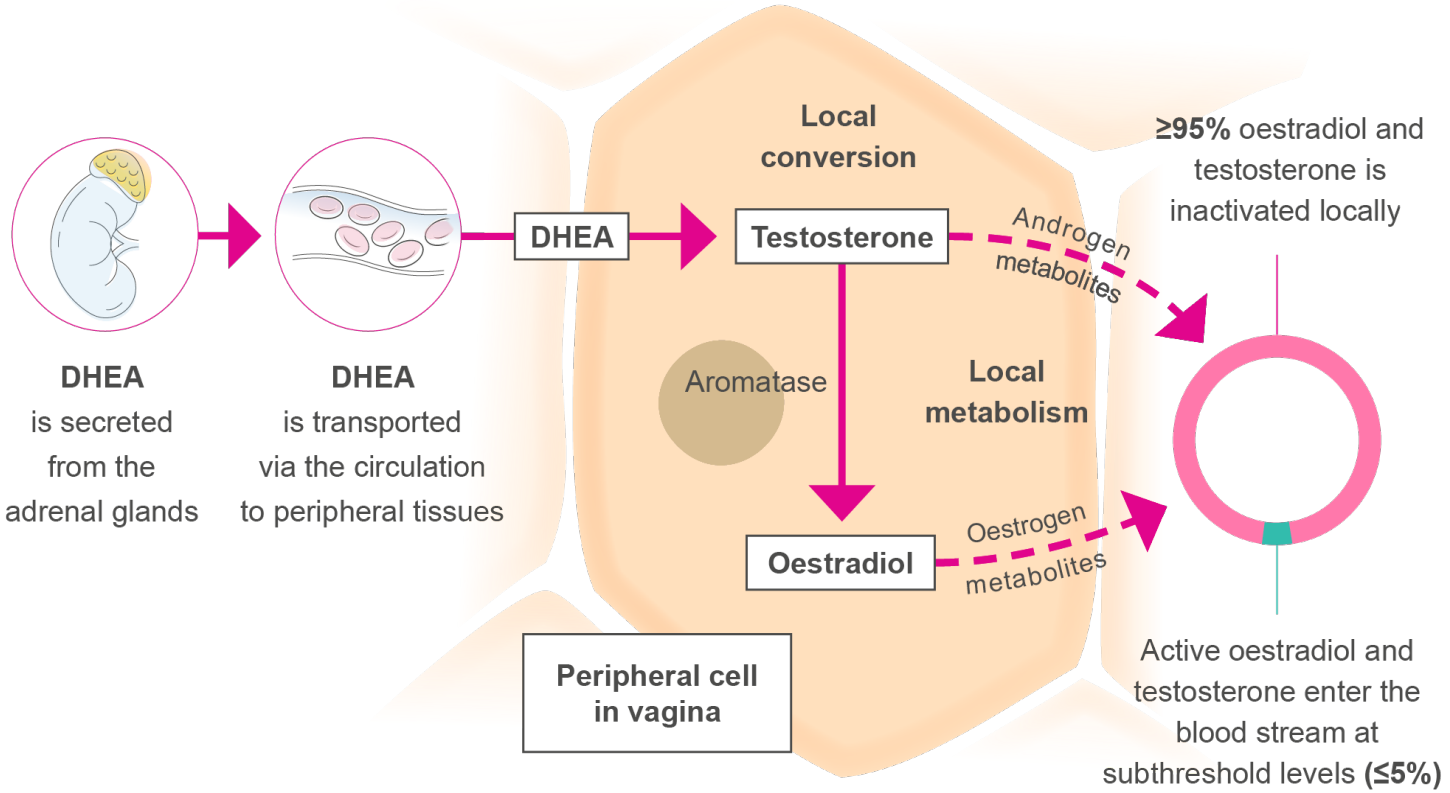
Laboratory conditions:
basal vaginal vasocongestion (VPA) after 3 mo of tibolone



Laan et al, Climacteric 2001; 4: 34

Vaginal DHEA (prasterone): intracellular conversion of DHEA → activation of the vaginal androgen and estrogen receptors[1]

- ≥95% of oestradiol and testosterone in the peripheral cell is inactivated locally
- A very small amount of active sex steroid diffuses into the blood and remains at biologically inactive levels



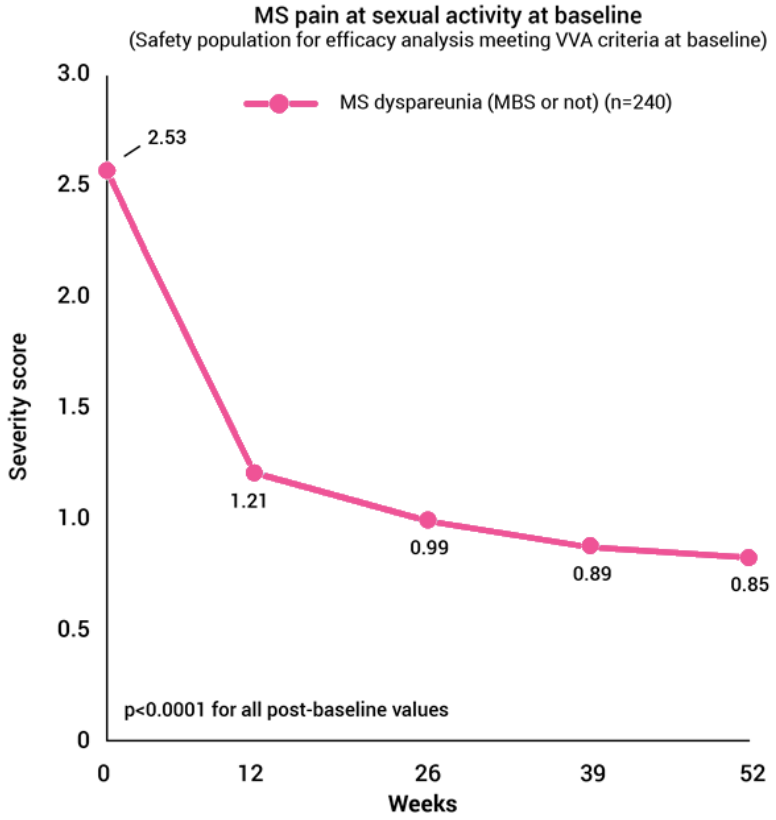
Adapted from Labrie F et al, 2013.[2]

1.Intrarosa, Summary of Product Characteristics 2.Labrie F *et al*. *Climacteric* 2013;16(2):205–13.

Vaginal DHEA (prasterone) Study ERC-230 / 52 week efficacy data – secondary endpoints

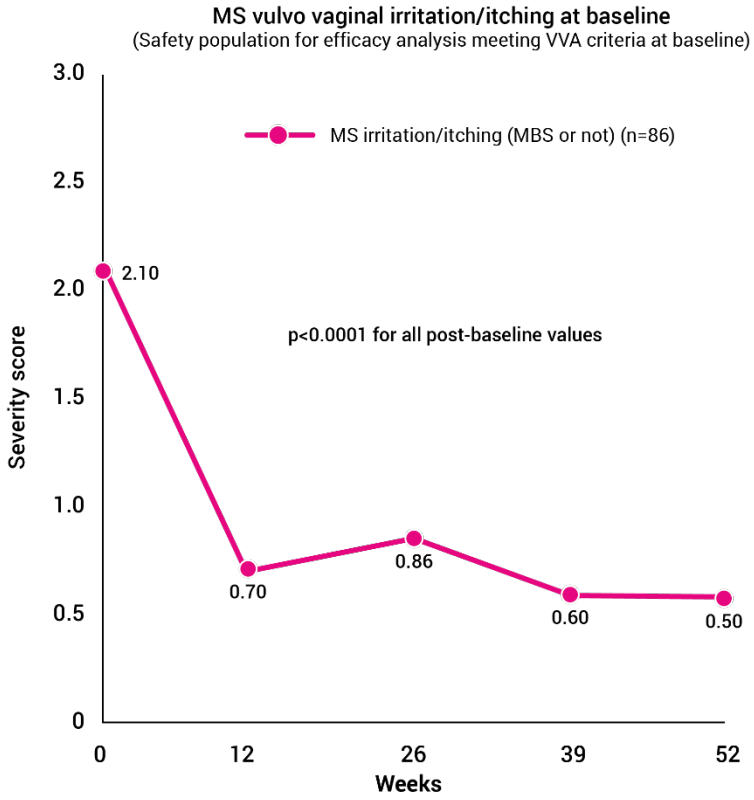
NOTE: ERC-230 inclusion criteria allowed self-identification of mild, moderate or severe VVA symptoms[1]

Change from baseline in severity score for dyspareunia[1]



The values decreased from 2.53 at baseline to 0.85 at 52 weeks (p<0.0001 versus baseline)

Change from baseline in severity score for vaginal irritation/itching[1]



The values decreased from 2.10 at baseline to 0.50 at 52 weeks (p<0.0001 versus baseline)

Graphs adapted from Labrie F *et al*, 2015.

Dyspareunia, vaginal dryness and vaginal irritation/itching: evaluated by questionnaire. Severity of vaginal atrophy symptoms were as follows: 0=none, 1=mild, 2=moderate, 3=severe. Assessed at day 1, week 12, week 26, week 39 and week 52.

MBS, most bothersome symptom; MS, moderate to severe.

Clinically and statistically significant beneficial effects of daily intravaginal 6.5 mg Intrarosa after up to 52 weeks of treatment[1]

1. Labrie F *et al*. *Maturitas* 2015;81(1):46–56.

Enkele besluiten

- Alhoewel de diagnose en behandeling van GSM evident zijn voor de arts, zijn er heel veel horden en is de algemene patiënt-tevredenheid met de ‘gouden standaard’, een topische oestrogeenbehandeling, laag
- Een aantal horden lijken moeilijk aanpasbaar: bv. de bijsluiter, vaginale toediening, langdurige behandeling, etc.

- Er is dus ruimte voor multipele therapeutische invalshoeken
- PRO zijn zinvoller dan ‘objectieve’ eindpunten: bv. seksueel functioneren en zelfbeeld (lichaam, als seksueel persoon) bij GSM, en distress in verband met lage seksuele drive bij HSDD
- Er is meer aandacht nodig voor female androgen insufficiency, en meer onderzoek omtrent de waarde van systemische/locale androgeentherapie