

Genitourinary Syndrome of Menopause/Local Estrogen/New Emerging Therapy

ISSWSH Fall Course 2014

Sharon J. Parish, MD, IF, NCMP

Disclosures

- **Advisory Board:** Sprout, Pfizer, SST, Emotional Brain, Apricus
- **Speaker:** Pfizer

Objectives

- **Recognize the clinical manifestations of Genitourinary Syndrome of Menopause (GSM)**
- **Apply evidence-based treatment options, both non-hormonal and hormonal, to the management of GSM**

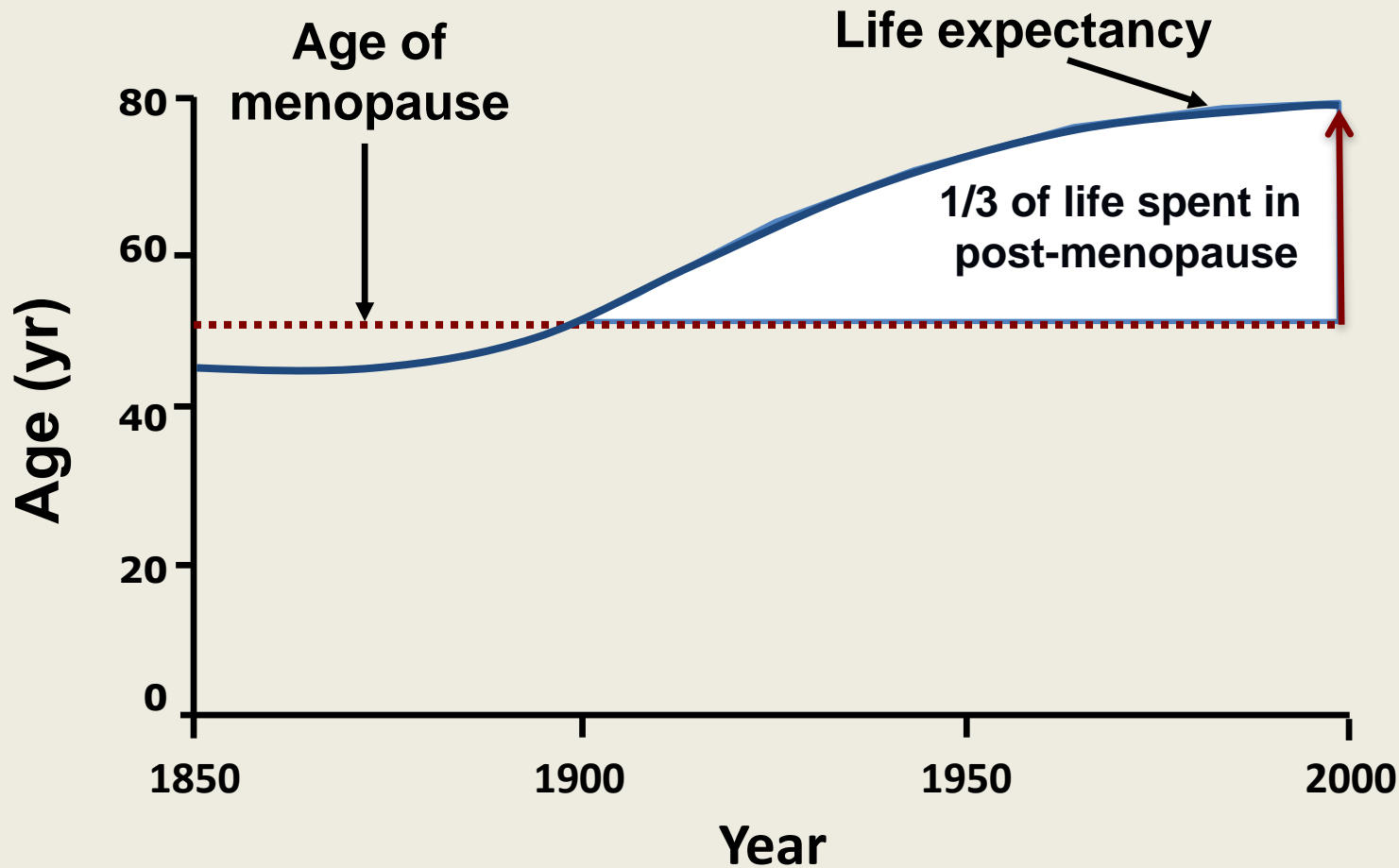
GSM

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

Members of the consensus conference agreed that the term genitourinary syndrome of menopause (GSM) is a medically more accurate, all-encompassing, and publicly acceptable term than vulvovaginal atrophy.

Portman et. al. 2014: Climateric, J Sex Med, Menopause

Gap Between Life Expectancy and Menopausal Age Has Widened



Surveys of Postmenopausal Women

- Since 2008, 6+ surveys on Women's Views of Impact of Menopause/VVA
 - REVEAL: REvealing Vaginal Effects At MidLife
 - VIVA: Vaginal Health: Insights, Views, and Attitudes
 - CLOSER: CLarifying Vaginal Atrophy's Impact On SEx and Relationships
 - REVIVE: REAL WOMEN'S VIEW OF TREATMENT OPTIONS FOR MENOPAUSAL VULVAR/VAGINAL CHANGES
 - Women's Voices in the Menopause
 - Healthy Women
- Consistent findings of Negative Impact of VVA on Sexual Health
- Barriers to Treatment

www.revealsurvey.com, Wyeth

Kingsberg SA, et al. *J Sex Med.* 2013 Jul;10(7):1790-9

Nappi RE, Kokot-Kerepa M. *Climateric* 2012;15(1)36-44.

Simon et al. *Menopause* 2013 June 3, Epub ahead of print

Nappi RE, Kingsberg S, Maamari R, Simon J.

J Sex Med. 2013 Jun 27. doi: 10.1111/jsm.12235. [Epub ahead of print]

Nappi RE, Kokot-Kierapa M. *Maturitas* 2010;67(3):233-238.

Simon et al. *Menopause* 2013;20:1043-1048.

www.issmsmsna2012.org

Parish et al: *International Journal of Women's Health.*
2013;5:437-447.

Vaginal Symptoms: Postmenopausal

- **45% post-menopausal & currently or previously experienced VVA sx**
- **Only 4% attributed sx to VVA; 63% failed to recognize VVA as chronic**
- **75% stated vaginal atrophy had negative impact**
- **60% past or never HT users: vaginal sx > 90% bothersome**
- **82% current HT users: sx prior to use**
- ***Trend away from oral, toward patch & topical hormones**
- **Safety concerns, lack of MD recommendation major reasons for discontinuing or not using**

Santoro N, Kornil J. Sex Med 2009;6:2133-2142.

Nappi RE, Kokot-Kierepa M. Climacteric 2012; Early Online 1-9.

REVEAL: VA Symptoms & Dyspareunia

- **47% experienced vaginal dryness (including itching, burning)**
 - 51% said they learned to live with vulvar /vaginal symptoms as normal part of aging
- **25% experienced dyspareunia**
 - **Despite pain, 72% engage in sex at least once a month, 34% engage in sex at least once weekly**
 - 36% stated that pain requires interruption, discontinuation or prevents any further attempts at sexual activity



Impact on Quality of Life (VIVA)

- **When asked about how a woman might feel about herself when having vaginal discomfort:**
 - **57% “less sexual”**
- **When asked how do they think vaginal discomfort affects women’s lives in general (80%):**
 - **65% negative consequences on sex life**
 - **40% negative consequences on marriage/relationship**
 - **36% lowers quality of life**
 - **31% makes them feel old**
 - **26% negative impact on self-esteem**
 - **13% negative impact on social life**

Parish et al: Impact of Vulvo-vaginal Health on post menopausal women: A review of Surveys on symptoms on VVA. International Journal of Women’s Health. 2013;5:437-447.

REVIVE: Impact and Rx Patterns

- **VVA sx affected enjoyment of sex/life/sleep**
- **Few women attributed symptoms to menopause (24%) or hormonal changes (12%)**
- **56% discussed VVA symptoms with HCP**
- **40% currently used VVA-specific topical treatments (vaginal OTC products [29%] and vaginal prescription therapies [11%])**
- **Concerns about side effects and cancer risk limited use of topical vaginal prescription therapies.**
- **OTC products (62%) - insufficient symptom relief and inconvenience**

Kingsberg et al. J Sex Med. 2013;10:1790-1799.

Nappi RE, Kokot-Kierepa M. Climacteric 2012; Early Online 1-9.

Santoro N, Kornj J. Sex Med 2009;6:2133-2142.

CLOSER: Implications for Couples

- *Clarifying Vaginal Atrophy's Impact on Sex and Relationships*
- Vaginal discomfort related to decreased libido and pain
- 28% women did not tell partner about discomfort
- 82% males wanted partner to share experiences with VA
- Sex less often, less satisfying, intimacy avoidance
- Both agreed LET improved sex life

Nappi et. al. J Sex Med 2013;10:2232-2241.
Simon et al. Menopause 2014;21:137-142.



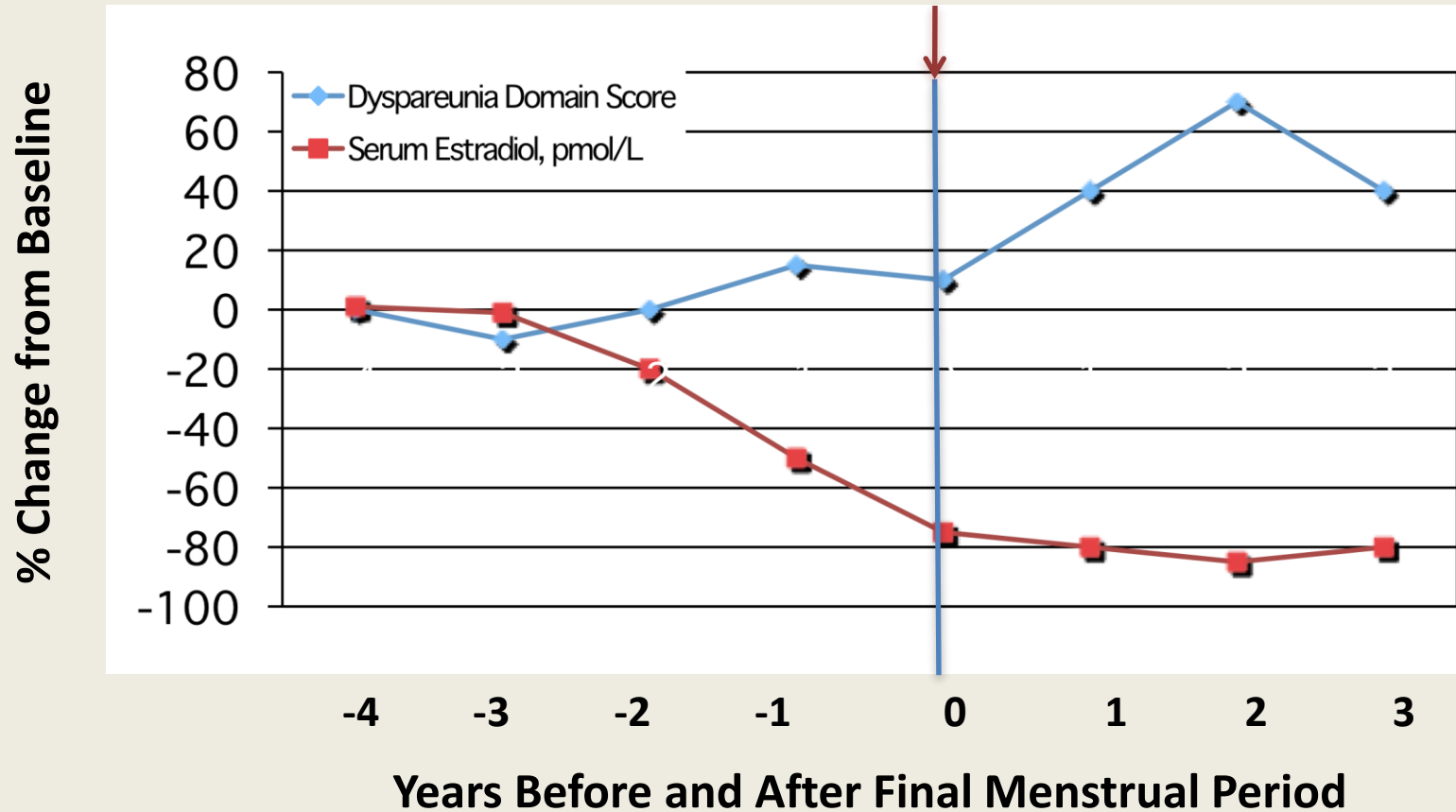
Patient Barriers – Women's Voices

- **70% of women with VA have not discussed with their HCP**
 - 77% believed that women do not feel comfortable discussing VA with HCP, 60% because of embarrassment
- **30% of women with VA had not spoken to anyone**
 - Reasons include embarrassment, private, doesn't concern others, just a part of growing old and don't think others want to hear about their vaginal problems
- **31% of women preferred that HCP initiate the conversation**
 - Range 13-50%, US 32%
- **Additional barriers: ageism, lack of awareness, cultural factors**

Parish et al. International Journal of Women's Health. 2013;5:437-447.

Estrogen Decline and Dyspareunia

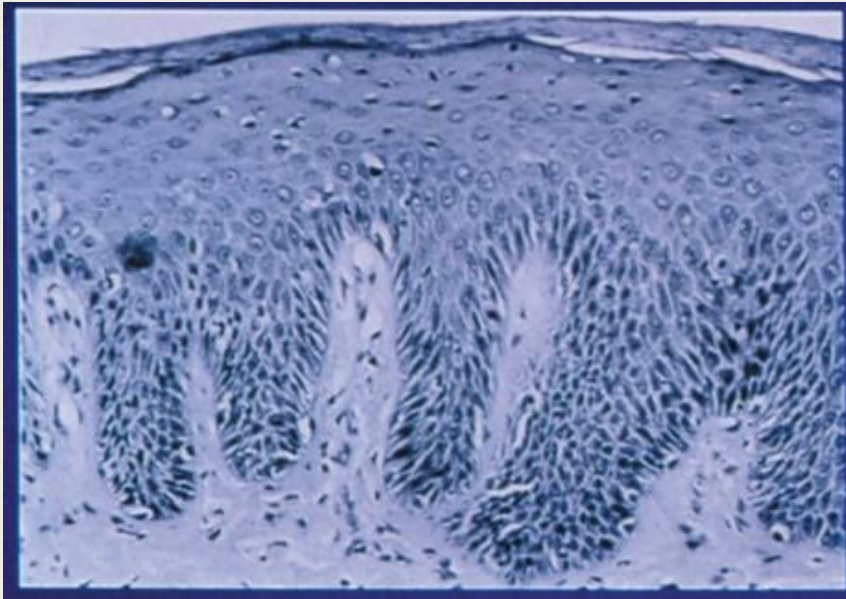
Final Menstrual Period



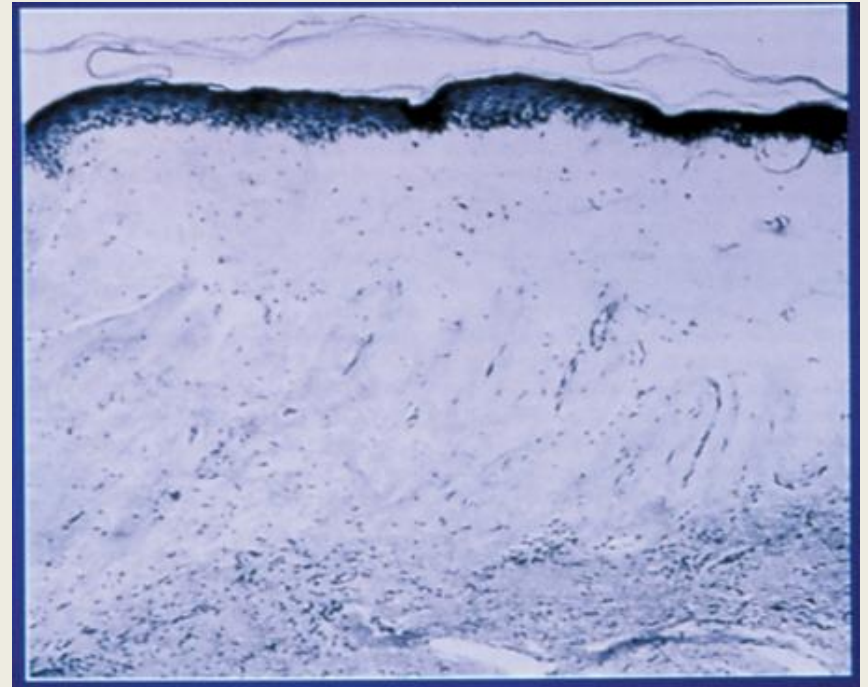
Vaginal Signs and Symptoms

- **Dryness and insufficient moistness**
- **Diminished blood flow**
- **Dyspareunia**
- **Itching**
- **Burning sensation**
- **Soreness**
- **Tightness**
- **Loss of elasticity**
- **Thinning of the vaginal tissue, alteration of keratinization**
- **Mucosal defects including petechiae, microfissures, ulceration and inflammation**
- **Shortening, fibrosis, obliteration of vaginal vault**
Narrowing of vaginal entrance
- **Smoothing of fornix, flattening of vaginal rugae**

Vaginal Cytology

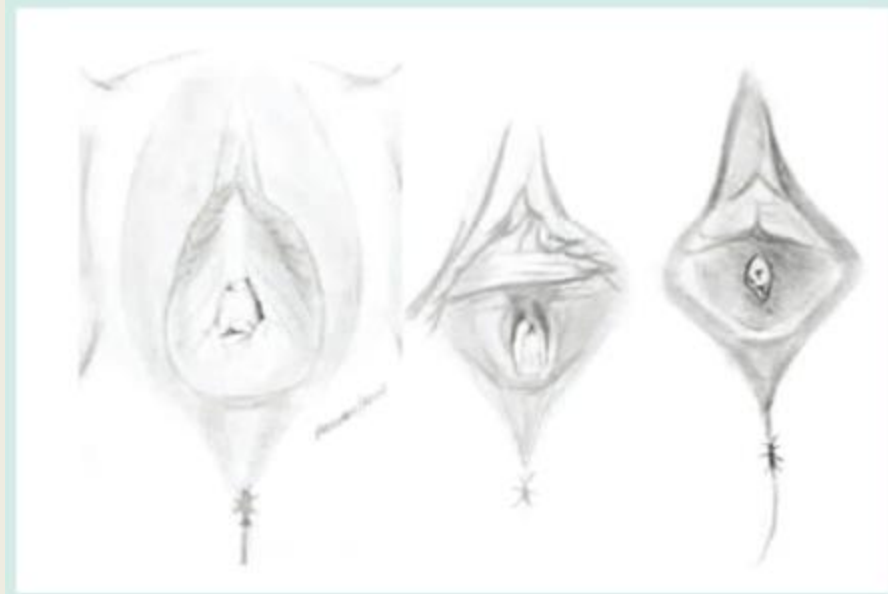


Premenoopause



Postmenopause

Diagnosis and Progression



Artist's representation of the progression of atrophic change (introital stenosis) that can be anticipated in most untreated postmenopausal women

External Genitalia in Vulvovaginal Atrophy



Estrogen Replacement

- Postmenopausal, oophorectomized women
- Oral (transdermal?) therapy improves vaginal tissue integrity and atrophy, decreases dyspareunia, enhances sensual touching
- Improves clitoral sensitivity, increases libido
- Increases SHBG, decreases free testosterone
- Benefits (symptomatic) vs. risk (progestins): WHI
- **VVA: First-line therapies include non-hormonal lubricants and moisturizers in combination with regular sexual activity**
- **When HT is considered solely for VVA, local vaginal ET recommended**
- **Topical therapy relieves pain, dryness, overactive bladder, UTI**

Berman JR, Goldstein I. Urol Clin North Am 2001;28:405-416.
NAMS Position Statement. Menopause 2012.

Estrogen Treatment and GSM

- Estrogen lowers vaginal pH, increases subepithelial capillary growth, thickens the epithelium
- Raises level of vaginal secretions, and increases the transvaginal potential difference
-
- VMI increases reflecting higher percentage of superficial cells relative to parabasal cells
- Estrogen therapy alleviates subjective vaginal symptoms of
 - Dryness, soreness, irritation, pruritus, and dyspareunia

Local Estrogen vs. Systemic for GSM

- **Thin atrophic vaginal epithelium absorbs locally applied estrogen faster than after the epithelium has been estrogenized**
- **Oral estrogens require achievement of serum estradiol levels of 35 to 55pg/mL for optimal vaginal symptom relief**
- **Much lower doses of estrogen applied vaginally are effective with minimal elevation of serum estradiol levels**
- **In one study, local vaginal cream associated with better symptom relief than oral dose, even with lower systemic levels seen**
- **Systemic estrogen, even at higher doses, fail to relieve symptoms in 10% to 25% of women**

Long CY, Liu CM, Hsu SC et al Menopause 2006;13:737-743.

Tsai CC, Semmens JP, Semmens EC et al Br J Hosp Med 1993;49:799-808.

Estrogen treatment and LUTS

- **UI during sexual activity prevalence 10-56%**
- **74% of urogynecologic not asked about sex: 46% FSD**
- **Supportive evidence for significant benefit of topical vaginal estrogen in reducing prevalence of recurrent UTI**
- **ERT: Improvement of urethral sphincter or pelvic floor function**
- **Mediated by growth stimulation of urethral epithelium**
- **17B estradiol ring and cream significantly reduce the incidence of symptomatic, confirmed UTI in postmenopausal women**

Available Moisturizers

Product	Ingredients	Use	Price	Studies
Replens	Polycarbophil Glycerin, mineral oil	Every 3 days	\$17.5/14 app	Yes
Me again	Hyaluronic acid Propylene glycol, paraben	7 days > 2/wk	\$18/8 app	HA-yes
KY Liquibeads (ovules)	Dimethicone , Gelatin, Glycerin, Dimethiconol	?		No
KY long lasting	Various polymers Glycerin, mineral oil	?	\$16/6 app	No
Emerita personal moisturizer	Aloe Vera Gel, Calendula, Vitamin E, Ginseng, Chamomile, Allantoin	As needed	\$16/4 oz	No
Moist Again	Carbomer, aloe vera glycerin, chlorhexidine	As needed	\$7/4 oz	No
Hyalofemme	Hyaluronic acid	7 days > 2/wk	\$17/30gram	HA-yes
Pre-seed	Hydroxyethylcellulose, Pluronic, Arabinogalactan	As needed	\$20/9 app	Yes

Lubricants

Base	Ingredients	Safe with latex?	Staining	Comments
Water	Deionized water, glycerin, propylene glycol	Yes	No	Rarely causes irritation but dries out with extended activity
Petroleum	Mineral oil, petroleum jelly, baby oil	No; do not use with condoms, diaphragms, or cervical caps	Yes	Irritating to vagina
Natural oil	Avocado, olive, peanut, corn	Yes	Yes	Safe (unless peanut allergy); non-irritating to vagina
Silicone	Silicone polymers	Yes	No	Non-irritating to vagina, long-lasting and waterproof

Kingsberg SA, et al. J Women's Health. 2009;1:105-111.

Kingsberg SA, et al. Female Patient. 2009;(Suppl April):1-6.

Vaginal Estrogen Products

Formulation	Composition (Product Name)	Dosing
**Cream	17 β estradiol (Estrace [®]) Conjugated estrogens (Premarin [®])	Initial: 2-4 g/d for 1-2 wk Maintenance: 1 g/d (0.1 mg active ingredient/g) 0.5-2 g/d (0.625 mg active ingredient/g)
Tablet	Estradiol hemihydrate (Vagifem [®])	Initial: *10 mcg/d for 2 wk Maintenance: 10 mcg twice/wk
**Ring	17 β estradiol (Estring [®])	Device contains 2 mg Releases 7.5 mcg/d for 90 d

*Ultra-low-dose vaginal estradiol tablets (10 μ g) as effective as low-dose tablets (25 μ g) and more effective than placebo (*Simon J, et al. Obstet Gynecol. 2008;112:1053-1060*).

**FDA approved for Dyspareunia

Vaginal Dilators



Ospemifene: Vaginal Atrophy Treatment

First non estrogen oral tablet (SERM) approved for moderate to severe dyspareunia, a symptom of VVA due to menopause

Portman et al. *Menopause* 2013

- Phase III study
- Study safety, efficacy, and tolerability of oral Ospemifene 60mg/day vs. placebo (12 weeks)
- N=605 women aged 40-80 years
 - Most bothersome symptom of dyspareunia, dx of vulvar and vaginal atrophy
- Results
 - Efficacy of ospemifene significantly greater than placebo in decreasing dyspareunia, parabasal cells, vaginal pH, increasing superficial cells
- Hot flushes
 - Most frequently reported treatment-related AE (ospemifene 6.6% and placebo 3.6%)

Ospemifene: Endometrial Safety

Simon J et al. *Menopause* 2012

- 52 week long-term safety extension study
- Placebo vs. Ospemifene 30mg/day vs. Ospemifene 60mg/day
- Results
 - Daily doses of Ospemifene 30mg and 60mg demonstrated *no endometrial changes* in postmenopausal women with a uterus
- Ospemifene effectively prevents and treats breast cancer in Mtag.TG Transgenic Mouse.

Ospemifene and Sexual Function

- Climacteric 2014
- NAMS 2014
- ***Ospemifene improves dyspareunia in postmenopausal women who used treatment for VVA***