새로운 폐경생식비뇨기증후군 치료제: Ospemifene

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Genitourinary syndrome of menopause

- High concentrations of estrogen receptors:
  - Vagina, Vulva, Vestibule, Labia majora/minora, Bladder trigone
- Estrogen loss at postmenopausal women
  - Decrease in vaginal lactobacilli, increase in pH
  - Vulvovaginal dysfunction
  - Genitourinary symptoms

Genitourinary symptoms

- Dryness
- Burning
- Pruritus
- Pressure sense
- Dyspareunia
- Prolapse
- *Urinary symptoms*

Menopause for 7 years

Urinary frequency for 3 months

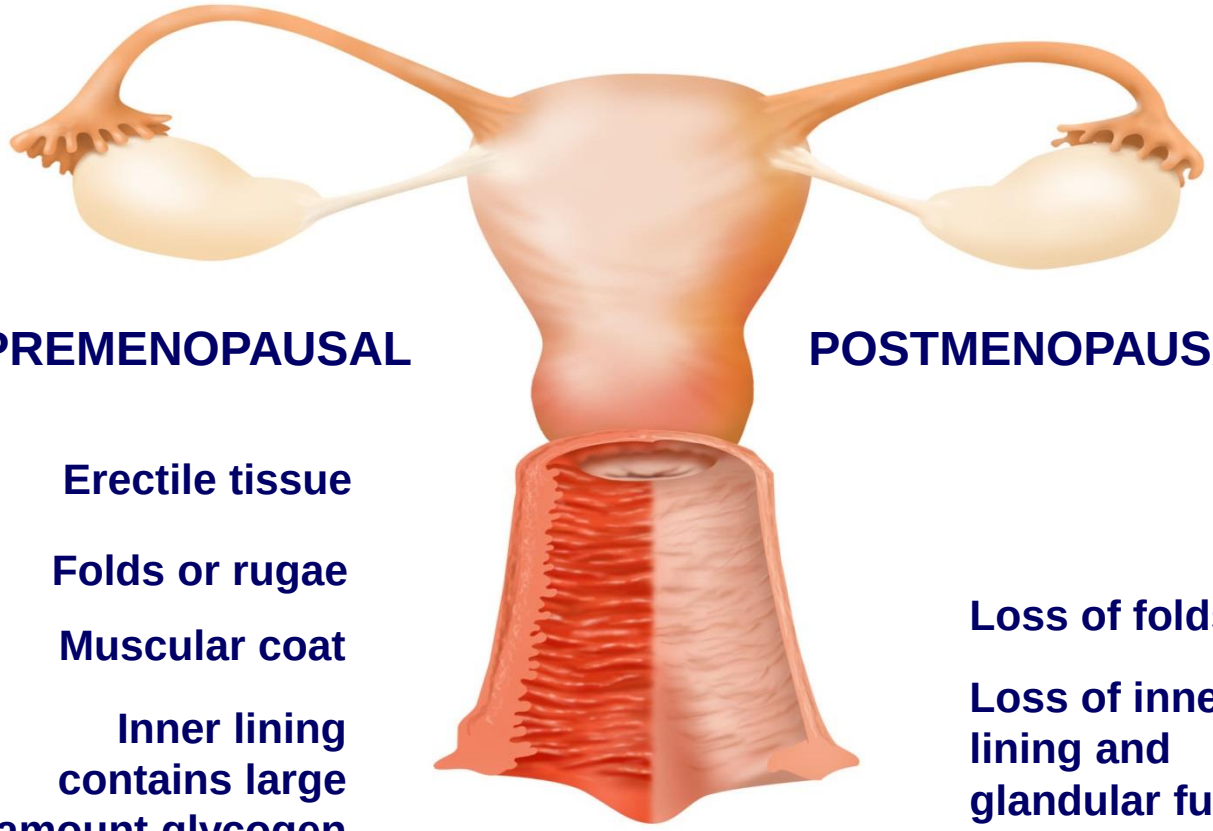
Urology clinic for 1 month with intermittent anti-biotics

3’ center evaluation for UT abnormalities

UA RBC trace

→topical estrogen relief of Sx

Postmenopausal changes in the vaginal epithelium



PREMENOPAUSAL

Erectile tissue

Folds or rugae

Muscular coat

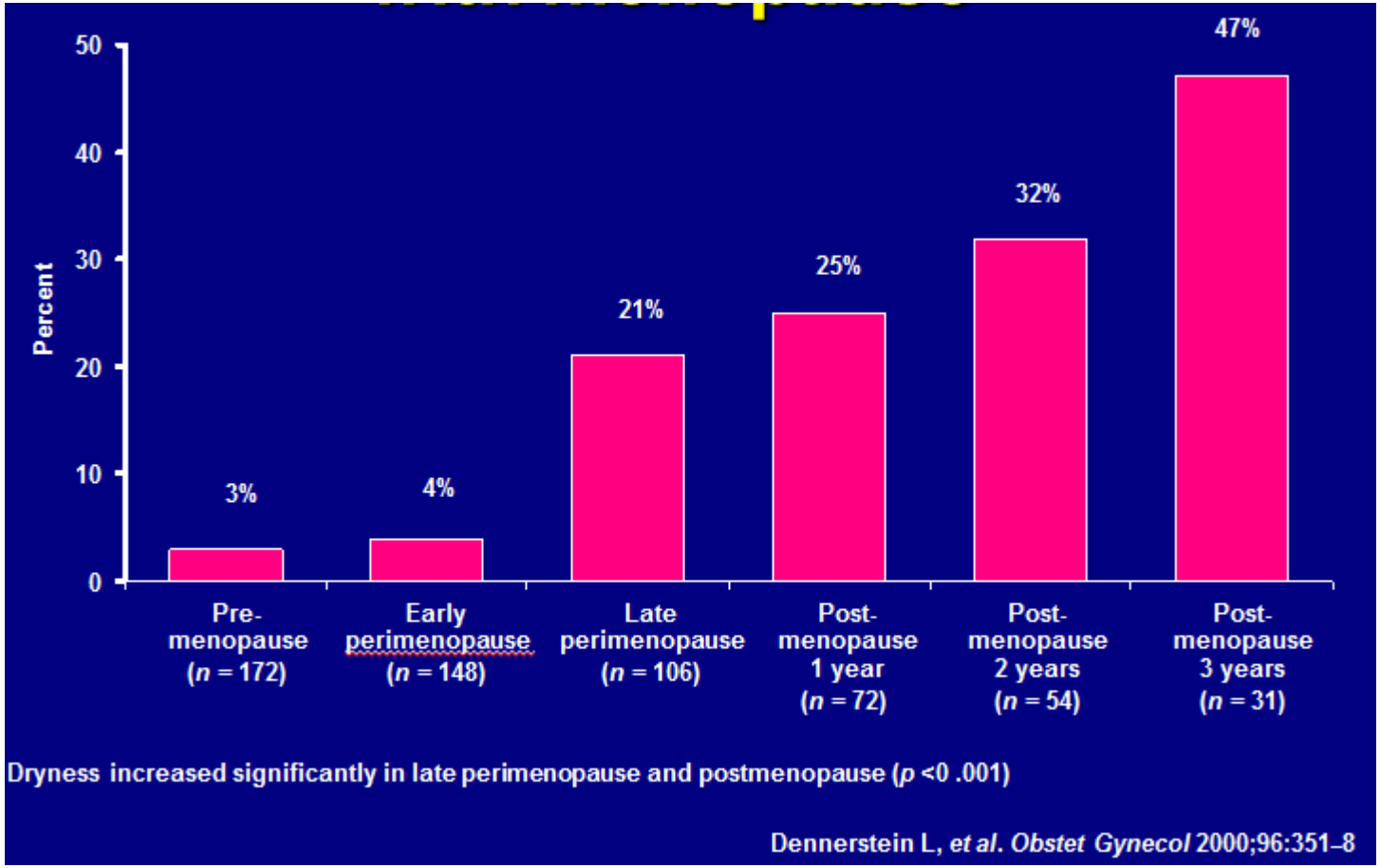
Inner lining contains large amount glycogen

POSTMENOPAUSAL

Loss of folds

Loss of inner lining and glandular function

Increase in vaginal dryness with menopause



Treatment

- Lifestyle modification:
  - Avoid smoking,BMI<27 kg/m2, physical exercise, Sexual activity, Vaginal dilators
- Vaginal moisturizers:
  - Primarily used to relieve vaginal dryness during intercourse
  - Do not provide a long-term solution

Treatment<Hormonal, local>

- A 2006 Cochrane review
  - 37 clinical trials, 19 RCT of estrogenic preparations administered intravaginally in 4162 postmenopausal women, at least 3 mo
  - Effectiveness: creams, pessaries, tablets and estradiol vaginal rings equally effective in relieving symptoms
  - Suggested for women solely with vaginal atrophy syndromes(Grade 1B)

Treatment<Hormonal, local>

Table 1 Estrogens for topical use: maintenance dose

Compound	*Presentation*	*Dose*
Estriol	ovules	*Initiation dose*: 0.5 µg/day for 2 weeks
	vaginal cream	
	vaginal gel	*Maintenance dose*: 50 µg/g daily for 3 weeks, then every 72 h
Estriol	ovules	0.5 µg twice a week
	vaginal cream	0.5 µg twice a week
	vaginal gel	50 µg twice a week
Promestriene	vaginal cream	10 µg twice a week
17β-Estradiol	vaginal tablets	10 µg twice a week
	vaginal ring	6.5–9.5 µg/day
Conjugated equine estrogens	vaginal cream	0.312 µg twice a week

Treatment<Hormonal, local>

- A 2006 Cochrane review
  - Safety analysis in 14 clinical trials
  - CEE cream: adverse effects on uterine bleeding, breast and perineal pain
  - All preparations associated with vaginal irritation, itching, or increased vaginal discharge

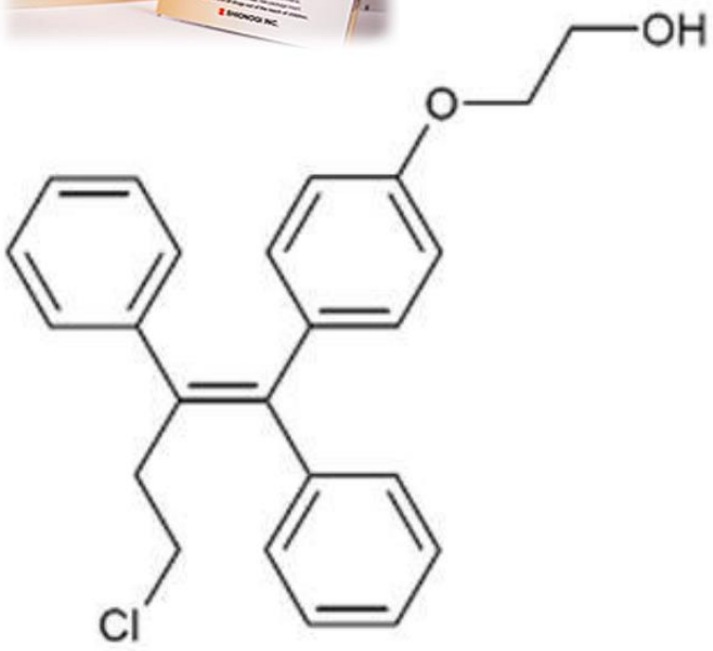
Treatment<Hormonal, local>

- Progestin
  - Not routinely treated with low-dosed vaginal estrogen ring or insert, or minidose of conjugated estrogen cream
  - Recommended for patients treated with higher doses of conjugated estrogens cream or any dose of estradiol cream(Grade 2C)

폐경생식비뇨기증후군에 새로운 제제가 필요한가?

- Not effective with restricted dose of transvaginal estrogen
- Low compliance with vaginal insertion
  - irritation, itching, or increased vaginal discharge
- Problems encountered with transvaginal administration
  - POP, irritation, previous surgery

Ospemifene



- Osphena: Selective estrogen receptor modulator(SERM)
  - estrogen agonist/antagonist
  - peak serum concentration after 2h
  - half-life 26h
- 60mg po daily tablet

Treatment<Ospemifene>

- Ospemifene: Selective estrogen receptor modulator(SERM)
-
  - Agonist in vagina, with no significant effect on endometrium and breast
  - *Moderate t*o severe dyspareunia
  - Suggested for women who cannot(severe arthritis, obesity, vulvodynia) or prefer not to use vaginal product(Grade 2B)

Treatment<Ospemifene>

- INDICATION:
  - Treatment of moderate to severe symptomatic vulvovaginal atrophy in postmenopausal women who are not candidates for local vaginal oestrogen therapy
  - FDA approven in 2013

The Evidence

Contents lists available at ScienceDirect

Maturitas

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

Ospemifene, a non-oestrogen selective oestrogen receptor modulator for the treatment of vaginal dryness associated with postmenopausal vulvar and vaginal atrophy: A randomised, placebo-controlled, phase III trial

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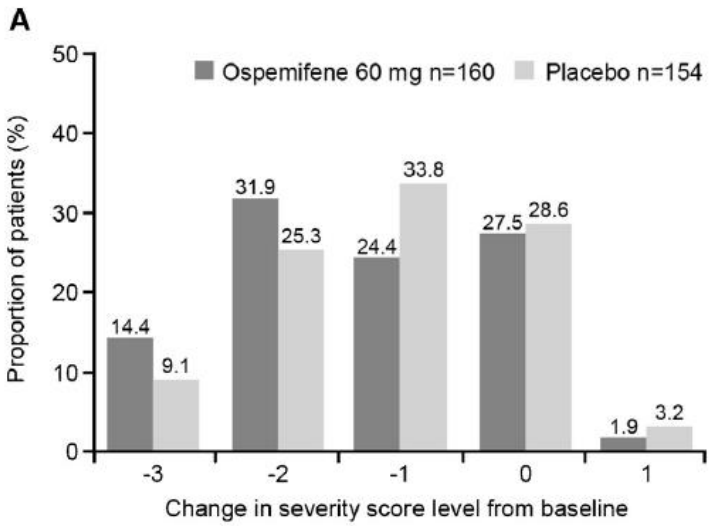

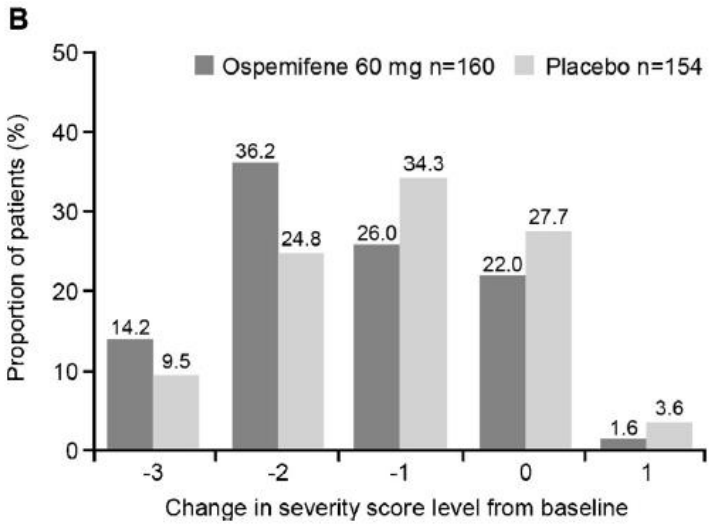

Endometrial thickness of patients with an intact uterus (ITT population).

Variable	Ospemifene 60 mg	Placebo
Baseline		
Number of patients	67	74
Mean (SD), mm	2.21 (0.70)	2.33 (0.85)
Week 12		
Number of patients	51	58
Mean (SD), mm	2.95 (1.78)	2.20 (1.06)
Change from baseline to Week 12		
Number of patients	51	57[a]
Mean (SD), mm	0.82 (1.68)	−0.11 (1.20)
Endometrial thickness ≥5 mm at Week 12	3	1
Endometrial thickness ≥8 mm at Week 12	2	0

Ospemifene *may* thicken endometrium

Table 2
Change from baseline for the ITT and PP population for parabasal cells, superficial cells, vaginal pH and severity scores for vaginal dryness as the most bothersome symptom at Week 12/LOCF.

	ITT population			PP population		
Change from baseline in:	Ospemifene 60 mg	Placebo	*p* value*	Ospemifene 60 mg (*n* = 127)	Placebo (*n* = 137)	*p* value*
% Parabasal cells (LS mean ± SE)	−31.7 ± 2.11	−3.9 ± 2.18	*p* < 0.001	−36.6 ± 2.39	−4.7 ± 2.28	*p* < 0.001
% Superficial cells (median [min, max])	7.0 (−4, 65)	0.0 (−11, 57)	*p* < 0.001	8.0 (−4, 65)	0.0 (−5, 57)	*p* < 0.001
Vaginal pH (LS mean ± SE)	−0.95 ± 0.067	−0.25 ± 0.068	*p* < 0.001	−0.99 ± 0.078	−0.23 ± 0.075	*p* < 0.001
Severity of vaginal dryness (mean ± SD)	−1.3 ± 1.08	−1.1 ± 1.02	*p* = 0.080	−1.4 ± 1.03	−1.1 ± 1.03	*p* = 0.014

LS, least squares; SD, standard deviation; SE, standard error.

CLIMACTERIC 2015;18:233–240

The clinical relevance of the effect of ospemifene on symptoms of vulvar and vaginal atrophy

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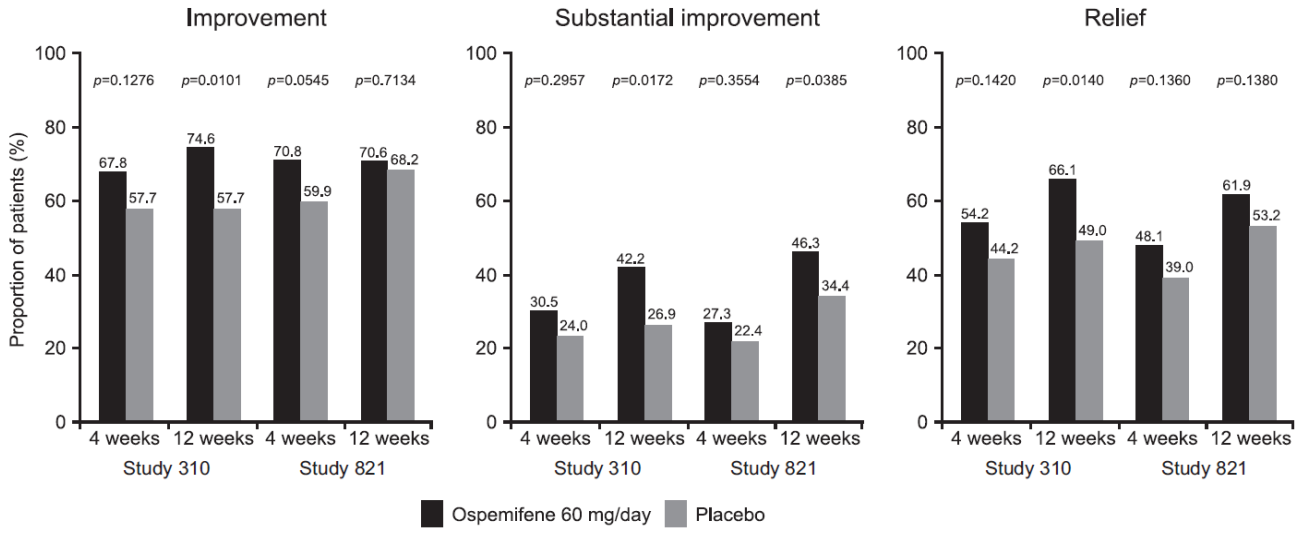
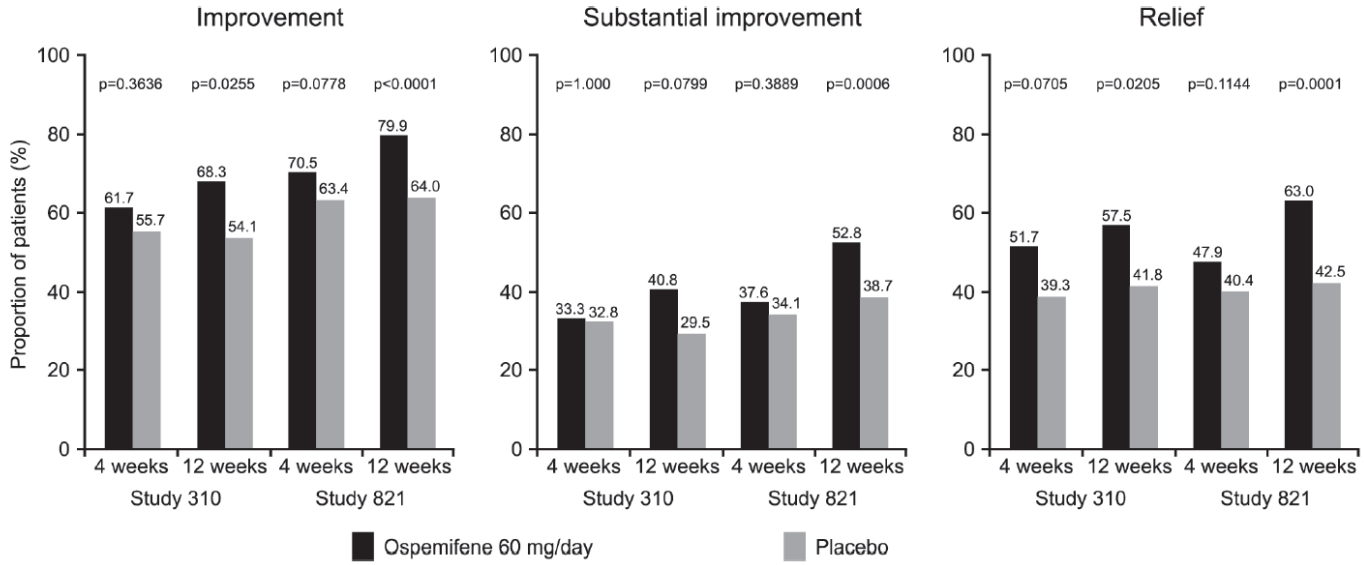


Figure 2 Clinically relevant differences based on the most bothersome symptom of vaginal dryness in Study 310 ($n = 222$) and Study 821 ($n = 214$) (ITT, LOCF). ITT, intent to treat; LOCF, last observation carried forward. p Values for treatment comparisons (ospemifene 60 mg/day vs. placebo) from Fisher's exact two-sided test



igure 3 Clinically relevant differences based on the most bothersome symptom of dyspareunia in Study 310 ($n = 242$) and Study 821 ($n =$ 05) (ITT, LOCF). ITT, intent to treat; LOCF, last observation carried forward. p Values for treatment comparisons (ospemifene 60 mg/ ay vs. placebo) from Fisher's exact two-sided test

Other potential impact

- BMD
  - Phase II clinical study, ospemifene decreased bone resorption, compatible with actions of raloxifene *(Qu et al. 1999, 2000)*

Safety: Breast

- Acts as an estrogen antagonist in animal models of breast cancer

- In clinical trials
  - no adverse effects on the breast and mammograms performed after 52 weeks (*Simon et al. 2013)*

Safety: Endometrium

- In a phase III trial
  - 12weeks 30 mg/60 mg/placebo
  - Minimal change in the endometrial thickness, and their endometrial
- Biopsy: no cases of endometrial hyperplasia or carcinoma
- Extension studies
  - no significant endometrial changes up to 1 year

Safety: Lipid profile

- Ospemifene vs Placebo (*Ylikorkala et al. 2003)*
  - Non-significant decrease in
    - T. cholesterol and LDL
  - Non-significant increase in HDL, TG

- Vs Raloxifene *(Komi et al. 2005)*
  - Comparable decrease in LDL
  - Non-significant increase in TG

**90mg dose

Contraindications

- Unexplained vaginal bleeding
- Hormone sensitive cancer
- Thromboembolic event
- Coronary/Cerebrovascular event
- Pregnancy not ruled out

감사합니다