



HISTORY OF HORMONAL THERAPIES FOR THE TREATMENT OF GENITOURINARY SYNDROME OF MENOPAUSE

PART 2

Tuesday, November 8, 2022

This webinar is made possible by an educational grant provided by Millicent Services Inc.

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Moderator



Rachel Rubin MD, IF

Panelists



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PART 2

USE AND SAFETY OF LOCAL ESTRADIOL IN THE WAKE OF THE WHI

James Simon, MD, CCD, NCMP, FACOG, IF

CURRENT VAGINAL THERAPIES: EFFICACY BASED ON PHYSIOLOGY

Irwin Goldstein, MD, IF

Q & A

Moderator Rachel Rubin

Use and Safety of Local Estradiol in the Wake of the Women's Health Initiative (WHI)

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Disclosures 2022 (Fall)

Advisory Boards/Consultant: Bayer Healthcare, Besins Healthcare, California Institute of Integral Studies (CIIS), Camargo Pharmaceutical Services, Covance Inc., Dare' Bioscience, DEKA M.E.L.A S.r.l., Femasys, KaNDy/NeRRe Therapeutics, Khyria, Madorra, Mitsubishi Tanabe Pharma Development America, QUE Oncology, Scynexis Inc, Sebela Pharmaceuticals, Sprout Pharmaceuticals, Vella Bioscience.

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Speaker: Mayne Pharma, Myovant Sciences, Pfizer, Pharmavite, Scynexis, TherapeuticsMD.



Use and Safety of Local Estradiol in the Wake of the Women's Health Initiative (WHI)

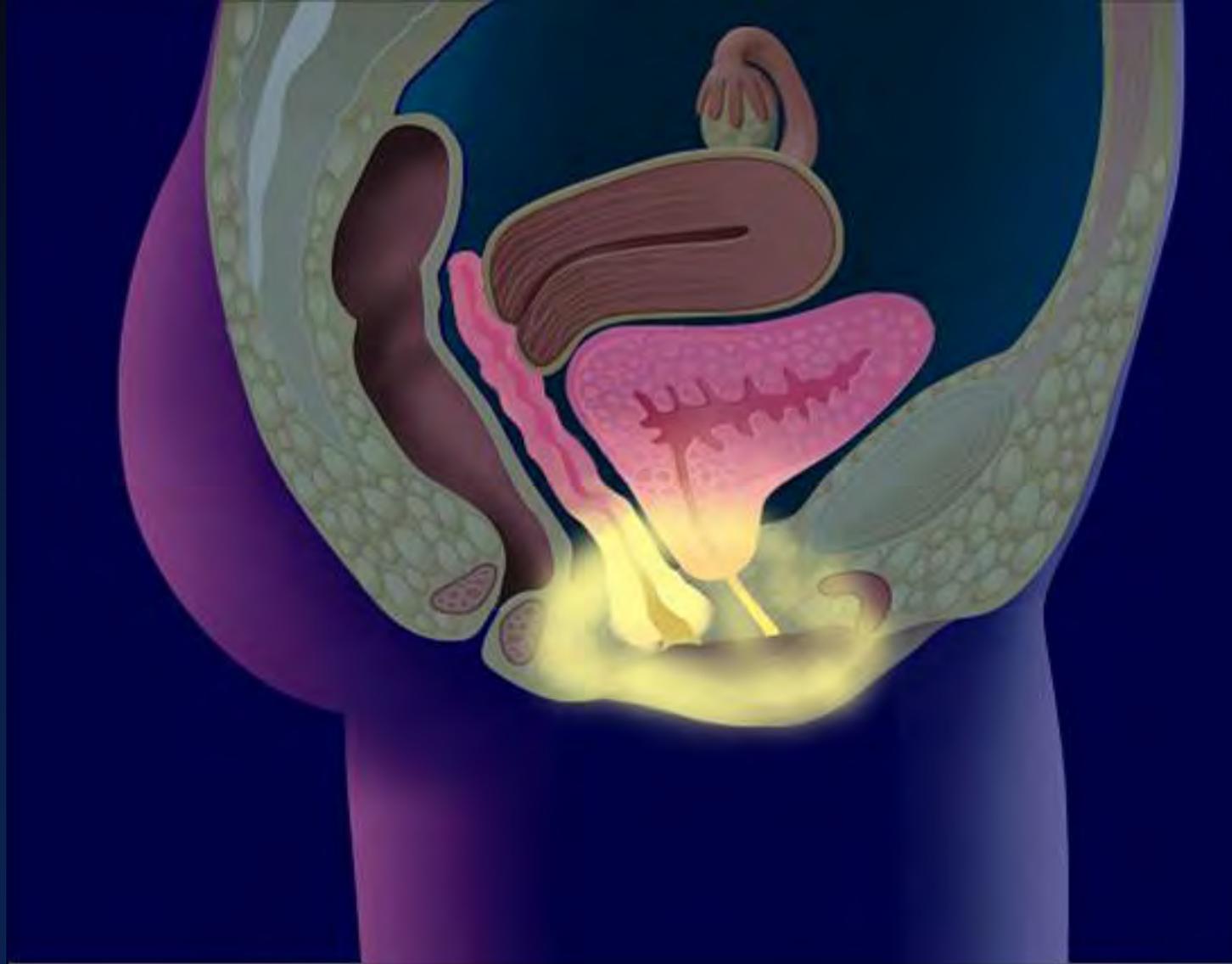
❖ Learning Objectives:

Upon completion of this lecture, participants will be able to:

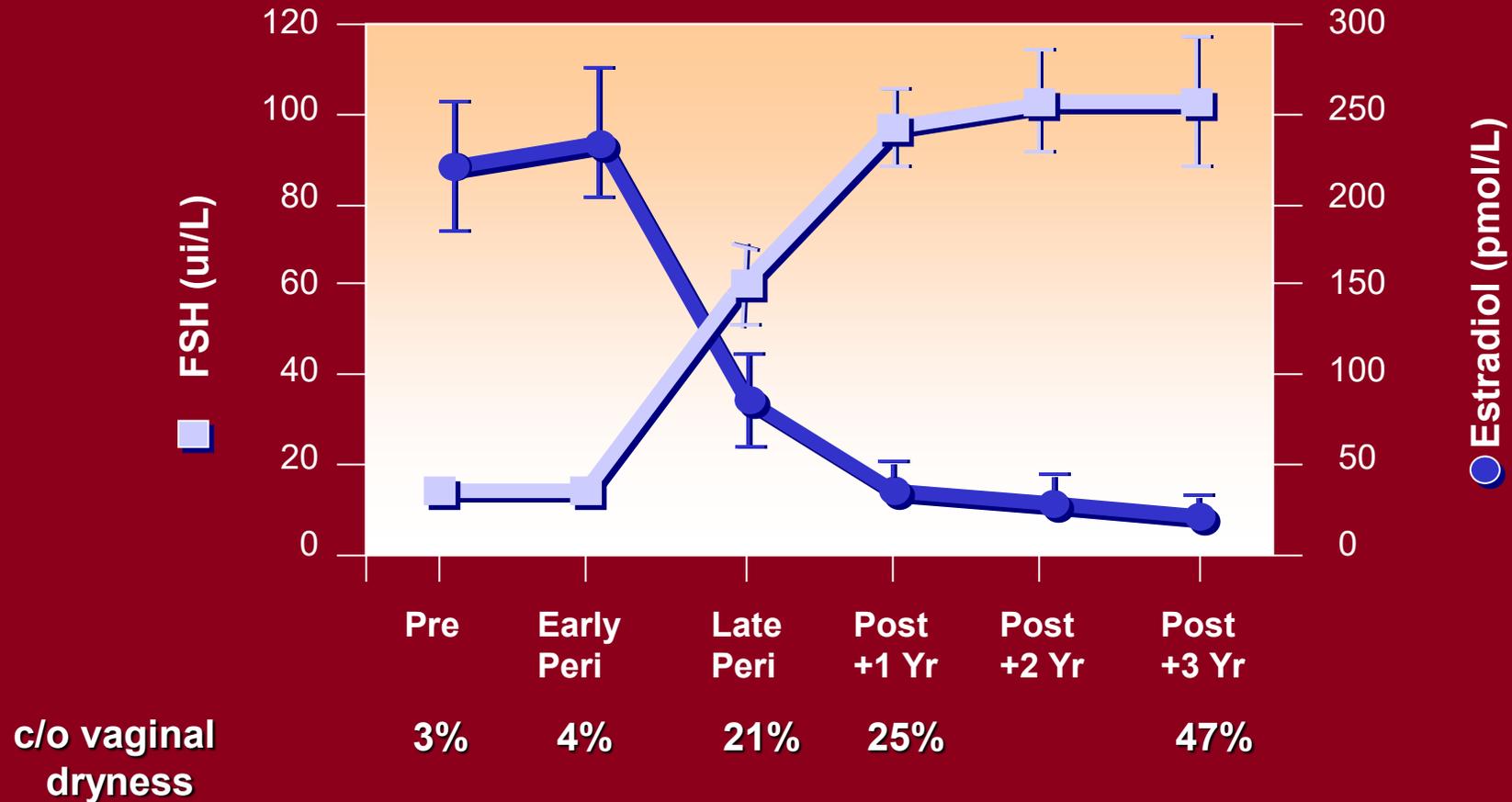
- (1) Apply evidence-based information to understand the current FDA approach to approval and labelling of vaginal estrogen products for VVA/GSM.
- (2) Appreciate the differences among the various available vaginal estradiol products and their systemic absorption.
- (3) Understand the implications of the delivered estradiol vaginal dose and its absorption for the management of VVA/GSM.



Estrogen Receptor Concentrations in Select Adult Genital Tissues



Hormone Levels by Menopausal Status



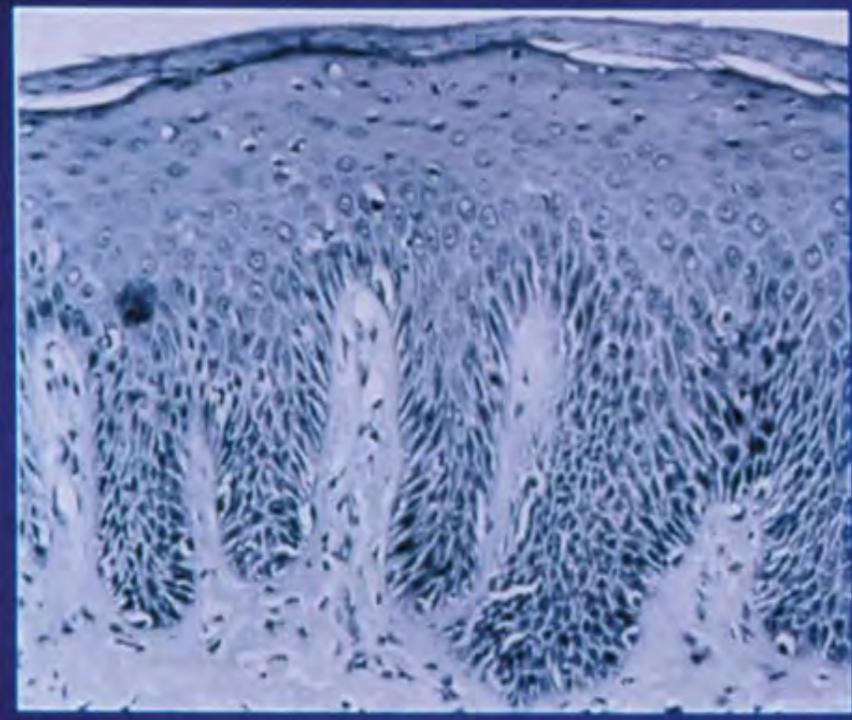
Goals of VVA/GSM Treatment

- ❖ Reverse anatomic changes
- ❖ Relieve symptoms
- ❖ Improve sexual function and quality of life

The NAMS 2020 GSM Position Statement Editorial Panel*. The 2020 genitourinary syndrome of menopause position statement of The North American Menopause Society. Menopause. 2020 Sep;27(9):976-992.

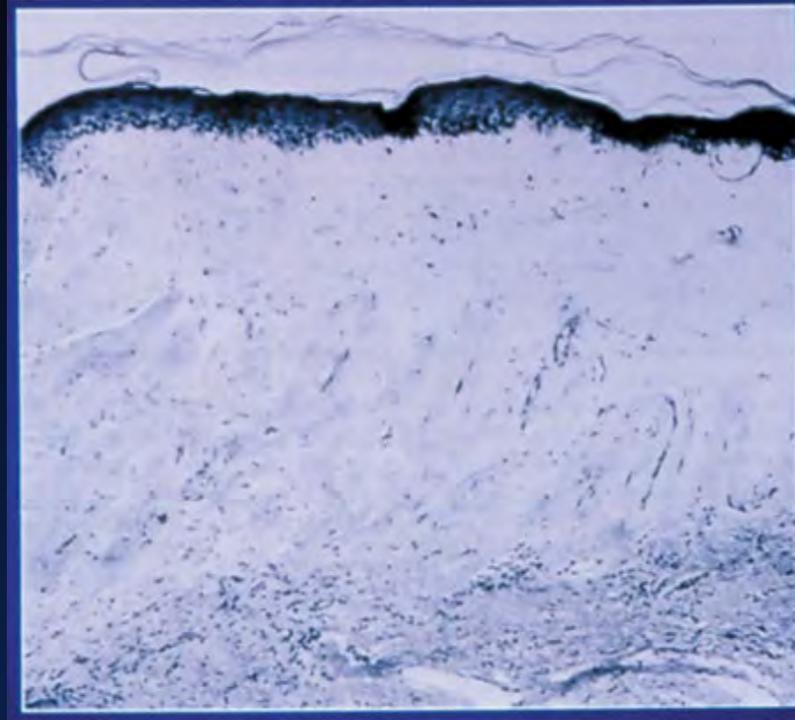


Vaginal Histology



Premenopause

Epithelium well-estrogenized, multi-layered with good blood supply, superficial cells rich in glycogen



Postmenopause

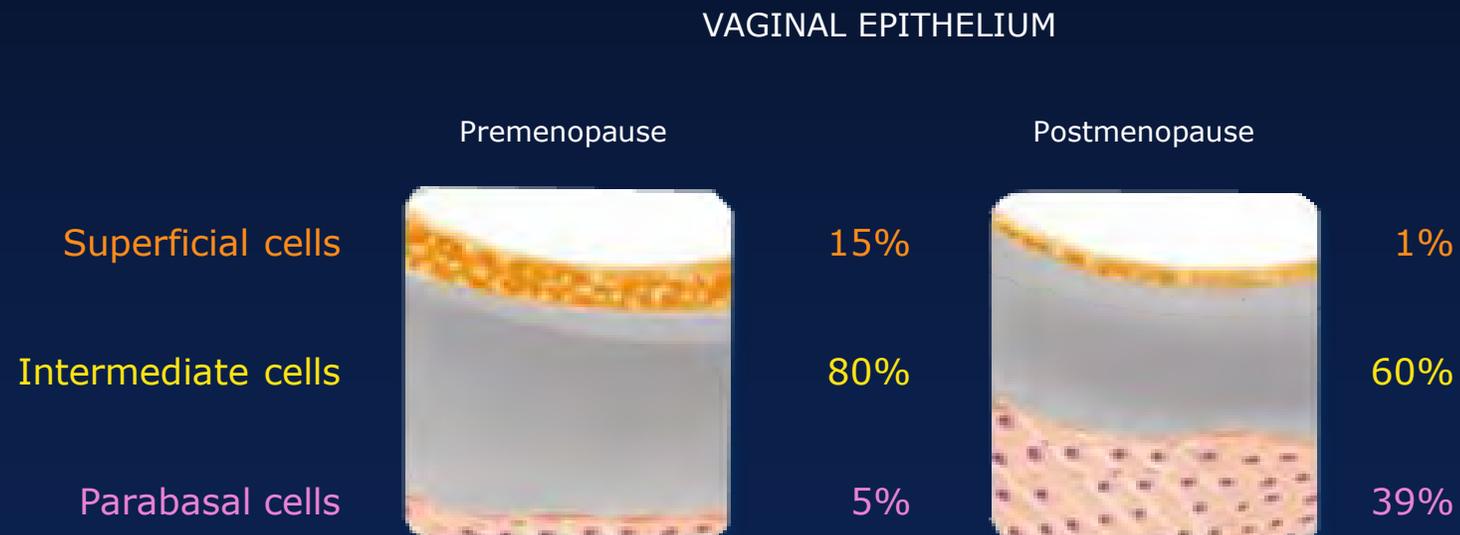
Estrogen-deficiency atrophy with marked thinning of epithelium, blood supply reduced, and loss of glycogen



Maturation Index

❖ Maturation index:

- Proportion of parabasal cells increased
- Proportion of superficial cells decreased



Freedman M. *Menopause Manag.* 2008;17:9-13. Reprinted with permission.



pH Confirms GSM/VVA

- ❖ Premenopausal vaginal luminal pH is acidic
 - pH 4.5–5.0
 - ~6.5 before ovulation
- ❖ Estrogen loss → more alkaline pH
 - pH 6.5–7.0
- ❖ pH test: Medicare eligible

Department of Health & Human Services. Centers for Medicare and Medicaid Services. New Waived Tests – December 17, 2002. Available at: <http://www.cms.gov/transmittals/downloads/AB03013.pdf> Accessed May 10, 2010.



Most Bothersome Symptom (MBS--FDA)

- ❖ Dyspareunia
- ❖ Vaginal dryness
- ❖ Vaginal/vulvar irritation
- ❖ Vaginal soreness
- ❖ Dysuria
- ❖ Bleeding associated with sexual activity

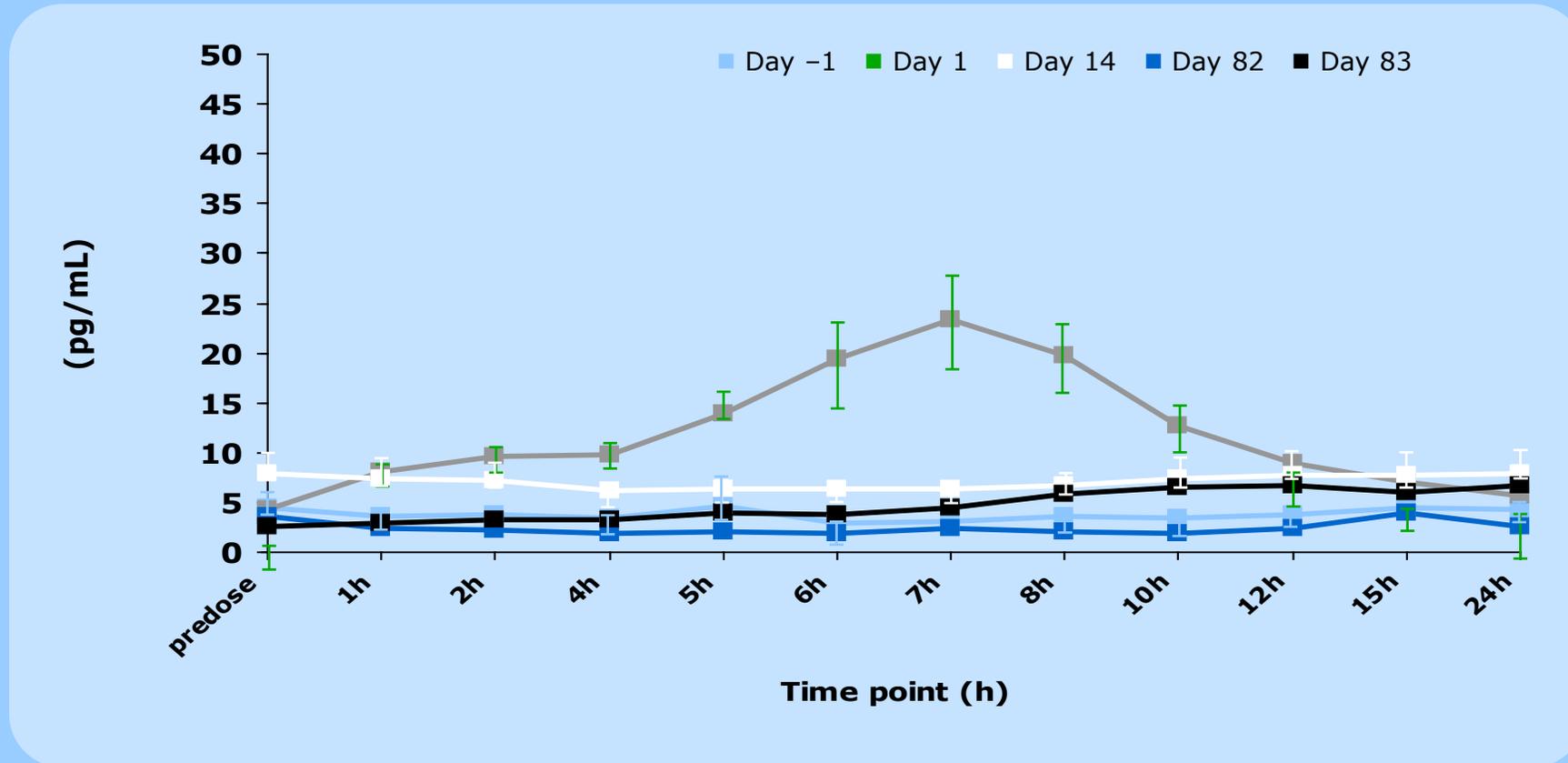


FDA-Approved Vaginal Estrogen Products for Vaginal Changes of Menopause (VVA/GSM)

- ❖ Estradiol vaginal cream (Estrace®) (Generics 2018)
- ❖ Conjugated equine estrogens vaginal cream (Premarin®)
- ❖ Estradiol hemihydrate vaginal tablet (Vagifem®) (Generics 10/20/16)
- ❖ Estradiol vaginal rings can deliver:
 - “Locally” (Estring®) or
 - Systemically (FemRing®); systemic ring is also indicated for vasomotor symptoms
- ❖ Estradiol vaginal insert (Imvexxy™)
 - (FDA approved and available 2018)



10 μ g E2 Hemihydrate – Mean* Serum Estradiol Concentrations at All Time Points



* Mean \pm SE

Eugster-Hausmann M et al. *Climacteric* 2010; 13(3): 219–227

Estradiol Vaginal Insert (IMVEXXY™) Significantly Improved Objective Endpoints vs. Placebo^{1,2}

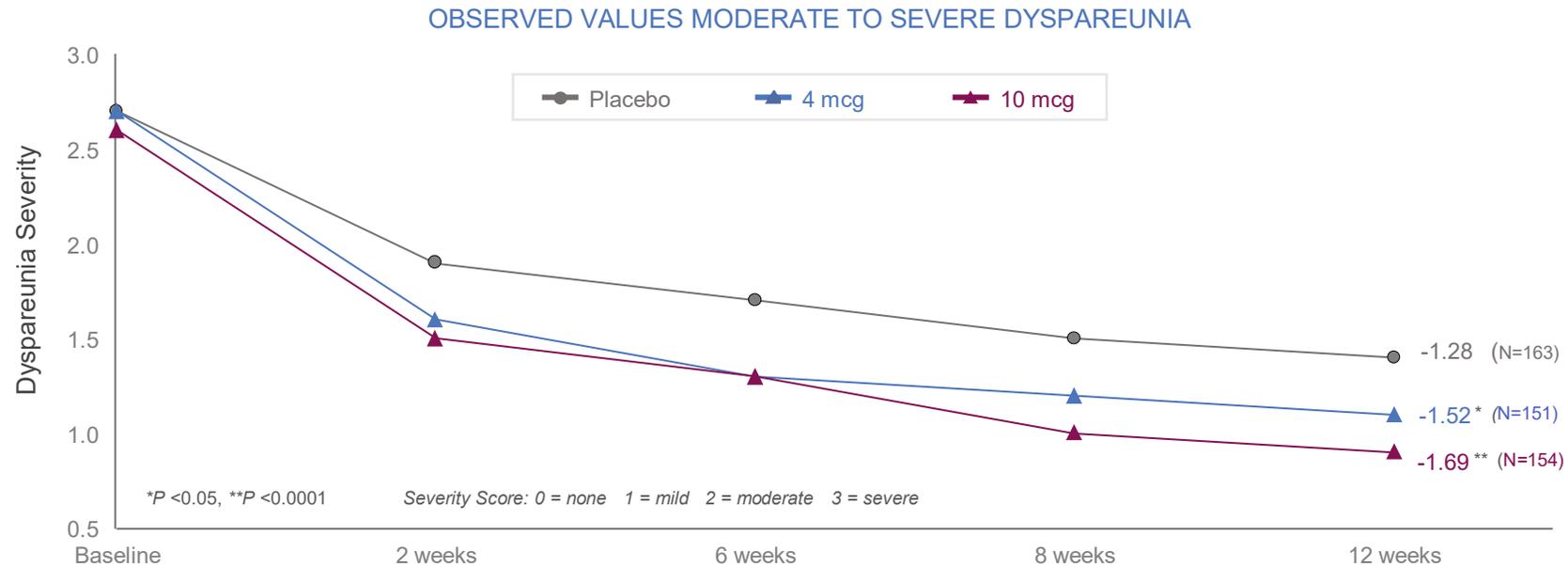
| | LS Mean Change from Baseline to Week 12 | | | 4 mcg <i>P</i> -value | 10 mcg <i>P</i> -value |
|-------------------|---|------------------------|------------------------|-----------------------|------------------------|
| | IMVEXXY 4 mcg | IMVEXXY 10 mcg | Placebo | | |
| Superficial Cells | 18% (n=170) | 17% (n=171) | 6% (n=172) | <0.0001 | <0.0001 |
| Parabasal Cells | -41% (n=170) | -44% (n=171) | -7% (n=172) | <0.0001 | <0.0001 |
| Vaginal pH | -1.3 (n=170) | -1.4 (n=171) | -0.3 (n=174) | <0.0001 | <0.0001 |

LS, least squares.

1. Imvexxy [package insert]. Boca Raton, FL: TherapeuticsMD, Inc; 2018. 2. Modified from: Constantine GD, Simon JA, Pickar JH, Archer DF, Kushner H, Bernick B, Gasper G, Graham S, Mirkin S; REJOICE Study Group. The REJOICE trial: a phase 3 randomized, controlled trial evaluating the safety and efficacy of a novel vaginal estradiol soft-gel capsule for symptomatic vulvar and vaginal atrophy. Menopause. 2017 Apr;24(4):409-416. 3. Data on File, CSR TXV14-01.



Estradiol Vaginal Insert (IMVEXXY™) Significantly Improved Moderate to Severe Dyspareunia Due to Menopause vs. Placebo As Early as Two Weeks Following Onset of Therapy^{1,2}



*, ** LS mean Change from Baseline
 P value vs placebo based on MMRM analysis.

1. Modified from: Constantine GD, Simon JA, Pickar JH, Archer DF, Kushner H, Bernick B, Gasper G, Graham S, Mirkin S; REJOICE Study Group. The REJOICE trial: a phase 3 randomized, controlled trial evaluating the safety and efficacy of a novel vaginal estradiol soft-gel capsule for symptomatic vulvar and vaginal atrophy. Menopause. 2017 Apr;24(4):409-416. 2. Data on File, CSR TXV14-01.



Estradiol Preparations and Maximum Annual Delivered Dose

| Product Name | Route/Type of Administration | Typical Regimen | Nominal daily delivery rate or administered lowest dose approved (mcg/day) | Typical Serum Level pg/mL | Maximum annual delivered dose (mg) ¹ |
|------------------------------|------------------------------|-------------------------------------|--|---------------------------|---|
| Vaginal Estradiol | | | | | |
| Imvexxy | Vaginal insert | 1 Insert daily x 14 then 2 x weekly | 4 | 3.6 | 0.46 |
| Imvexxy | Vaginal insert | 1 Insert daily x 14 then 2 x weekly | 10 | 4.6 | 1.14 |
| Vagifem | Vaginal tablet | 1 Tablet daily x 14 then 2 x weekly | 10 | 4.6 | 1.14 |
| Estring | Vaginal ring | 1 Ring vaginally q 3 months | 7.5 | 8.0 | 2.74 |
| Estrace | Vaginal cream | 1 g Cream vaginally q week | variable | Na | 7.1 |
| Femring | Vaginal ring | 1 Ring vaginally q 3 months | 0.05 mg | 40.6 | 18.25 |
| Oral Estradiol | | | | | |
| Estrace tablets and generics | Oral tablet | 1 Tablet p.o. qd | 0.5mg | 55.4 | 182.5 |
| Transdermal estradiol | | | | | |
| Divigel | Gel | 0.25 mg packet qd | 0.003 | 9.8 | 1.09 |
| Estrogel | Gel | 0.75 mg/pump qd | 0.035 | 28.3 | 12.78 |
| Evamist | Spray | 1.53mg spray qd | 0.021 | 19.6 | 7.67 |
| Climara | Patch | 1 Patch weekly | 0.025 | 22 | 9.13 |
| Menostar | Patch | 1 Patch weekly | 0.014 | 13.7 | 5.11 |
| Vivelle-Dot | Patch | 1 Patch twice weekly | 0.0375 | 34 | 12.78 |

Serum estradiol concentrations obtained from respective prescribing information and / or published clinical trials, not comparative clinical studies. Studies may have used different analytical methods to measure serum concentrations. Relative differences in efficacy and safety, if any, may not correlate with the serum estradiol concentrations measured in these studies.

1 Assumes perfect use (i.e., daily = 365 doses) and rounded to two decimal places.

2 1 g cream equals 0.1 mg estradiol. Assumes 1 week of 0.2 mg/day; 1 week of 0.1 mg/day; then 0.1 mg weekly.

3 Unadjusted for baseline. Mean serum estradiol concentration on day 14.

4 Mean serum estradiol concentration on day 7.

5 Unadjusted for baseline. Mean serum estradiol concentration over the applied period.

Divigel (Prescribing Information). Upsher-Smith, Maple Grove, MN; June 2007.

Climara (Prescribing Information), Bayer, Wayne, NJ; June 2007.

EstroGel (Prescribing Information), Ascend, Herndon, VA; January 2007.

Vivelle-Dot (Prescribing Information), Novartis, East Hanover, NJ; August 2004.

Vagifem Package Insert Version 6, Novo A/S, Bagsvaerd, Denmark; November 2009.

Estring (Prescribing Information) Pharmacia & Upjohn Company, Division of Pfizer, Inc, NY; August, 2008.

Femring (Prescribing Information), Warner Chilcott (UK) Ltd, Larne, Northern Ireland, UK; April 2010.

Imvexxy (Prescribing Information), TherapeuticsMD, Inc. Boca Raton, FL. 2018.

Modified from: Pruthi S, Simon JA, Early AP. Current overview of the management of urogenital atrophy in women with breast cancer. Breast J. 2011;17(4):403-8.



Imvexxy™ 4µg vs Intrarosa® Labels

IMVEXXY™ (estradiol vaginal inserts)
Initial U.S. Approval: 1975

WARNING: ENDOMETRIAL CANCER, CARDIOVASCULAR DISORDERS, BREAST CANCER and PROBABLE DEMENTIA

See full prescribing information for complete boxed warning.

Estrogen-Alone Therapy

- There is an increased risk of endometrial cancer in a woman with a uterus who uses unopposed estrogens (5.3)
- Estrogen-alone therapy should not be used for the prevention of cardiovascular disease or dementia (5.2, 5.4)
- The Women's Health Initiative (WHI) estrogen-alone substudy reported increased risks of stroke and deep vein thrombosis (DVT) (5.2)
- The WHI Memory Study (WHIMS) estrogen-alone ancillary study of WHI reported an increased risk of probable dementia in postmenopausal women 65 years of age and older (5.4)

Estrogen Plus Progestin Therapy

- Estrogen plus progestin therapy should not be used for the prevention of cardiovascular disease or dementia (5.2, 5.4)
- The WHI estrogen plus progestin substudy reported increased risks of stroke, DVT, pulmonary embolism (PE) and myocardial infarction (MI) (5.2)
- The WHI estrogen plus progestin substudy reported increased risks of invasive breast cancer (5.3)
- The WHIMS estrogen plus progestin ancillary study of WHI reported an increased risk of probable dementia in postmenopausal women 65 years of age and older (5.4)

| | Estradiol | |
|---------|-----------------------------|------------------------------------|
| | C _{max} (pg/mL) | C _{avg (0-24)} (pg/mL) |
| 4 mcg | 4.8 (2.3) | 3.6 (1.8) |
| 10 mcg | 7.3 (2.4) | 4.6 (2.3) |
| Placebo | 5.5 (3.4) | 4.3 (2.8) |

INTRAROSA- prasterone insert AMAG Pharmaceuticals, Inc.

4 CONTRAINDICATIONS

Undiagnosed abnormal genital bleeding: Any postmenopausal woman with undiagnosed, persistent or recurring genital bleeding should be evaluated to determine the cause of the bleeding before consideration of treatment with INTRAROSA.

5 WARNINGS AND PRECAUTIONS

5.1 Current or Past History of Breast Cancer

Estrogen is a metabolite of prasterone. Use of exogenous estrogen is contraindicated in women with a known or suspected history of breast cancer. INTRAROSA has not been studied in women with a history of breast cancer.

| | Placebo (N=9) | INTRAROSA (N=10) |
|-------------------------------|----------------|------------------|
| Estradiol | | |
| C _{max} (pg/mL) | 3.33 (±1.31) | 5.04 (±2.68) |
| AUC ₀₋₂₄ (pg·h/mL) | 66.49 (±20.70) | 96.93 (±52.06) |

Estradiol C_{avg (0-24)} 4.04 pg/mL (est.)

FDA Workshop on Product Labeling and Boxed Warning for Lower-Dose Vaginal Estrogen for Symptoms of Vulvar and Vaginal Atrophy (Genitourinary Syndrome of Menopause)

We are writing to you for two reasons:

1. To provide information about an upcoming US Food and Drug Administration (FDA) Workshop to be held on Tuesday, November 10, 2015, in Silver Spring, Maryland, on the subject of the product labeling of lower-dose vaginal estrogen. This meeting provides you the opportunity to provide public comments and testimonials on this subject.
2. To inform you of a Citizens' Petition proposed by NAMS that is being submitted to NAMS members and other colleagues for electronic signature by those who support the NAMS proposal for a label change.

FDA Workshop—November 10, 2015

FDA is announcing a public workshop and an opportunity for public comment on the topic of the labeling for lower-dose estrogen products delivered vaginally, to treat moderate to severe symptoms of vulvar and vaginal atrophy due to menopause. The workshop will address whether the current "Boxed Warning" section in the labeling is applicable in whole or in part to these lower-dose estrogen products. This meeting, a scientific workshop, will provide the opportunity for you to seek input from experts on the Boxed Warnings section and estrogen exposure relative to labeling of these lower-dose estrogen-alone products.

Detailed information about this workshop is provided [here](#). The meeting will be held at the FDA White Oak Campus, 10903 New Hampshire Avenue, Building 31 Conference Center, Section A of the Great Room (Room 1503), Silver Spring, Maryland, 20993. Entrance for the public meeting participants (non-FDA employees) is through Building 1.

Public Comment: For those who wish to give public comment during the November 10, 2015, public meeting, please [email](#) FDA by October 16, 2015, to register for the session. Additional registration will occur at the registration desk on the day of the meeting on a first-come, first-served basis if there is still time available during the session. Seating will be limited, so early registration is recommended.

Electronic Comments: Send your comments electronically by going [here](#) and clicking the "Comment Now!" button on the upper right (must be received by October 16, 2015, and you must identify your comments with the Agency/Docket Number 2015-N-3275). Submit written comments to the Division of Dockets Management (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Room 1061, Silver Spring, Maryland, 20852.

By signing on to this proposal and the Citizens' Petition, please provide your name, title, affiliations, and email [here](#).



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The North American Menopause Society
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Mayfield Heights, OH 44124

MAY 29 2018

Re: Docket No. FDA-2016-P-1246

Dear Dr. Manson and Dr. Pinkerton:

This letter responds to the citizen petition submitted by the Working Group on Women's Health and Well-Being in Menopause and the North American Menopause Society (collectively, Petitioners), which the Food and Drug Administration (FDA or the Agency) received on May 12, 2016 (Petition). Petitioners request FDA to "modify the label for low-dose vaginal estrogen products approved for treating symptoms of vulvovaginal atrophy (VVA)" (also referred to as vulvar and vaginal atrophy) and correspondingly amend FDA's draft guidance for industry: *Noncontraceptive Estrogen Drug Products for the Treatment of Vasomotor Symptoms and Vulvar and Vaginal Atrophy Symptoms — Recommended Prescribing Information for Health Care Providers and Patient Labeling* (Draft Guidance).^{1,2} Petitioners maintain that "[t]he label should be modified to accurately reflect the relevant evidence-based information for low-dose vaginal estrogen products."³

Specifically, Petitioners make the following requests regarding the prescribing information (which Petitioners refer to variously as the "package labeling," "label," "labeling," "product label," and "package label") of these products for treating VVA symptoms:

¹ Petition at 1. The Petition states that the requests do not apply to estrogen products approved for the treatment of vasomotor symptoms (hot flashes).

² The Draft Guidance recommends language for prescribing information for estrogen drug products that treat moderate to severe vasomotor symptoms and/or moderate to severe symptoms related to VVA. It also provides labeling recommendations for the patient package information. See Section I.D. of this letter for more information. To make sure you have the most recent version of a guidance, check the FDA Drugs guidance Web page at <http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm>.

³ Petition at 1.



WHI (Observational Study) To The Rescue!

From: Crandall CJ, Hovey KM, Andrews CA, et al. Breast cancer, endometrial cancer, and cardiovascular events in participants who used vaginal estrogen in the Women's Health Initiative Observational Study. *Menopause*. 2018 Jan;25(1):11-20

1993 to 2005

N=32,433 women without hysterectomy
3,003 women using vaginal estrogen

N=14,133 women with hysterectomy
1,207 using vaginal estrogen

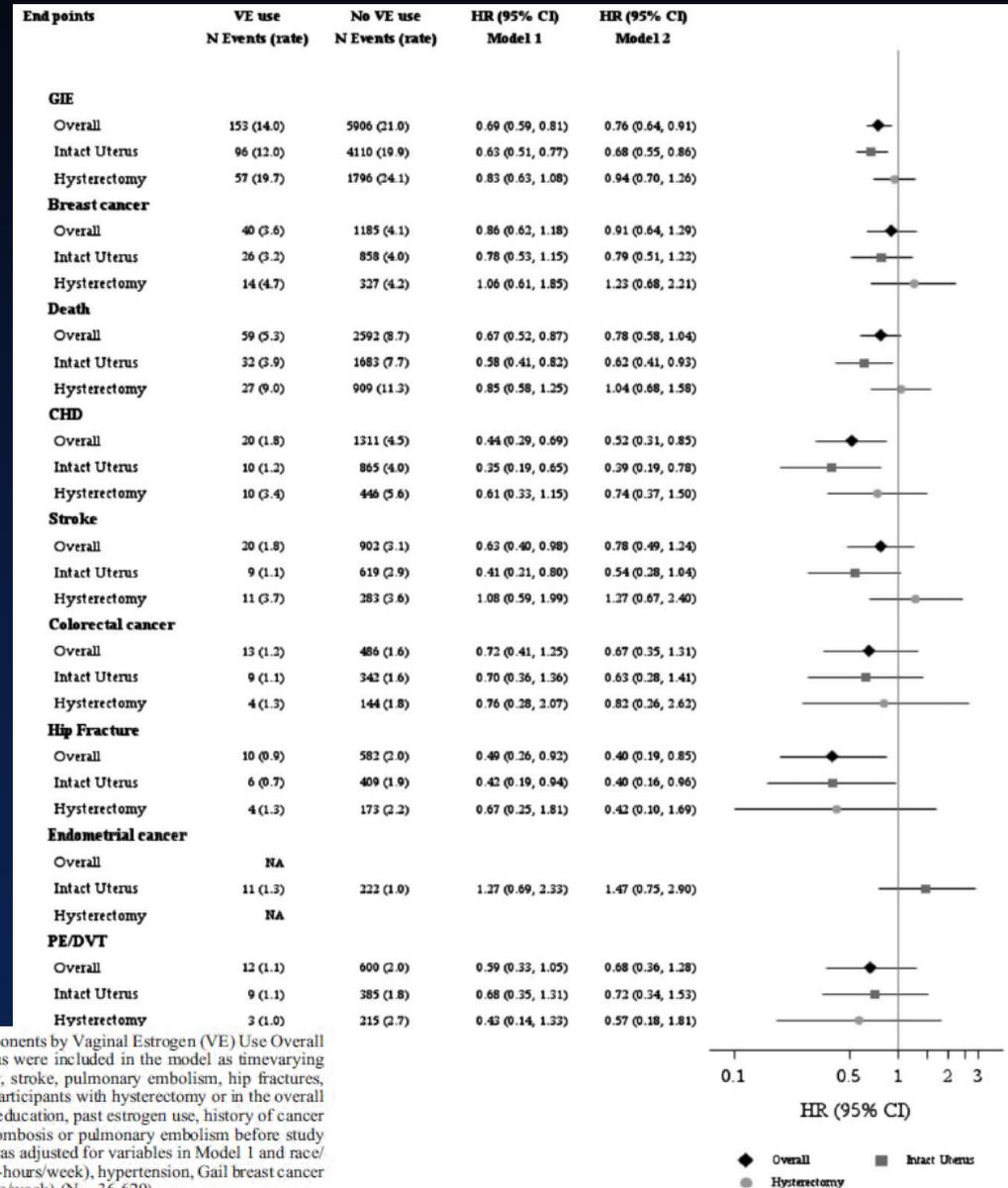


FIG. 2. Hazard Ratio (HR) and 95% Confidence Interval (CI) for Global Index Events (GIE) and Components by Vaginal Estrogen (VE) Use Overall and by Hysterectomy Status. VE includes vaginal cream or vaginal tablet. VE and hysterectomy status were included in the model as timevarying covariates. Global Index Event (GIE) is defined as time to first coronary heart disease, breast cancer, stroke, pulmonary embolism, hip fractures, colorectal cancer, endometrial cancer, or death. Analysis for endometrial cancer was not conducted in participants with hysterectomy or in the overall analytic sample. Rate are crude rates per 1000 person-years (N= 45,663). Model 1 is adjusted for age, education, past estrogen use, history of cancer before study baseline, history of cardiovascular disease before study baseline, history of deep vein thrombosis or pulmonary embolism before study baseline. Model for overall analytic sample also includes hysterectomy status. (N = 45,251). Model 2 was adjusted for variables in Model 1 and race/ethnicity, baseline body mass index, baseline diagnosis of diabetes, baseline physical activity (total MET-hours/week), hypertension, Gail breast cancer risk score, fracture after age 55 prior to study enrollment, smoking, income, and alcohol use (servings/week) (N = 36,629).



Support for the Contrary View (aka: “local is *not* local”)

- ❖ Kendall et. al. cautions that vaginal estradiol is contraindicated in postmenopausal women on adjuvant aromatase inhibitors¹.
- ❖ Labrie et. al. demonstrate that even small doses of vaginal preparations (Vagifem[®] 25 µg; Premarin[®] vaginal cream) result in significant systemic absorption through estrogen naive vaginas².
- ❖ Naessen et. al. showed that even 7.5 µg/24h could improve the lipid profile and bone density without affecting the endometrium³⁻⁵.

¹Kendall A, et. al. Ann Oncol 2006;17:584-587. ²Labrie F, et. al. Menopause 2009;16:30-36.

³⁻⁵Naessen T, et. al. J Clin Endocrinol Metab 2001;86:2757-2762.; Am J Obstet Gynecol 1997;177:115-119.; Am J Obstet Gynecol 2002;186:944-947.

AUGS SPECIAL ISSUE SUBMISSION

Vaginal Estrogen as First-Line Therapy for Recurrent Urinary Tract Infections in Postmenopausal Women and Risk Factors for Needing Additional Therapy

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Renee Bassaly, DO,* Allison Wyman, MD,* and Kristie Greene, MD**

Female Pelvic Medicine & Reconstructive Surgery • Volume 27, Number 3, March 2021

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How Soon Is Response Evident?

- ❖ Typically within a few weeks
 - May take up to 6 weeks
 - Full effect by 12 weeks
- ❖ 80% to 90% report subjective improvement

Conclusions

- ❖ VVA/GSM is natural sign of aging. It has significant biological, psychological and social consequences. Estrogen based treatment options, particularly current low dose therapies are:
 - Effective FDA-approved treatment options.
 - Result in minimal systemic absorption.
 - Provide long-term safety without medical risk or endometrial stimulation.



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NAMS POSITION STATEMENT

The 2020 genitourinary syndrome of menopause position statement of The North American Menopause Society

The NAMS 2020 GSM Position Statement Editorial Panel*. The 2020 genitourinary syndrome of menopause position statement of The North American Menopause Society. *Menopause*. 2020 Sep;27(9):976-992.
Stephanie S. Faubion, Sheryl A. Kingsberg, Jan L. Shifren, Caroline Mitchell, Andrew M. Kaunitz, Lisa Larkin, Susan Kellogg Spadt, Amanda Clark, James A. Simon

CURRENT VAGINAL THERAPIES: EFFICACY BASED ON PHYSIOLOGY

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Editor Emeritus, *The Journal of Sexual Medicine*

**Editor Emeritus, *International Journal of Impotence
Research***



Basic facts about menopause

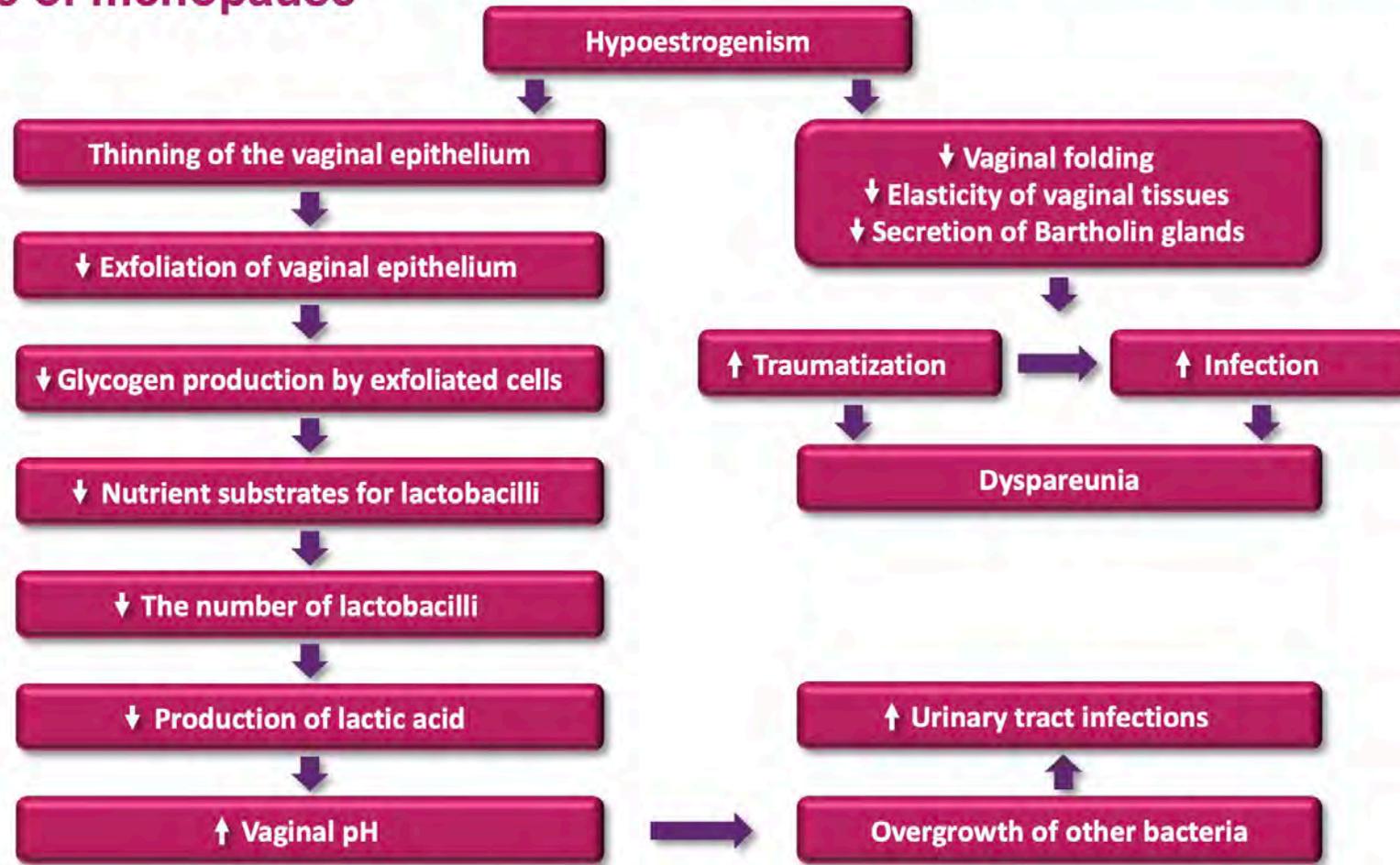
**FDA approved local vaginal treatments –
estrogen based**

**FDA approved local vaginal treatments –
estrogen and androgen based**

**Can vaginal treatments safely and effectively
treat the vestibule**

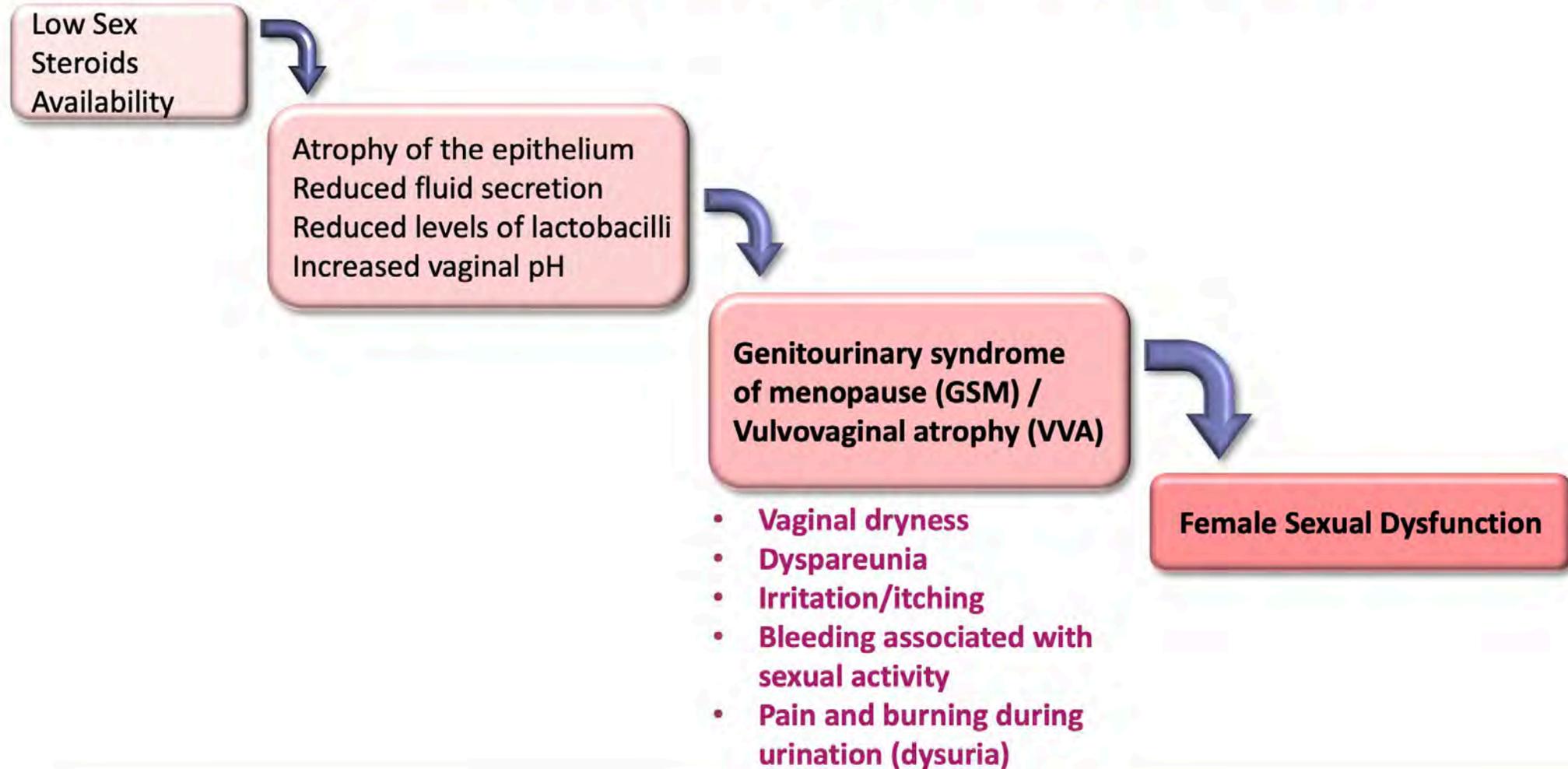
CURRENT VAGINAL THERAPIES: EFFICACY BASED ON PHYSIOLOGY

Multiple changes in the vulvovaginal environment lead to Genitourinary syndrome of menopause¹

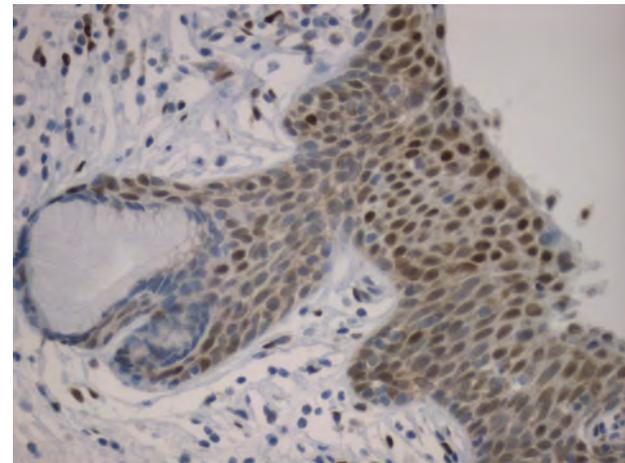
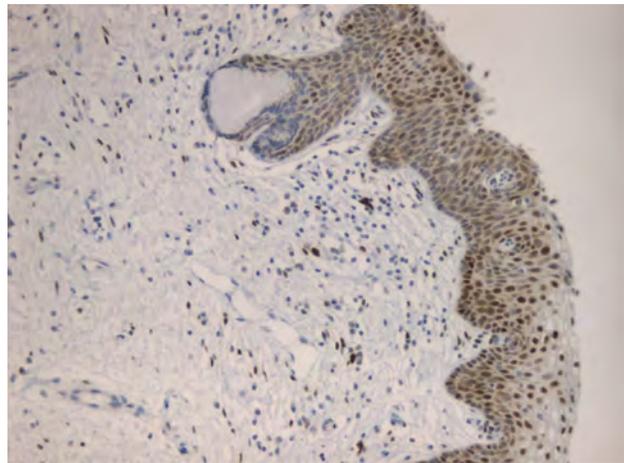
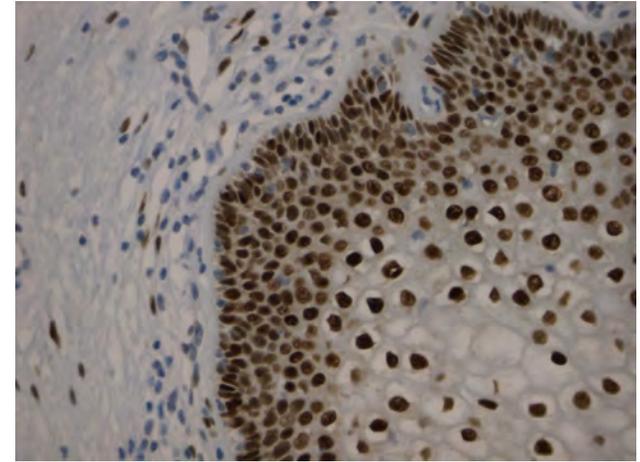
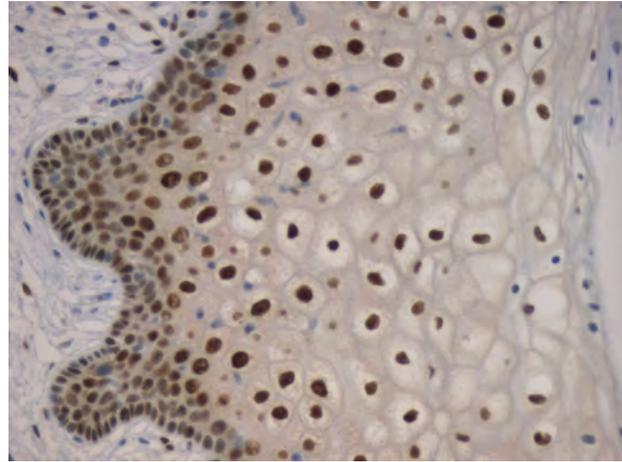
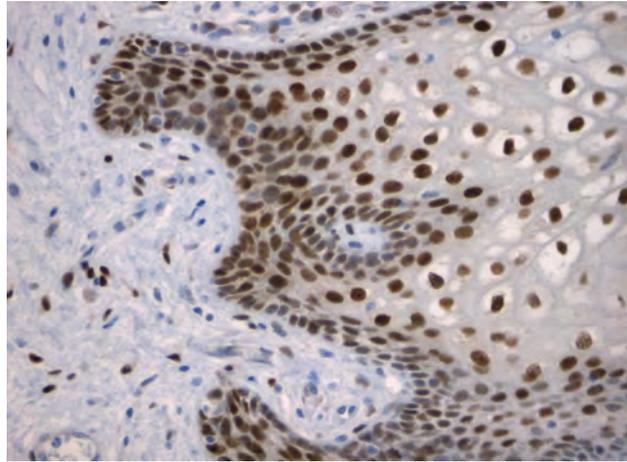


CURRENT VAGINAL THERAPIES: EFFICACY BASED ON PHYSIOLOGY

Menopause – Genitourinary disorders, a cascade of events

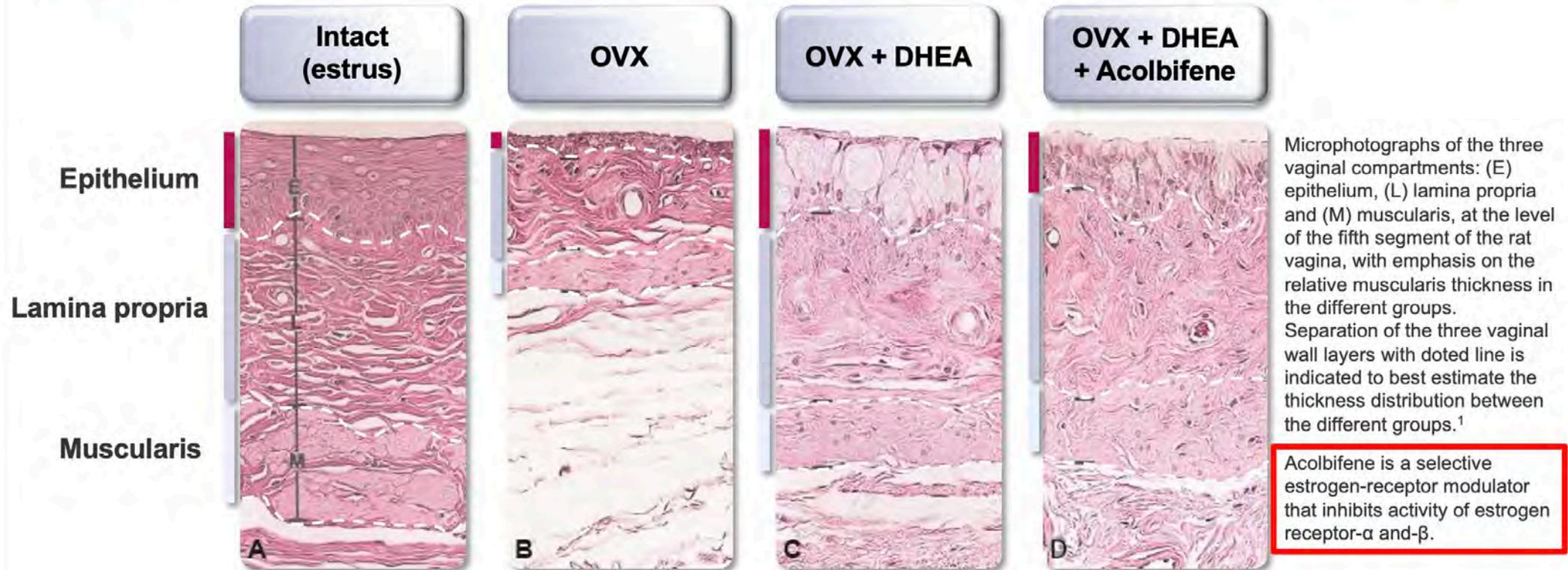


Estrogen Receptors in the Vestibule



CURRENT VAGINAL THERAPIES: EFFICACY BASED ON PHYSIOLOGY

Vaginal health is maintained by both androgens and estrogens¹



Micrographs of rat vagina: A) intact, B) after ovariectomy, C) after ovariectomy but treated with DHEA D) after ovariectomy but treated with DHEA and the anti-estrogen compound acolbifene¹

OVX, ovariectomy

1. Berger L et al. *J Ster Biochem Mol Biol* 2005;96:201-215.

Differential expression of oestrogen receptor isoforms and androgen receptor in the normal vulva and vagina compared with vulval lichen sclerosus and chronic vaginitis

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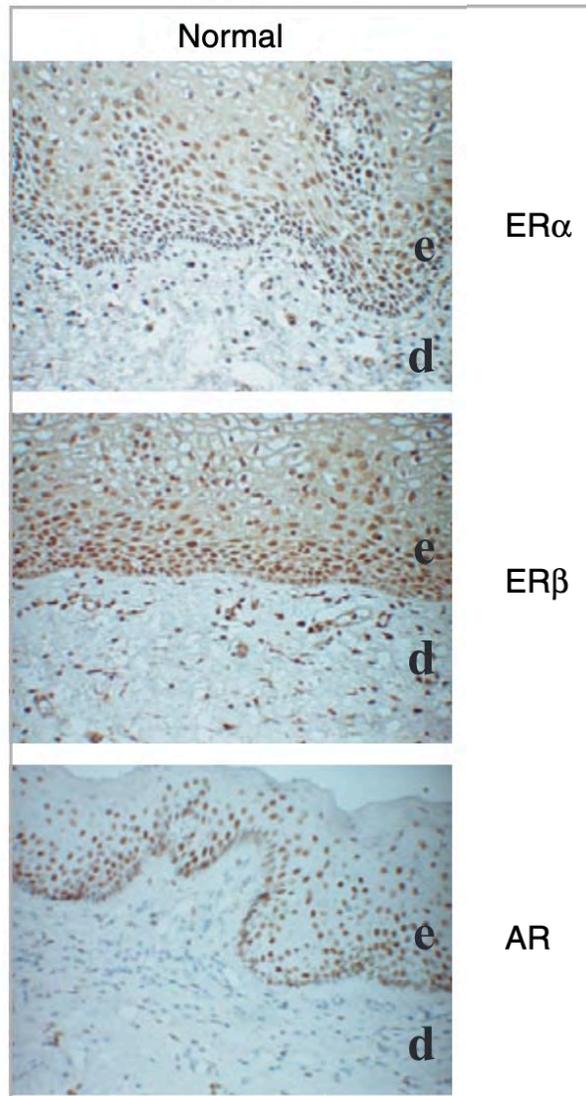


Fig 2. Oestrogen receptor α (ER α), oestrogen receptor β (ER β), androgen receptor (AR) and Ki-67 staining of normal vulva, vulval lichen sclerosus (VLS) and vulval squamous hyperplasia (VSH). ER α is expressed in the nuclei of squamous epithelial cells proximal to nondifferentiated basal epithelial cells (e) and subepithelial connective tissue dermal cells (d); ER β is expressed in the nuclei of squamous epithelial cells proximal to nondifferentiated basal epithelial cells (e) and subepithelial connective tissue cells (d); AR is expressed in the nuclei of nondifferentiated basal epithelial cells (e) and connective tissue cells (d). AR immunoreactivity in basal epithelial cells appears to be significantly weaker in VSH and VLS compared with normal vulva. Ki-67 is expressed in the nuclei of squamous epithelial cells (*) proximal to nondifferentiated parabasal epithelial cells (arrow). Numbers of proliferating squamous epithelial cells are markedly increased in squamous hyperplasia (large bracket), and reduced in VLS compared with normal vulval epithelial cell populations (small bracket). Original magnification $\times 200$.

Correlation of androgen receptors, aromatase, and 5- α reductase in the human vagina with menopausal status

Jennifer R. Berman M.D.^{a,*,} Fernando G. Almeida M.D.^a, Julie Jolin M.D.^b, Shlomo Raz M.D.^a, Gautam Chaudhuri M.D.^b, Nestor F. Gonzalez-Cadavid Ph.D.^{a, c}

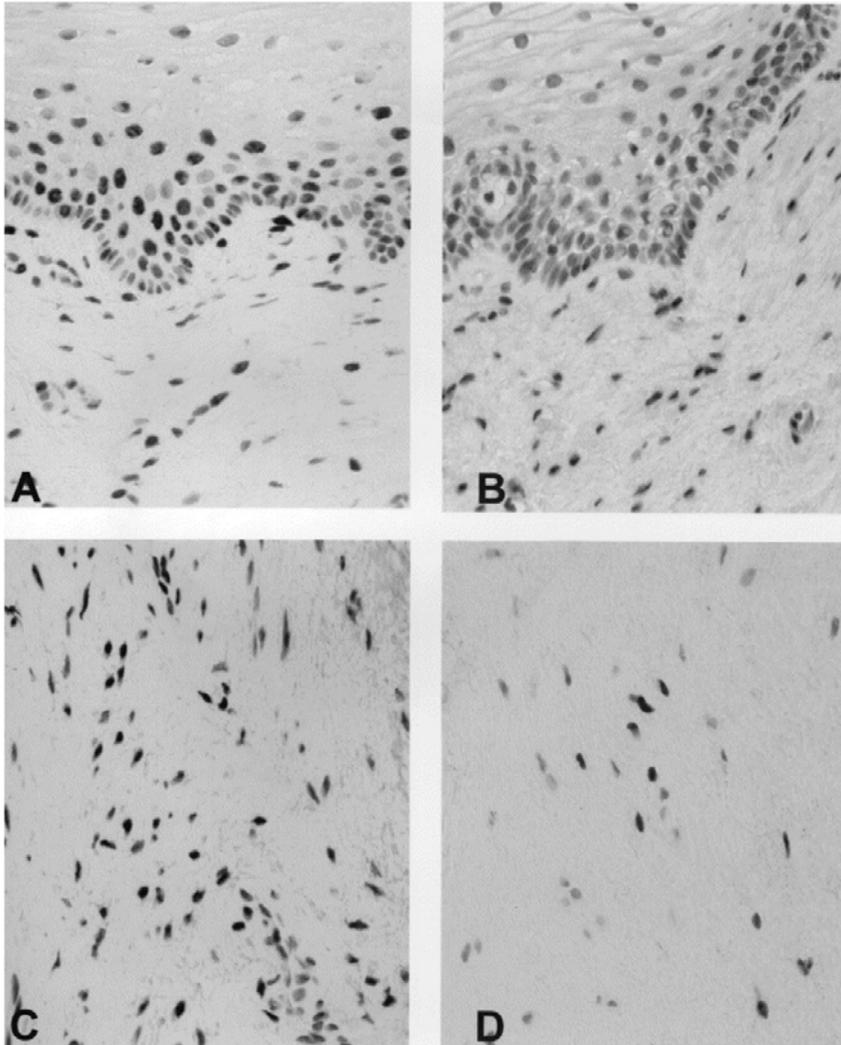


FIGURE 2. Immunohistochemical detection of vaginal stromal androgen receptors in women with and without hormone therapy (HT). Paraffin-embedded sections were immunostained with an antibody against the androgen receptor. (A), Vaginal stroma and epithelium; (B), negative control; (C), stromal androgen receptor expression from a patient not receiving HT; and (D), from a patient with HT. Magnification, $\times 200$.

Correlation of androgen receptors, aromatase, and 5- α reductase in the human vagina with menopausal status

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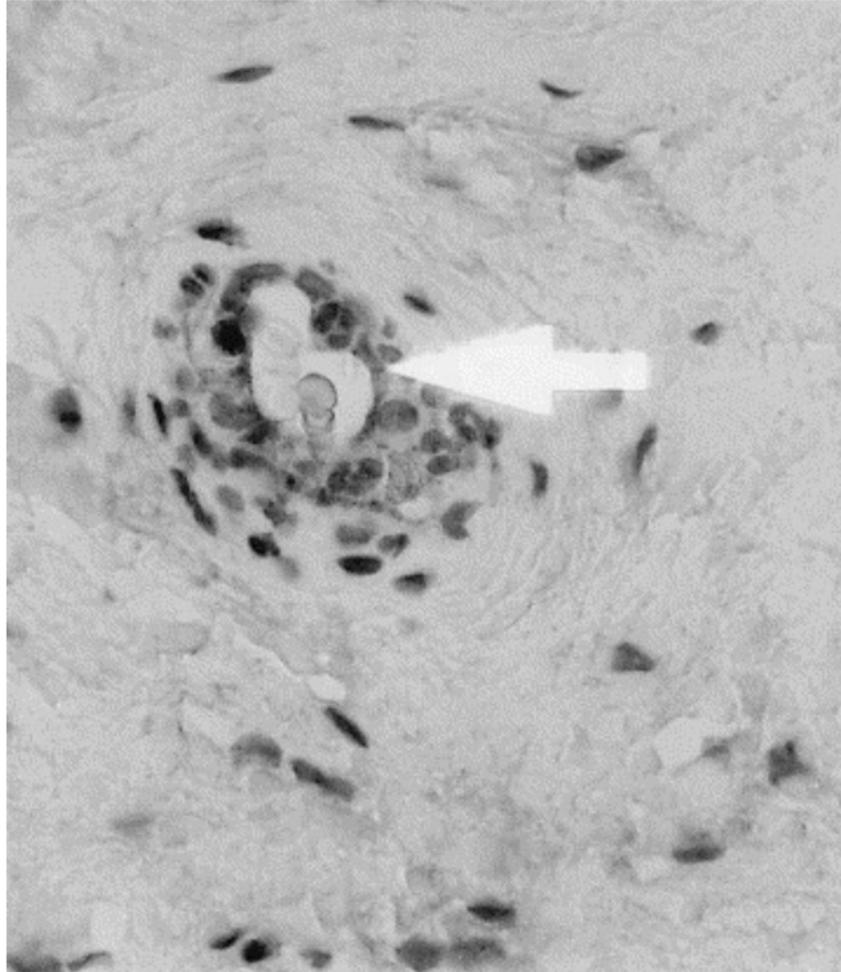


FIGURE 3. Immunohistochemical detection of androgen receptors in vascular endothelial smooth muscle of the vagina; *arrow*: androgen receptor staining in vascular endothelial cell.

Androgen receptor expression in the human vagina under different physiological and treatment conditions

M Baldassarre^{1,2,3}, AM Perrone^{2,4}, FA Giannone^{1,3}, F Armillotta^{2,4}, C Battaglia^{2,4}, A Costantino^{2,4}, S Venturoli^{2,4} and MC Meriggiola^{2,4}

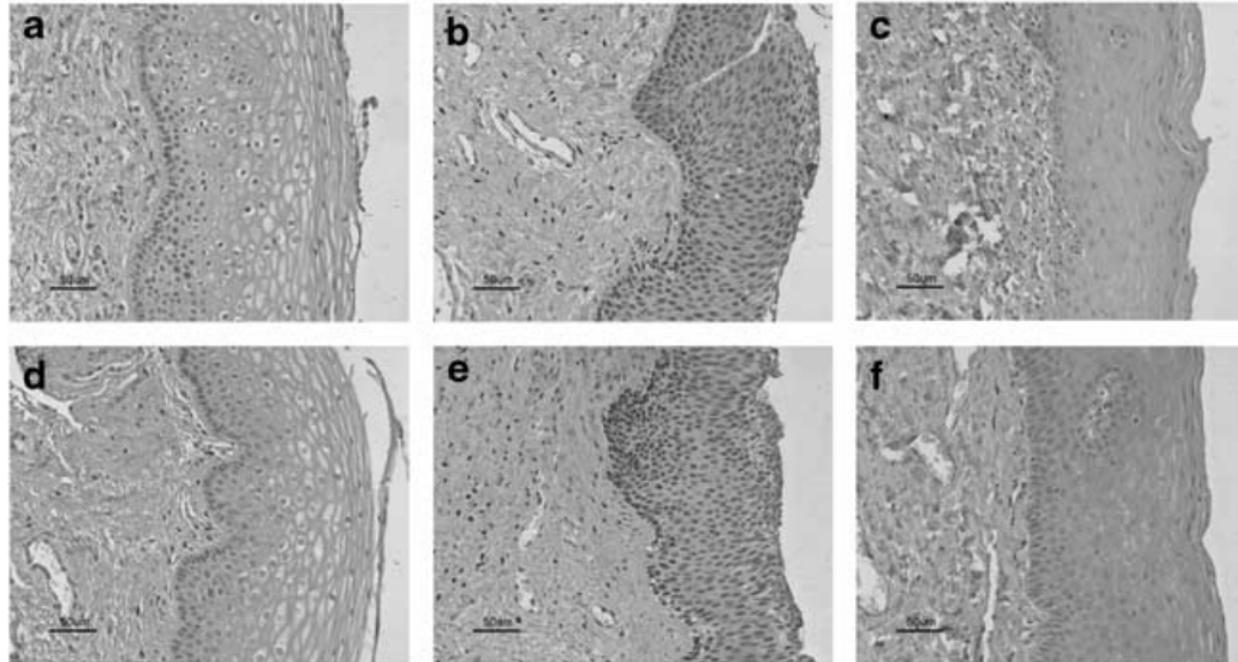


Figure 1. Androgen receptor (AR) localization in vaginal tissue. Immunohistochemical detection of AR in the human vaginal mucosa and stroma of premenopausal (PrM) (a) proximal and (d) distal, female to male (FtM) (b) proximal and (e) distal and menopausal (M) (c) proximal and (f) distal subjects.

Androgen receptor expression in the human vagina under different physiological and treatment conditions

M Baldassarre^{1,2,3}, AM Perrone^{2,4}, FA Giannone^{1,3}, F Armillotta^{2,4}, C Battaglia^{2,4}, A Costantino^{2,4}, S Venturoli^{2,4} and MC Meriggiola^{2,4}

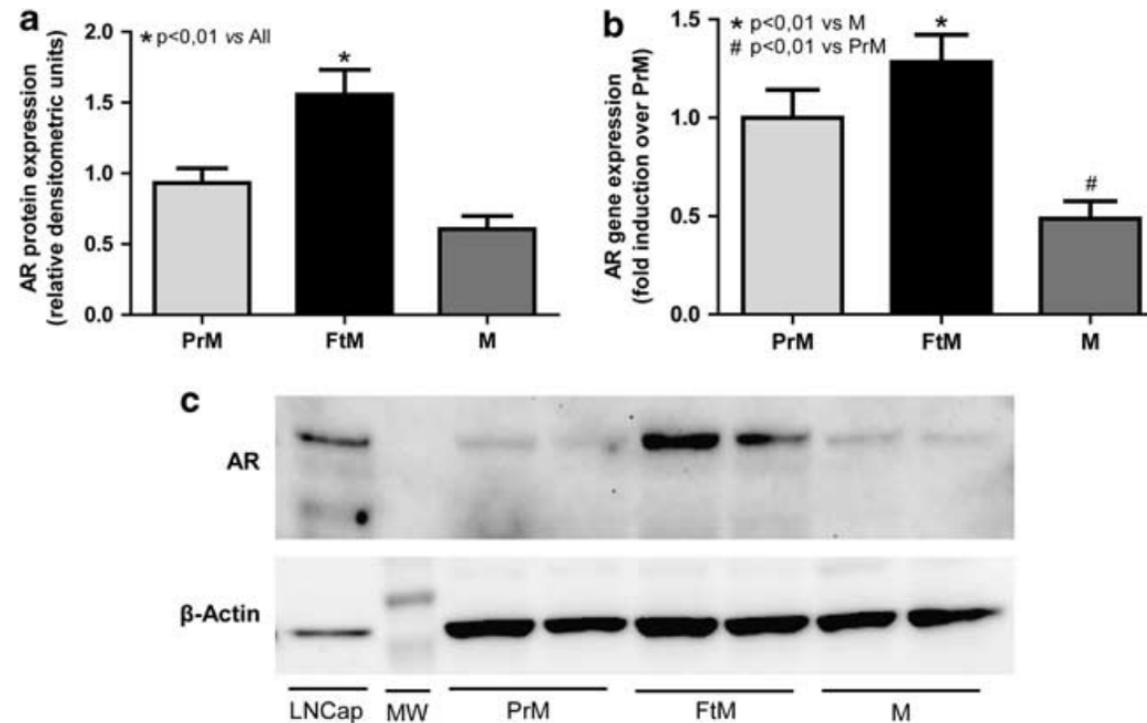
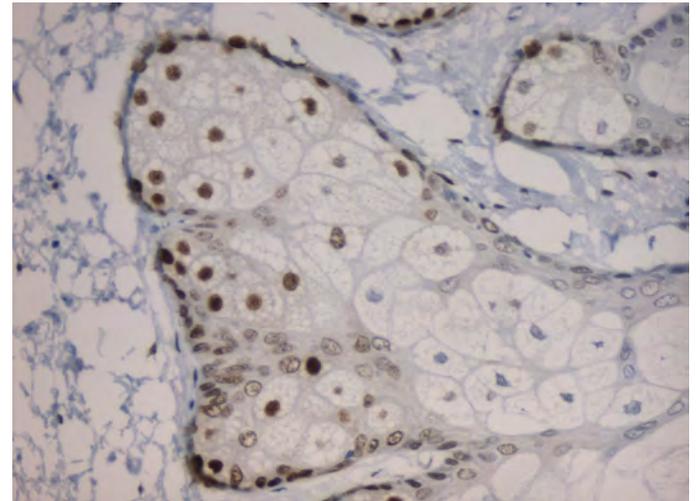
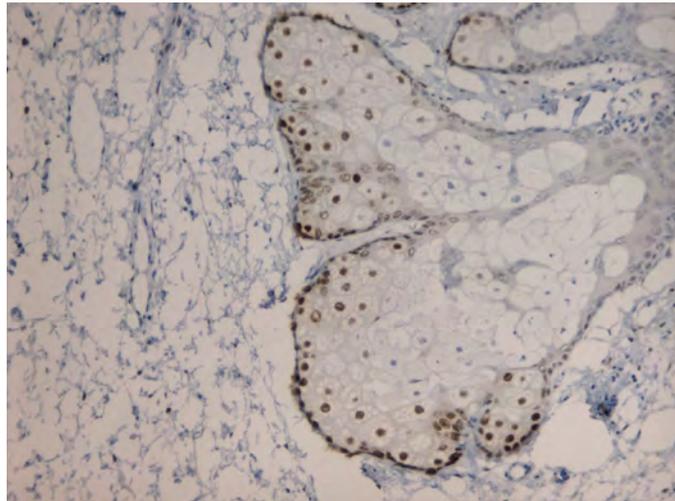
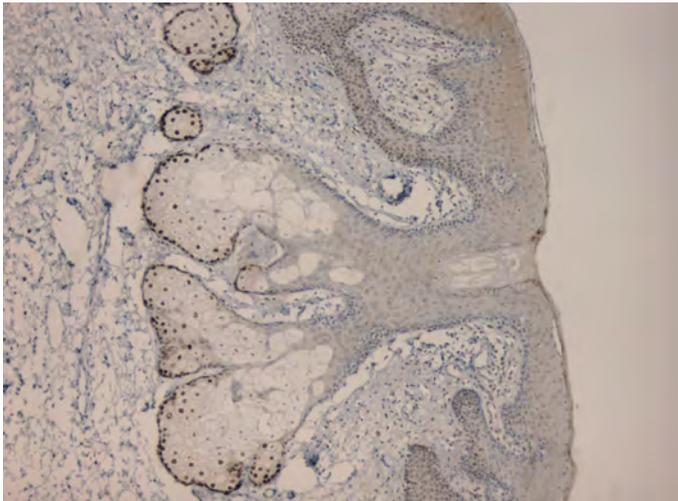
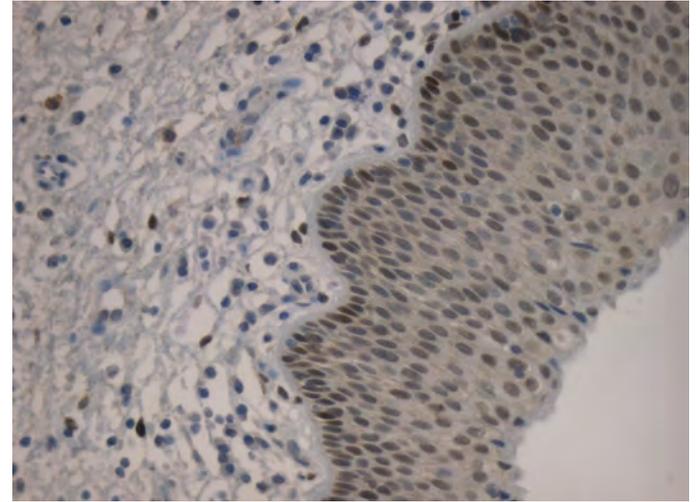
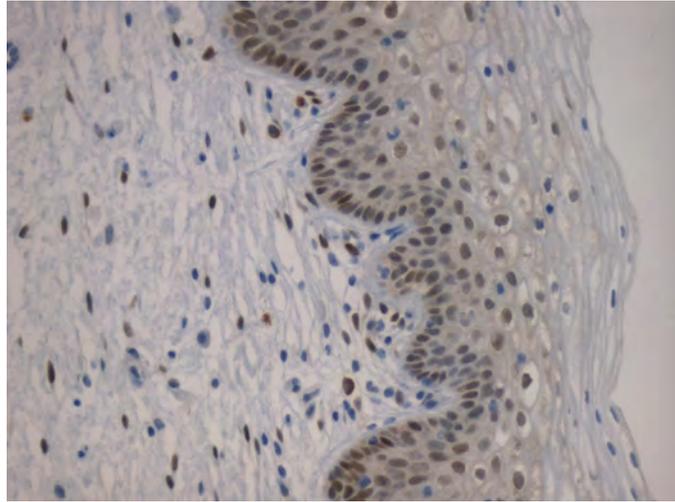
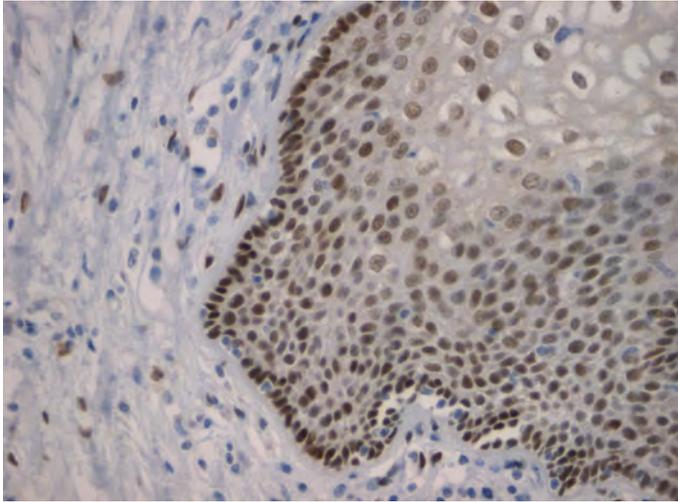


Figure 2. Androgen receptor (AR) gene and protein expression. Change in AR protein (a) and gene (b) expression in vaginal biopsies from the three experimental groups. Representative western blot analysis of AR in vaginal tissue (c). Data are expressed as mean \pm s.e.m.

Androgen Receptors in the Vestibule



CURRENT VAGINAL THERAPIES: EFFICACY BASED ON PHYSIOLOGY

DECREASE OF BOTH ANDROGENS AND ESTROGENS AFTER MENOPAUSE

Serum estrogen levels drop markedly after menopause, while androgens decline with age.^{1,2}

| | ESTRADIOL (pg/mL) | TESTOSTERONE (ng/dL) |
|---------------------------------|-------------------|----------------------|
| CHILDHOOD ³ | <13 | 20 |
| REPRODUCTIVE YEARS ³ | 40-350 | 20-70 (mean=35) |
| POSTMENOPAUSAL ³ | 13 | 25 |

1 ng/dL=10 pg/mL (ie, 25 ng/dL = 250 pg/mL).

Women have higher levels of testosterone than estradiol. Testosterone is the most abundant active female sex hormone⁴

"...decreasing androgens with advancing age and cessation of estrogen production during menopause are important contributory factors in the development of the signs and symptoms of GSM."^{3*}

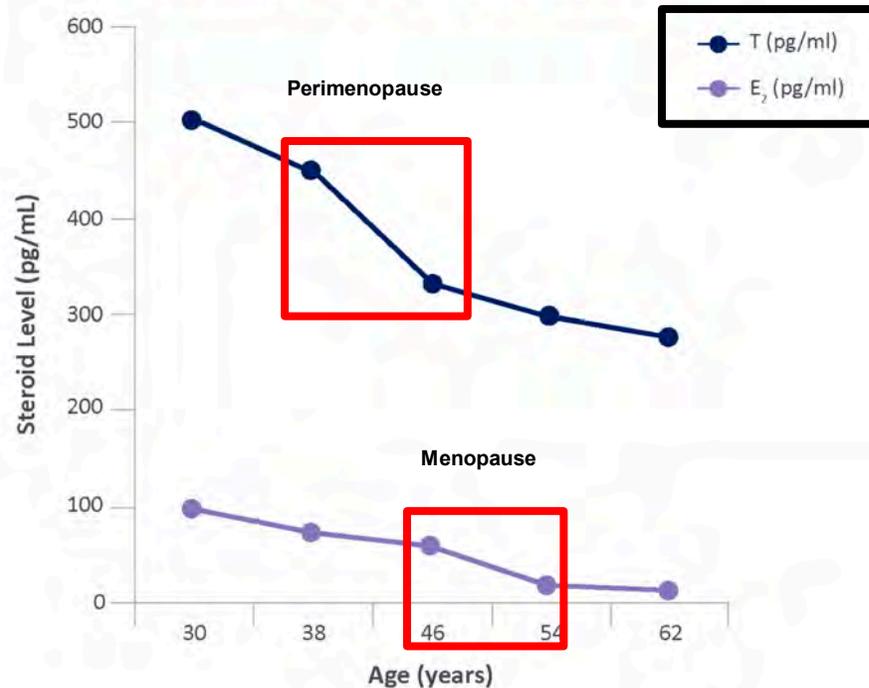
-Traish et al. *Sex Med Rev.* 2018.

CURRENT VAGINAL THERAPIES: EFFICACY BASED ON PHYSIOLOGY

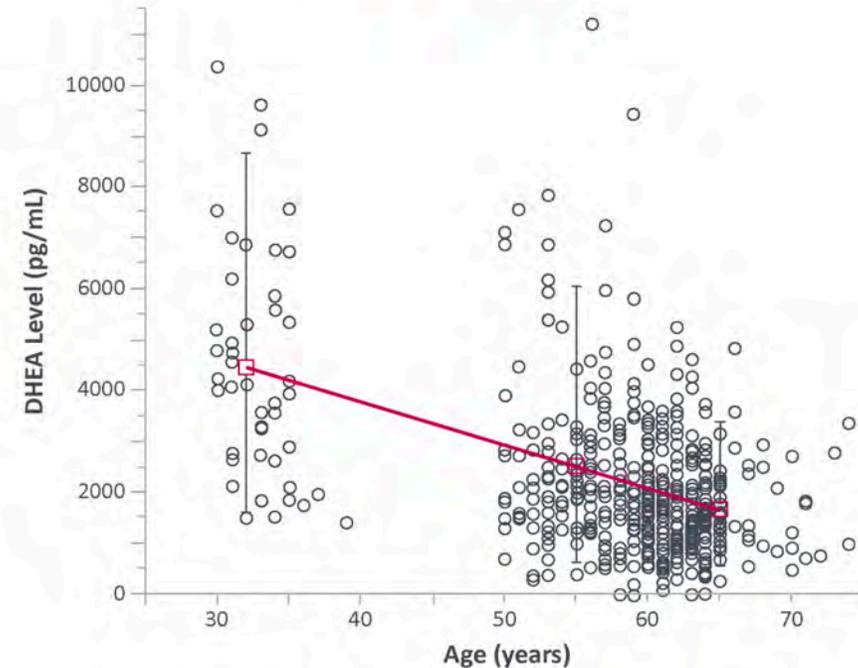
Decline of Sex Steroids

1 ng/dl = 10 pg/ml
40 ng/dl = 400 pg/ml

Testosterone and Estradiol Levels¹



DHEA Levels²



DHEA=dehydroepiandrosterone. E₂=estradiol. T=testosterone.

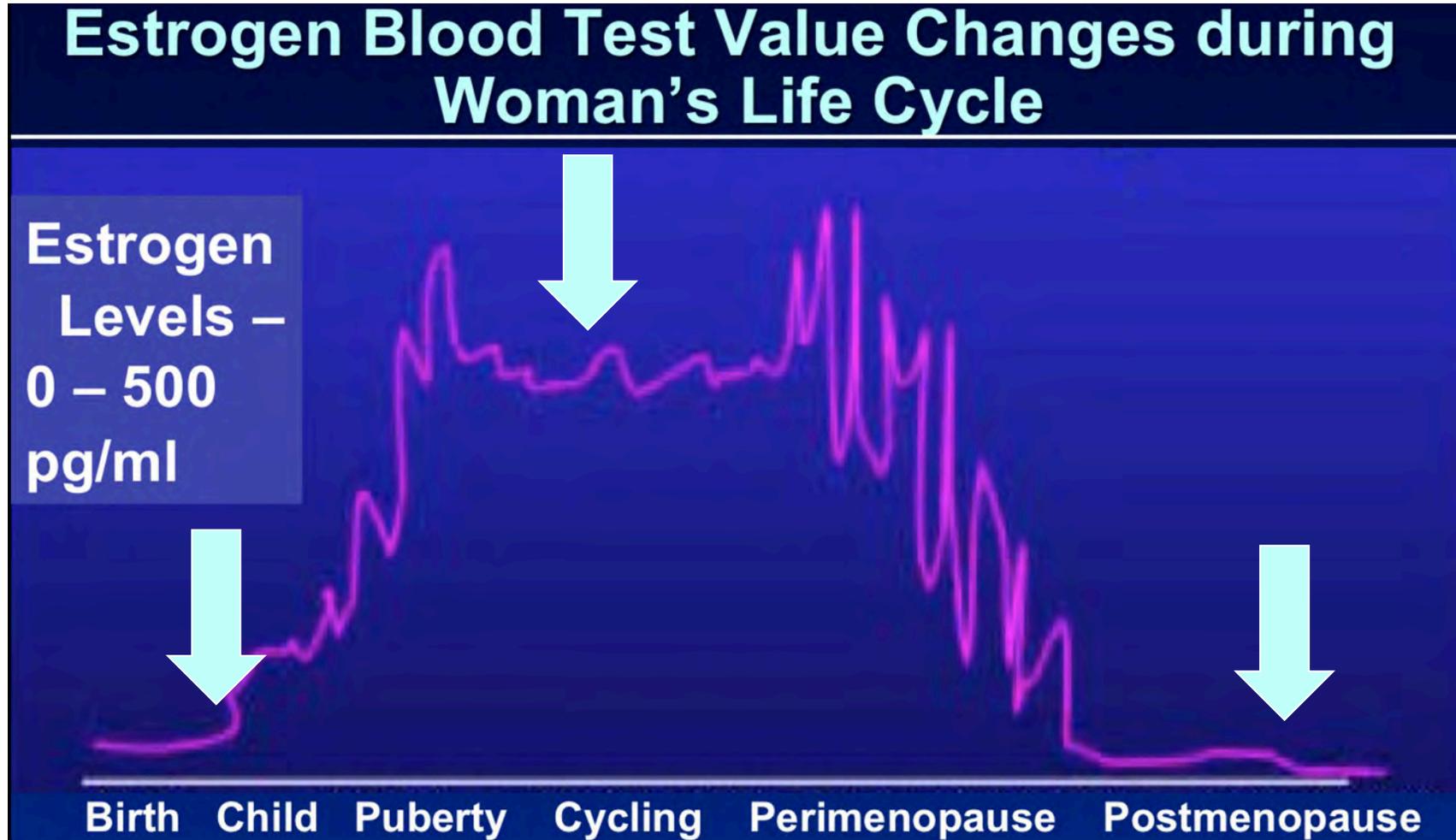
Figures adapted from: 1. Glaser R, Dimitrakakis C. *Maturitas*. 2013;74(3):230-234. 2. Labrie F. *Menopause Manag*. 2010;19:14-24.

Women have higher levels of testosterone than estradiol. Testosterone is the most abundant active female sex hormone⁴

"...decreasing androgens with advancing age and cessation of estrogen production during menopause are important contributory factors in the development of the signs and symptoms of GSM."^{3*}

-Traish et al. *Sex Med Rev*. 2018.

CURRENT VAGINAL THERAPIES: EFFICACY BASED ON PHYSIOLOGY



CURRENT VAGINAL THERAPIES: EFFICACY BASED ON PHYSIOLOGY



CURRENT VAGINAL THERAPIES: EFFICACY BASED ON PHYSIOLOGY

ANDROGEN EFFECTS

Three Testosterone-Dependent
Organs in the Vestibule

Glans clitoris
Minor Vestibular Glands
Peri-urethral tissue – G-spot

Pre-Testosterone Treatment

Post-Testosterone Treatment



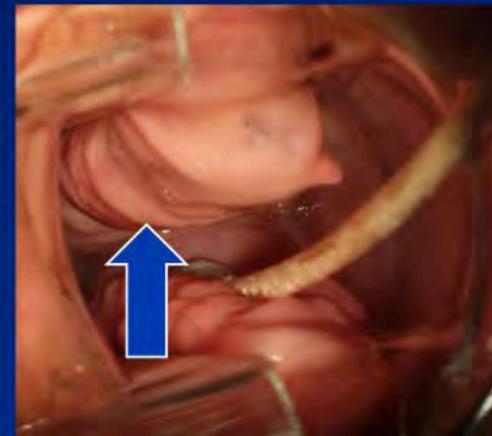
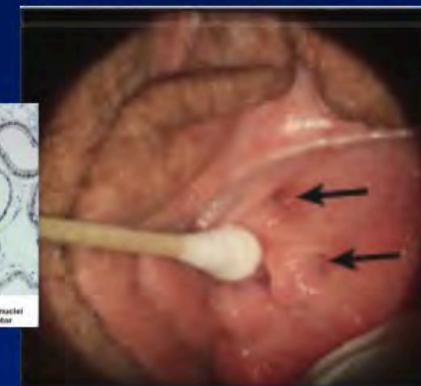
A Live output to patient monitor
B Zoom setting
C Vulvoscopy scope with camera
Focus adjustment
Live output to patient monitor
Vulvoscopy light source and output

Vulvoscopy diagnostic examination

Q-tip indicating Hart's line

Epidermal cyst

Fibroma pendulans

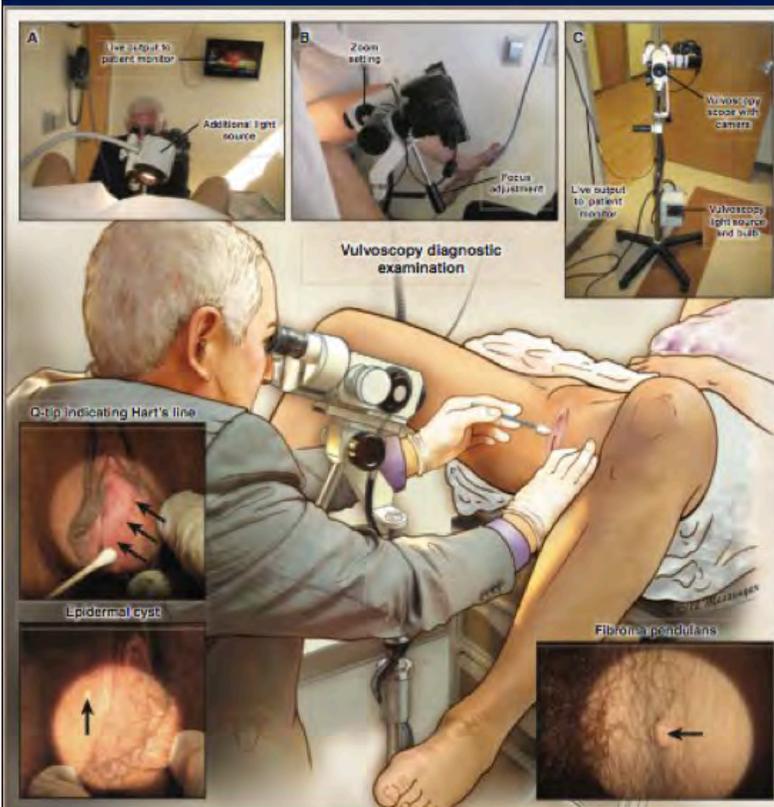
A diagram illustrating the vulvoscopy diagnostic examination. It shows a patient lying on their back with a vulvoscopy scope inserted into the vagina. The diagram includes labels for 'Live output to patient monitor', 'Zoom setting', 'Vulvoscopy scope with camera', 'Focus adjustment', and 'Live output to patient monitor'. Below the main diagram are three smaller images: 'Q-tip indicating Hart's line' showing a Q-tip touching the clitoris, 'Epidermal cyst' showing a small bump on the vulva, and 'Fibroma pendulans' showing a larger, pendulous growth on the vulva.

CURRENT VAGINAL THERAPIES: EFFICACY BASED ON PHYSIOLOGY

ESTROGEN EFFECTS

Two Estradiol-Dependent
Organs – During Vulvoscopy

Labia minora
Vagina



Low Estrogen State



Resorption of Labia Minora



Reduced vaginal rugae, pH >5

Robust Estrogen State



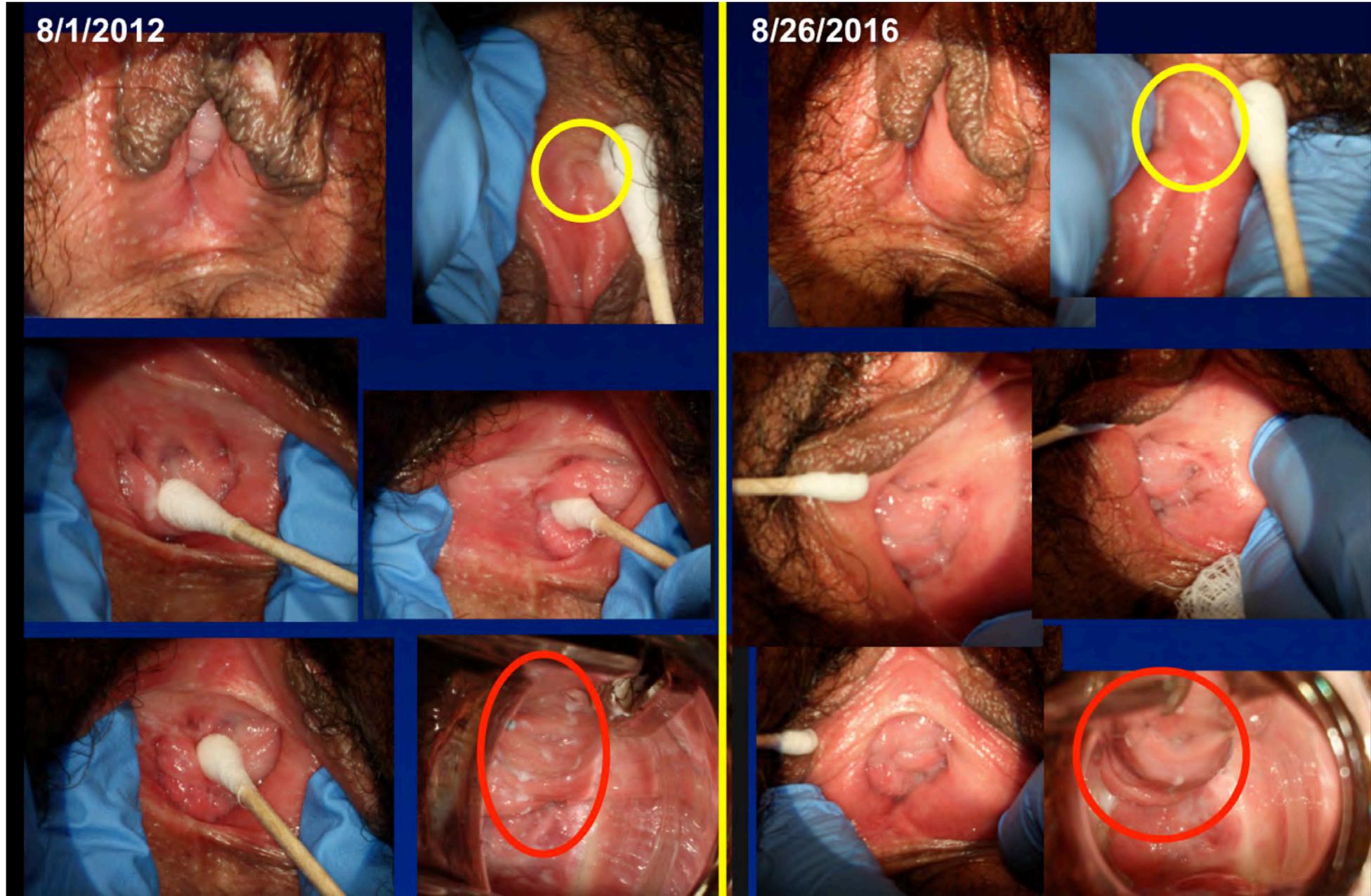
Labia Minora Normally Meet at
Posterior Fourchette



Robust vaginal rugae, pH 4

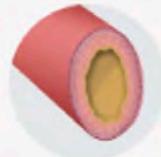
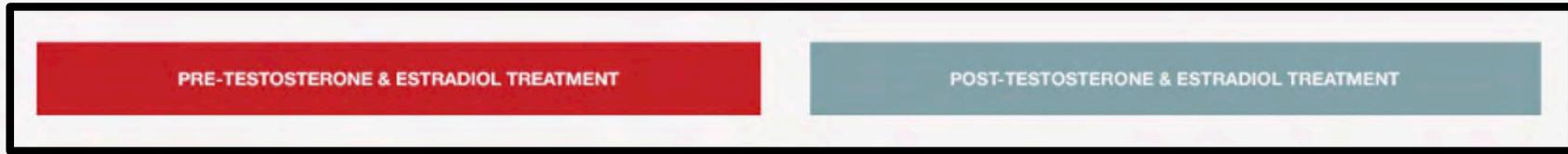
CURRENT VAGINAL THERAPIES: EFFICACY BASED ON PHYSIOLOGY

ANDROGEN AND ESTROGEN COMBINED TREATMENT



CURRENT VAGINAL THERAPIES: EFFICACY BASED ON PHYSIOLOGY

ANDROGEN AND ESTROGEN COMBINED TREATMENT



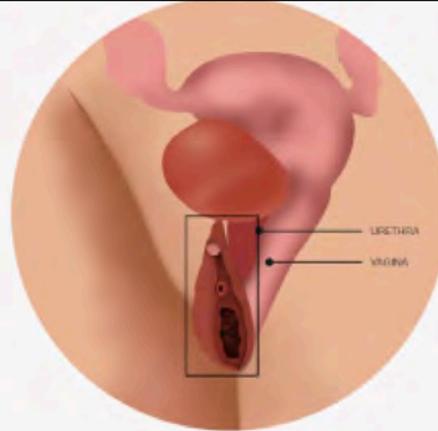
URETHRA



URETHRAL MEATUS



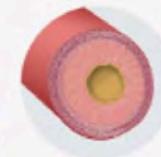
VULVA, VESTIBULE, URETHRAL MEATUS & CLITORIS



URETHRA
VAGINA



VULVA, VESTIBULE, URETHRAL MEATUS & CLITORIS



URETHRA

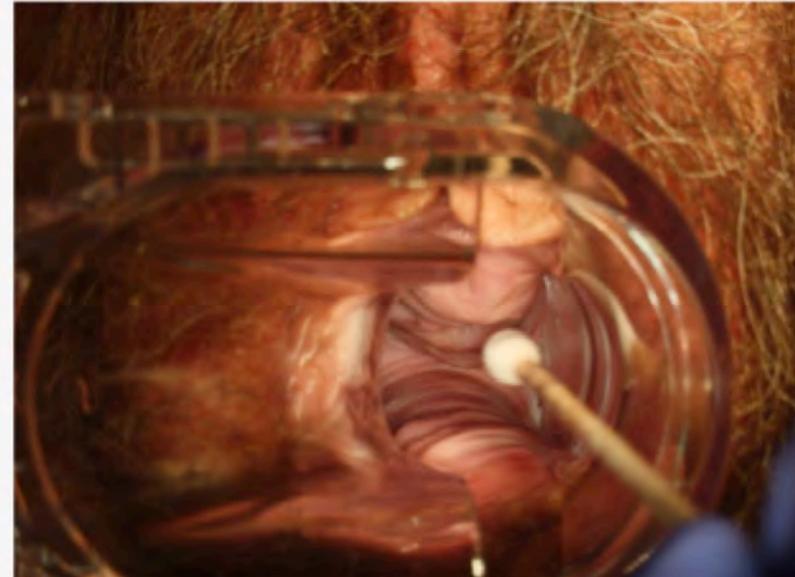
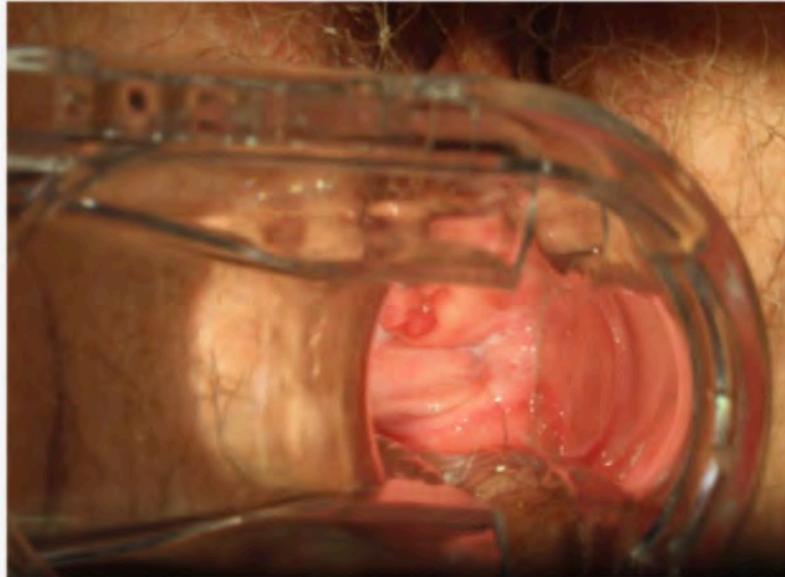
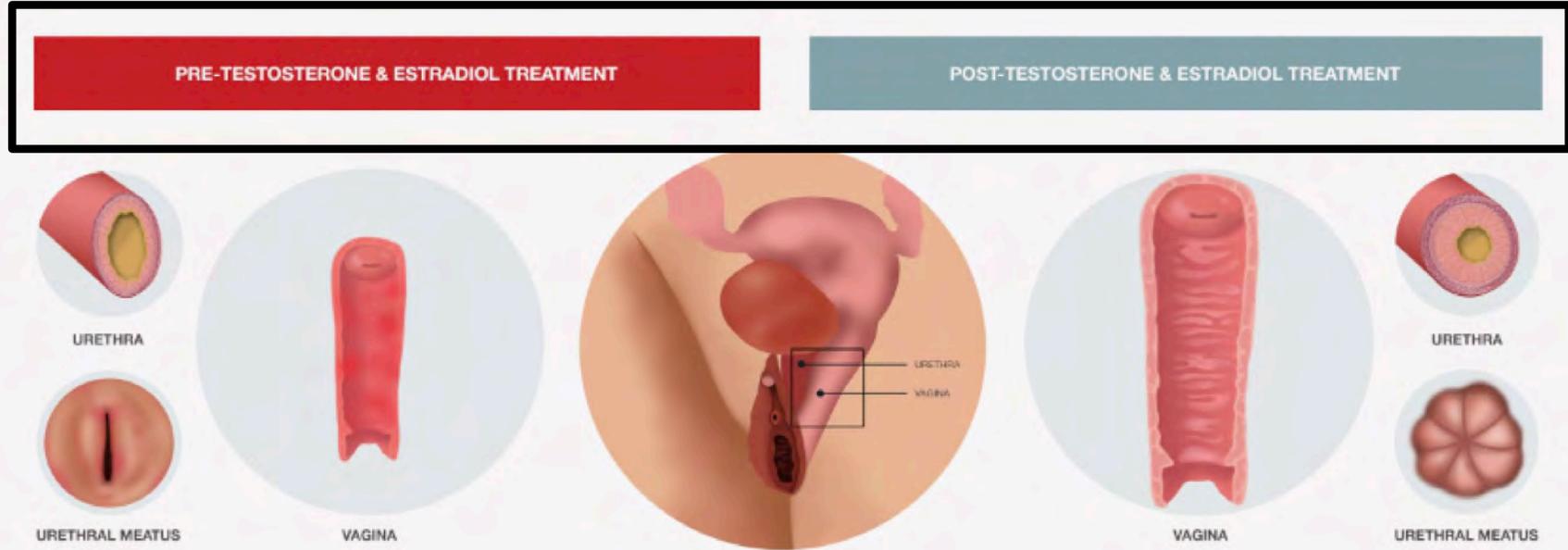


URETHRAL MEATUS



CURRENT VAGINAL THERAPIES: EFFICACY BASED ON PHYSIOLOGY

ANDROGEN AND ESTROGEN COMBINED TREATMENT



Take Home Message:

Menopause = ↓ estradiol blood test value, ↓ progesterone blood test value, ↑ FSH/LH and ↓ testosterone, ↓ calculated free testosterone, ↓ dihydrotestosterone

Do NOT treat some women with biologically identical hormones

These women usually not distressed by menopausal (especially sexual dysfunction) symptoms or usually view hormone risks greater than hormone benefits

Treat some women with biologically identical hormones

These women usually distressed by menopausal (especially sexual dysfunction) symptoms or usually view hormone benefits greater than hormone risks

CURRENT VAGINAL THERAPIES: EFFICACY BASED ON PHYSIOLOGY

| Labs | | Request - Test Name | Value | Units | Range | Observed Date |
|----------------|-----------------------------|--|--------|--------|-------------|---------------|
| ■ ANDROGENS | Calculated Fr Testo. | | | | | |
| | | Calculated Free Testosterone [SDSM code] | 0.0139 | ng/dL | 0.6-0.8 | 7/24/2021 |
| ■ ESTROGENS | FSH | | | | | |
| | | Follicle-Stimulating Hormone (FSH, Follitropin), Serum | 59.8 | mIU/mL | 1-19 | 7/24/2021 |
| ■ PROGESTERONE | Testosterone Tot Ser | | | | | |
| | | Testosterone, Total, Serum | <3 | ng/dL | 3-67 | 7/24/2021 |
| | LH | | | | | |
| | | Luteinizing Hormone (Lutropin), Serum | 39.1 | mIU/mL | 1-9 | 7/24/2021 |
| | TSH | | | | | |
| | | Thyroid Stimulating Hormone (TSH) | 2.660 | uIU/mL | 0.450-4.500 | 7/24/2021 |
| | Dihydrotestosterone | | | | | |
| | | Dihydrotestosterone (DHT) | 3.4 | ng/dL | 4-22 | 7/24/2021 |
| | Prolactin | | | | | |
| | | Prolactin | 10.5 | ng/mL | 4.8-23.3 | 7/24/2021 |
| | Vitamin D, 25-Hydrox | | | | | |
| | | Vitamin D 25-OH Total | 55.6 | ng/mL | 30-100 | 7/24/2021 |
| | Estradiol, Serum | | | | | |
| | | Estradiol, Serum (Oestradiol, E2, 17-beta Estradiol, E-17) | <5.0 | pg/mL | <20-47 | 7/24/2021 |
| | Progesterone | | | | | |
| | | Progesterone | <0.1 | ng/mL | 0.1-0.8 | 7/24/2021 |
| | Hematocrit | | | | | |
| | | Hematocrit (HCT) | 40.7 | % | 34.0-46.6 | 7/24/2021 |
| | Sex Horm. Bind. Glob | | | | | |
| | | Sex Hormone Binding Globulin (Testosterone-estrogen Binding Globulin; TeBG), Serum | 121 | nmol/L | 17.3-125 | 7/24/2021 |

CURRENT VAGINAL THERAPIES: EFFICACY BASED ON PHYSIOLOGY

| Labs | | Request - Test Name | Value | Units | Range | Observed Date |
|--------------|-----------------------------|--|--------|--------|-------------|---------------|
| ANDROGENS | Estradiol, Serum | Estradiol, Serum (Oestradiol, E2, 17-beta Estradiol, E-17) | <5.0 | pg/mL | <20-47 | 12/29/2020 |
| | ESTROGENS | Calculated Fr Testo. | | | | |
| PROGESTERONE | | Calculated Free Testosterone [SDSM code] | 0.0428 | ng/dL | 0.6-0.8 | 12/18/2020 |
| | | Sex Horm. Bind. Glob | | | | |
| | | Sex Hormone Binding Globulin (Testosterone-estrogen Binding Globulin; TeBG), Serum | 140.0 | nmol/L | 17.3-125.0 | 12/18/2020 |
| | Vitamin D, 25-Hydrox | Vitamin D 25-OH Total | 17.4 | ng/mL | 30.0-100.0 | 12/18/2020 |
| | Progesterone | Progesterone | 0.1 | ng/mL | 0.0-0.1 | 12/18/2020 |
| | Testosterone Tot Ser | Testosterone, Total, Serum | 7 | ng/dL | 3-41 | 12/18/2020 |
| | Prolactin | Prolactin | 7.6 | ng/mL | 4.8-23.3 | 12/18/2020 |
| | TSH | Thyroid Stimulating Hormone (TSH) | 1.680 | uIU/mL | 0.450-4.500 | 12/18/2020 |
| | Dihydrotestosterone | Dihydrotestosterone (DHT) | 2.2 | ng/dL | 4-22 | 12/18/2020 |
| | Hematocrit | Hematocrit (HCT) | 42.8 | % | 34.0-46.6 | 12/18/2020 |
| | LH | Luteinizing Hormone (Lutropin), Serum | 21.5 | mIU/mL | 7.7-58.5 | 12/18/2020 |
| | FSH | Follicle-Stimulating Hormone (FSH, Follitropin), Serum | 66.4 | mIU/mL | 25.8-134.8 | 12/18/2020 |

CURRENT VAGINAL THERAPIES: EFFICACY BASED ON PHYSIOLOGY

| Labs | | Request - Test Name | Value | Units | Range | Observed Date |
|----------------|-----------------------------|--|--------|--------|-------------|---------------|
| ■ ANDROGENS | Estradiol, Serum | Estradiol, Serum (Oestradiol, E2, 17-beta Estradiol, E-17) | <5.0 | pg/mL | <20-47 | 12/29/2020 |
| | ■ ESTROGENS | Calculated Fr Testo. | | | | |
| | | Calculated Free Testosterone [SDSM code] | 0.0428 | ng/dL | 0.6-0.8 | 12/18/2020 |
| ■ PROGESTERONE | Sex Horm. Bind. Glob | Sex Hormone Binding Globulin (Testosterone-estrogen Binding Globulin; TeBG), Serum | 140.0 | nmo/L | 17.3-125.0 | 12/18/2020 |
| | | Vitamin D, 25-Hydrox | | | | |
| | | Vitamin D 25-OH Total | 17.4 | ng/mL | 30.0-100.0 | 12/18/2020 |
| | Progesterone | Progesterone | 0.1 | ng/mL | 0.0-0.1 | 12/18/2020 |
| | Testosterone Tot Ser | Testosterone, Total, Serum | 7 | ng/dL | 3-41 | 12/18/2020 |
| | Prolactin | Prolactin | 7.6 | ng/mL | 4.8-23.3 | 12/18/2020 |
| | TSH | Thyroid Stimulating Hormone (TSH) | 1.680 | uIU/mL | 0.450-4.500 | 12/18/2020 |
| | Dihydrotestosterone | Dihydrotestosterone (DHT) | 2.2 | ng/dL | 4-22 | 12/18/2020 |
| | Hematocrit | Hematocrit (HCT) | 42.8 | % | 34.0-46.6 | 12/18/2020 |
| | LH | Luteinizing Hormone (Lutropin), Serum | 21.5 | mIU/mL | 7.7-58.5 | 12/18/2020 |
| | FSH | Follicle-Stimulating Hormone (FSH, Follitropin), Serum | 66.4 | mIU/mL | 25.8-134.8 | 12/18/2020 |

MENOPAUSE MANAGEMENT – FIVE TREATMENTS

Testosterone Therapy

Use FDA-approved testosterone at 10% of male dose

1. Daily transdermal gel - 1/10th tube daily to calf/thigh
Daily transdermal solution (0.3 ml daily underarm)
2. Weekly IM injections - 0.1 ml - 50 mg/ml testosterone enanthate/cypionate - into vastus lateralis muscle – anterolateral mid-thigh; 27 gauge needle; 1 ml syringe
3. 4-6 month subcutaneous testosterone pellet

Use free testosterone calculator (0.6 - 0.8 ng/dl)

Estradiol Therapy

Consider FDA-approved biologically identical estradiol

1. Daily oral (↑ SHBG, ↑ VTE, ↑ lipids)
2. Daily transdermal gel, emulsion, spray
3. Twice weekly, weekly transdermal patch
4. Three month vaginal ring
5. Weekly IM injections - 0.1 ml – estradiol valerate 10 mg/ml; 5 ml bottle; vastus lateralis muscle – anterolateral mid-thigh - 27 gauge needle; 1 ml syringe

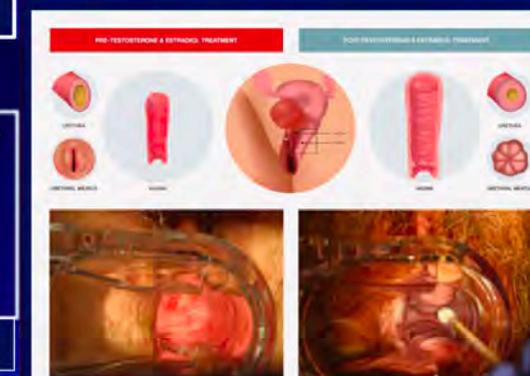
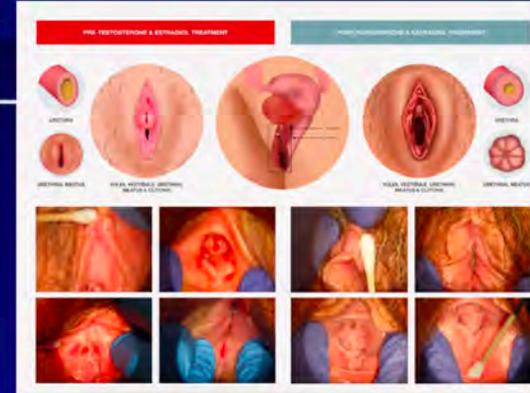
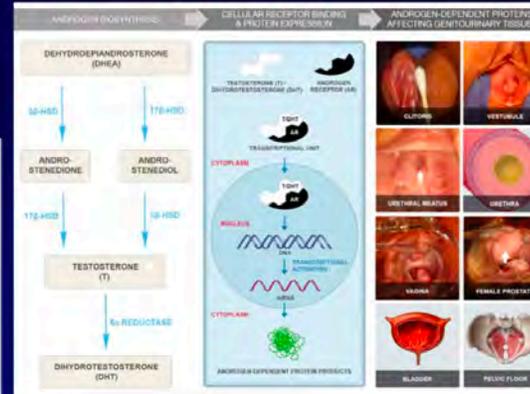
Aim for 25 - 50 pg/ml

Progesterone Therapy

Consider FDA-approved biologically identical progesterone

1. Oral micronized progesterone 100 mg q MWF (intact uterus, q MTh hysterectomy)
2. Vaginal progesterone suppository – 6 per month
3. Compound progesterone cream

Aim for 1 ng/ml



Vestibular Hormonal Therapy

Compound estradiol 0.02%/testosterone 0.1% in hypoallergenic base (methylcellulose); apply pea-sized volume x 2 (right and left sides); directly onto entire vestibule; QD – BID

Intravaginal Hormone Therapy

1. Estrogen cream (Premarin cream, Estrace cream)
1. Three month estradiol ring (Estring)
2. Estradiol vaginal insert (Vagifem, Softgel)
3. Selective estrogen receptor modulator (oral ospemifene)
4. DHEA vaginal insert
5. Daily compound estradiol 0.02%/testosterone 0.1% in hypoallergenic base (methylcellulose) – apply pea-sized volume directly into vagina

9 Blood Tests: Testosterone, SHBG, Dihydrotestosterone, Estradiol, Progesterone, LH, FSH, TSH, prolactin

Total testosterone, SHBG,
calculated free testosterone (ng/dl)

Use free testosterone calculator
(0.6 - 0.8)

DHT (ng/dl)

Suspicious in lower tertile

Peri/post-menopausal Estradiol (pg/ml)

Aim for 25 - 50 pg/ml

Peri/post-menopausal Progesterone (ng/ml)

Aim for 1 ng/ml

TSH (mIU/L)

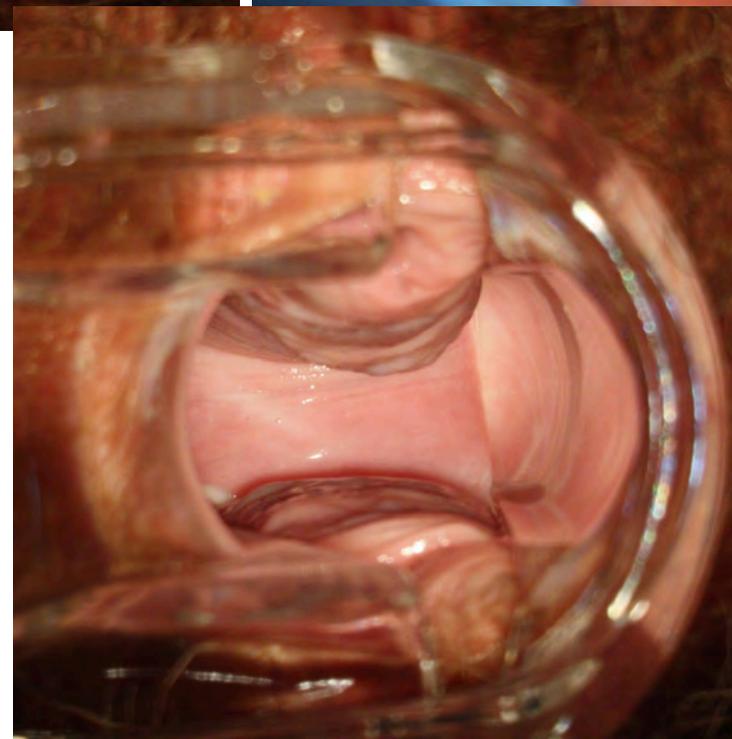
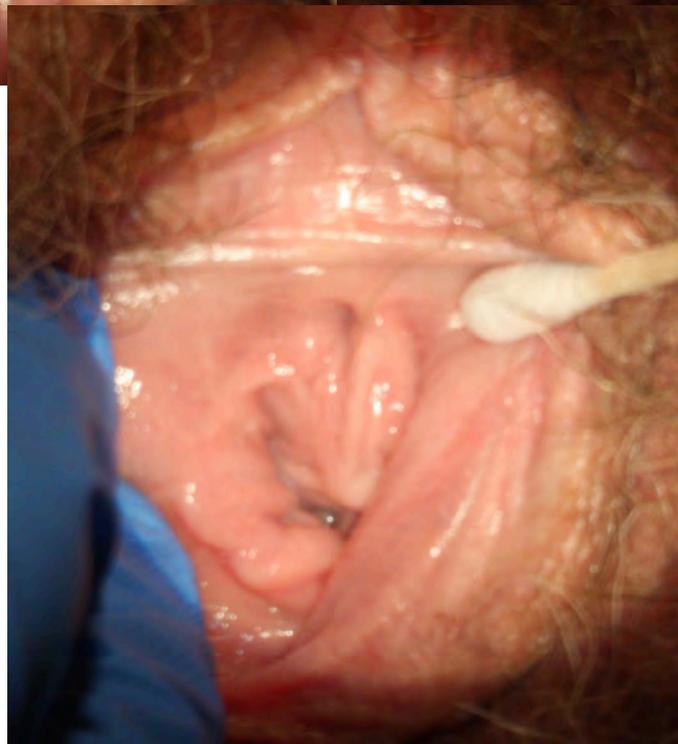
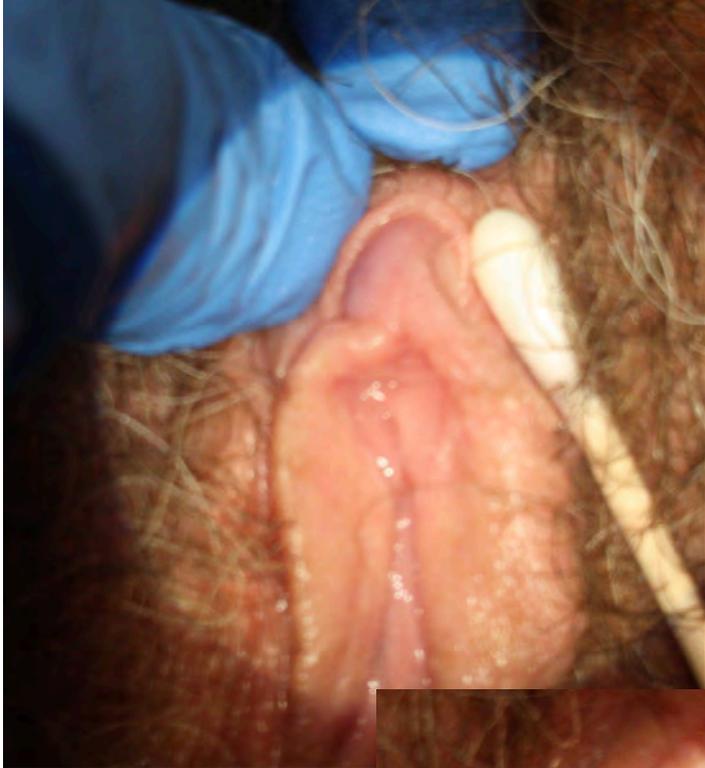
Suspicious > 3.0

LH/FSH (mIU/ml)

Range established

Prolactin (ng/ml)

Range established



| | Normal (0) | Mild (1) | Moderate (2) | Severe (3) |
|------------------------|--|--------------------------------|------------------------------------|----------------------------------|
| Lips | | | | |
| Lips: upper lip | Normal lip fullness and position | Mild loss of fullness | Moderate loss of fullness | Severe loss of fullness |
| Lips: lower lip | Normal lip fullness and position | Mild decrease in size | Moderate decrease in size | Severe decrease in size |
| Chin | Normal chin and position | Mild normal prominence | Moderate normal prominence | Severe normal prominence |
| Orbit | Normal for party, mild fullness and position | Mild decrease in size of orbit | Moderate decrease in size of orbit | Severe decrease in size of orbit |
| Eye | Normal eye and position | Mild decrease in size of eye | Moderate decrease in size of eye | Severe decrease in size of eye |
| Ear | Normal ear and position | Mild decrease in size of ear | Moderate decrease in size of ear | Severe decrease in size of ear |
| Neck | Normal neck and position | Mild decrease in size of neck | Moderate decrease in size of neck | Severe decrease in size of neck |
| Hand | Normal hand and position | Mild decrease in size of hand | Moderate decrease in size of hand | Severe decrease in size of hand |
| Foot | Normal foot and position | Mild decrease in size of foot | Moderate decrease in size of foot | Severe decrease in size of foot |
| Face | Normal face and position | Mild decrease in size of face | Moderate decrease in size of face | Severe decrease in size of face |
| Upper lip | Normal upper lip | Mild upper lip | Moderate upper lip | Severe upper lip |
| Lower lip | Normal lower lip | Mild lower lip | Moderate lower lip | Severe lower lip |
| Chin | Normal chin | Mild chin | Moderate chin | Severe chin |
| Orbit | Normal orbit | Mild orbit | Moderate orbit | Severe orbit |
| Eye | Normal eye | Mild eye | Moderate eye | Severe eye |
| Ear | Normal ear | Mild ear | Moderate ear | Severe ear |
| Neck | Normal neck | Mild neck | Moderate neck | Severe neck |
| Hand | Normal hand | Mild hand | Moderate hand | Severe hand |
| Foot | Normal foot | Mild foot | Moderate foot | Severe foot |

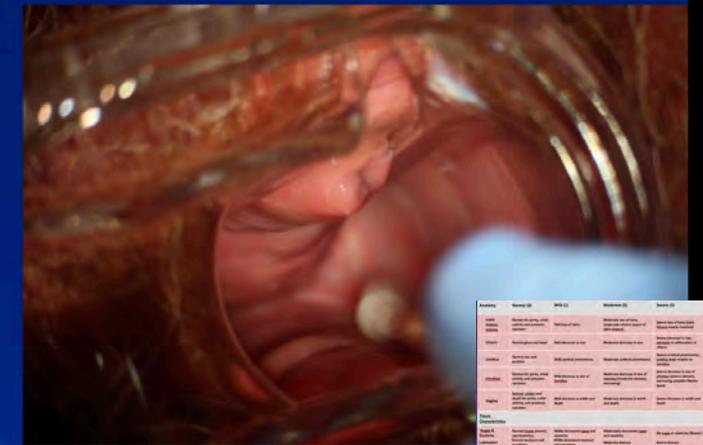
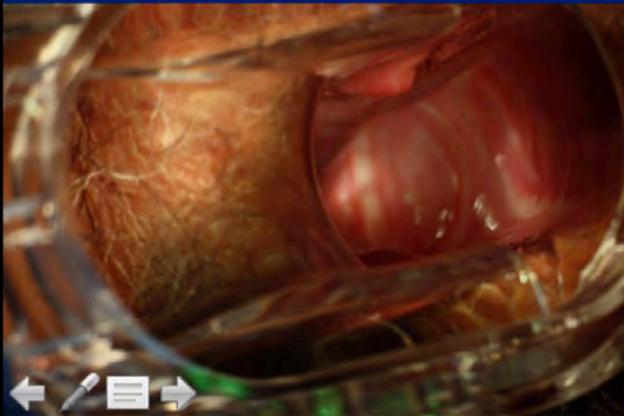
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KN - 12-29-14



KN - 8-11-15



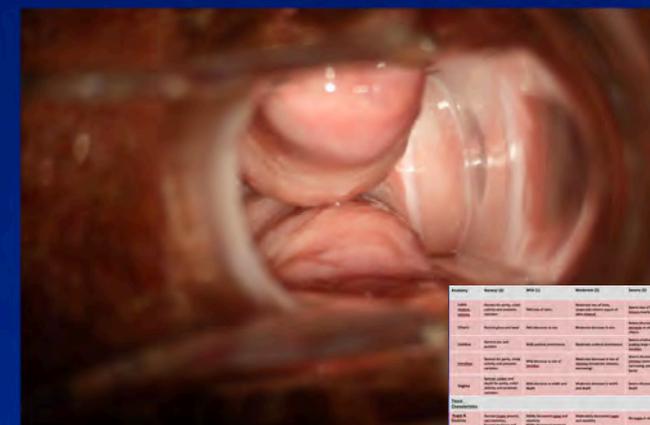
| System | Normal (N) | Abn (A) | Reference (R) | Notes (N) |
|------------------|---------------------------|----------------------|---------------|-----------|
| General | Alert, responsive, bright | Lethargic, depressed | | |
| HEENT | Normal | Abnormal | | |
| Heart | Normal | Abnormal | | |
| Lungs | Normal | Abnormal | | |
| GI | Normal | Abnormal | | |
| GU | Normal | Abnormal | | |
| Neuro | Normal | Abnormal | | |
| Skin | Normal | Abnormal | | |
| Mucous Membranes | Normal | Abnormal | | |
| Reflexes | Normal | Abnormal | | |
| Diagnosis | | | | |
| Plan | | | | |
| Prognosis | | | | |
| Owner | | | | |
| Notes | | | | |



KS – Age 53: 7 - 24 - 13

KS – Age 54: 7 - 23 - 14

KS – Age 55: 7 - 28 - 15



| System | Normal (N) | KS (K) | KS (K) | KS (K) |
|------------------|-------------------------|------------------------|------------------------|------------------------|
| General | Well-nourished, healthy | Weight loss, cachectic | Weight loss, cachectic | Weight loss, cachectic |
| Head | Normal | Normal | Normal | Normal |
| Eyes | Normal | Normal | Normal | Normal |
| Ears | Normal | Normal | Normal | Normal |
| Nose | Normal | Normal | Normal | Normal |
| Throat | Normal | Normal | Normal | Normal |
| Heart | Normal | Normal | Normal | Normal |
| Lungs | Normal | Normal | Normal | Normal |
| Stomach | Normal | Normal | Normal | Normal |
| Intestines | Normal | Normal | Normal | Normal |
| Genitourinary | Normal | Normal | Normal | Normal |
| Skin | Normal | Normal | Normal | Normal |
| Mucous Membranes | Normal | Normal | Normal | Normal |
| Pathology | Normal | Normal | Normal | Normal |
| Diagnosis | Normal | Normal | Normal | Normal |
| Prognosis | Normal | Normal | Normal | Normal |
| Treatment | Normal | Normal | Normal | Normal |
| Outcome | Normal | Normal | Normal | Normal |

MM – Age 61: 5 - 14 - 15



MM – Age 61: 8 - 20 - 15

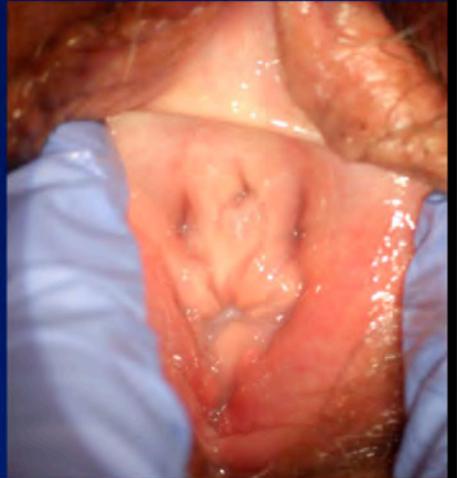


| System | Normal 01 | MM 01 | Normal 02 | MM 02 |
|------------------|-----------|--------|-----------|--------|
| HEENT | Normal | Normal | Normal | Normal |
| Neck | Normal | Normal | Normal | Normal |
| Cardiovascular | Normal | Normal | Normal | Normal |
| Respiratory | Normal | Normal | Normal | Normal |
| Gastrointestinal | Normal | Normal | Normal | Normal |
| Genitourinary | Normal | Normal | Normal | Normal |
| Musculoskeletal | Normal | Normal | Normal | Normal |
| Neurological | Normal | Normal | Normal | Normal |
| Psychiatric | Normal | Normal | Normal | Normal |
| Skin | Normal | Normal | Normal | Normal |
| Endocrine | Normal | Normal | Normal | Normal |
| Immunology | Normal | Normal | Normal | Normal |
| Laboratory | Normal | Normal | Normal | Normal |
| Imaging | Normal | Normal | Normal | Normal |
| Pathology | Normal | Normal | Normal | Normal |

3/9/16



9/14/16



CURRENT VAGINAL THERAPIES: EFFICACY BASED ON PHYSIOLOGY

Basic facts about menopause

**FDA approved local vaginal treatments –
estrogen based**

**FDA approved local vaginal treatments –
estrogen and androgen based**

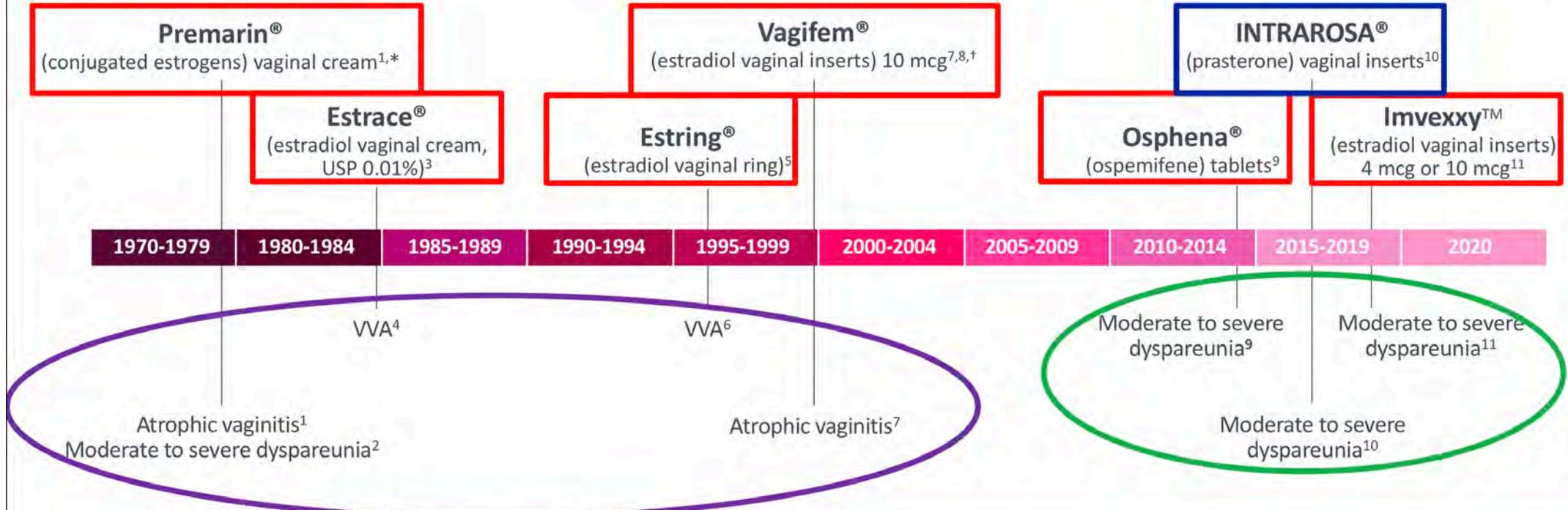
**Can vaginal treatments safely and effectively
treat the vestibule**

CURRENT VAGINAL THERAPIES: EFFICACY BASED ON PHYSIOLOGY

FDA-Approved Treatments

Estradiol based

Estradiol and Androgen based



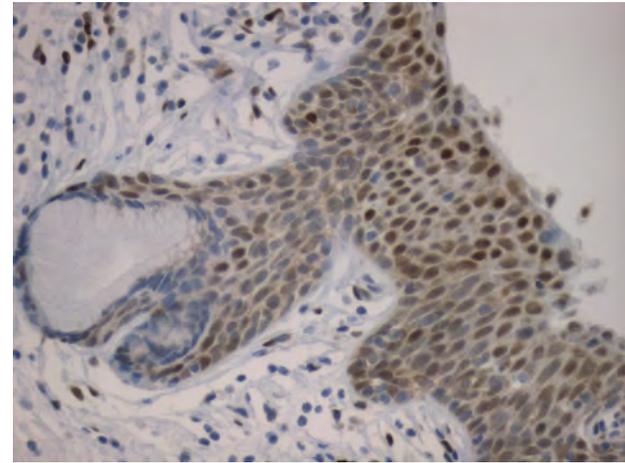
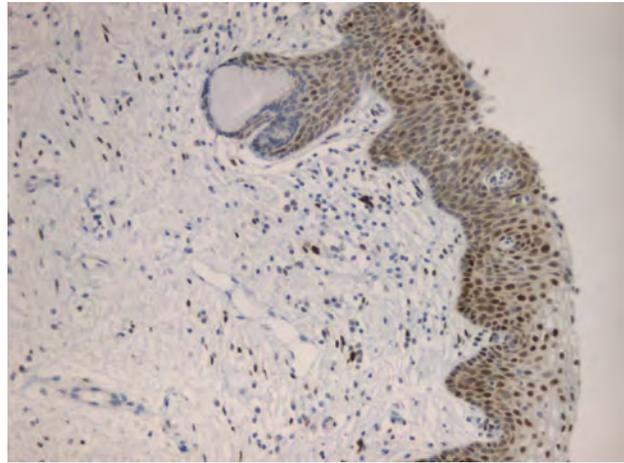
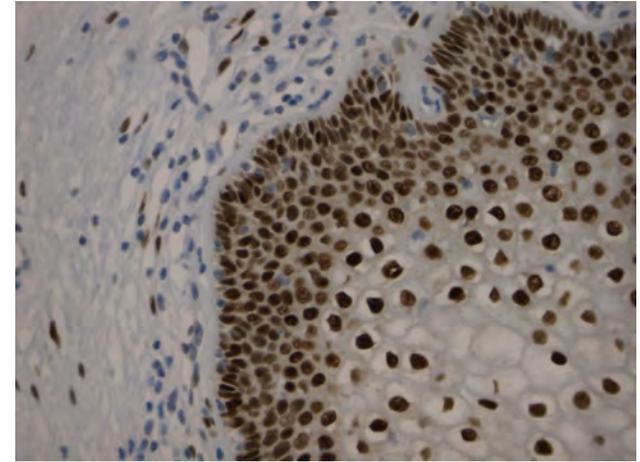
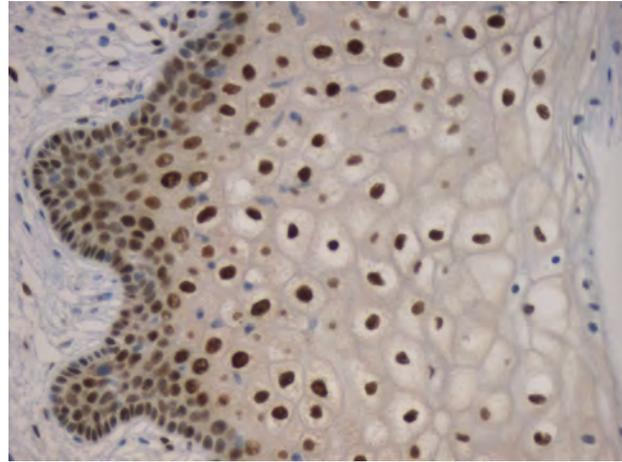
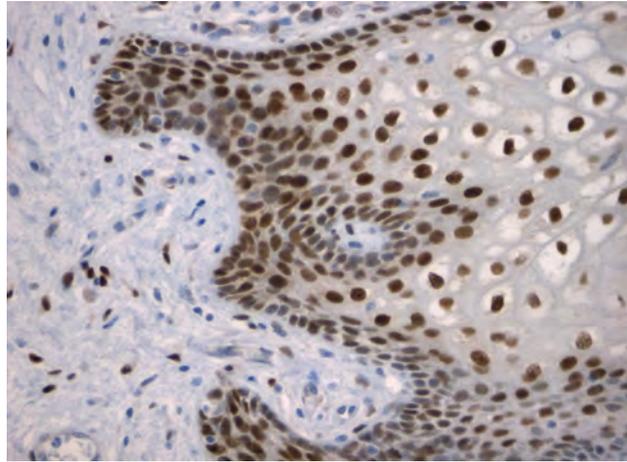
*Atrophic vaginitis indication approved in 1978; dyspareunia indication approved in 2008.²

[†]25 mcg dosage approved in 1999; 10 mcg dosage approved in 2009.^{7,8}

Premarin, Estrace, Estring, Vagifem, Ospheña, and Imvexxy are trademarks or registered trademarks of their respective owners. INTRAROSA is a registered trademark of Endoceutics, Inc.

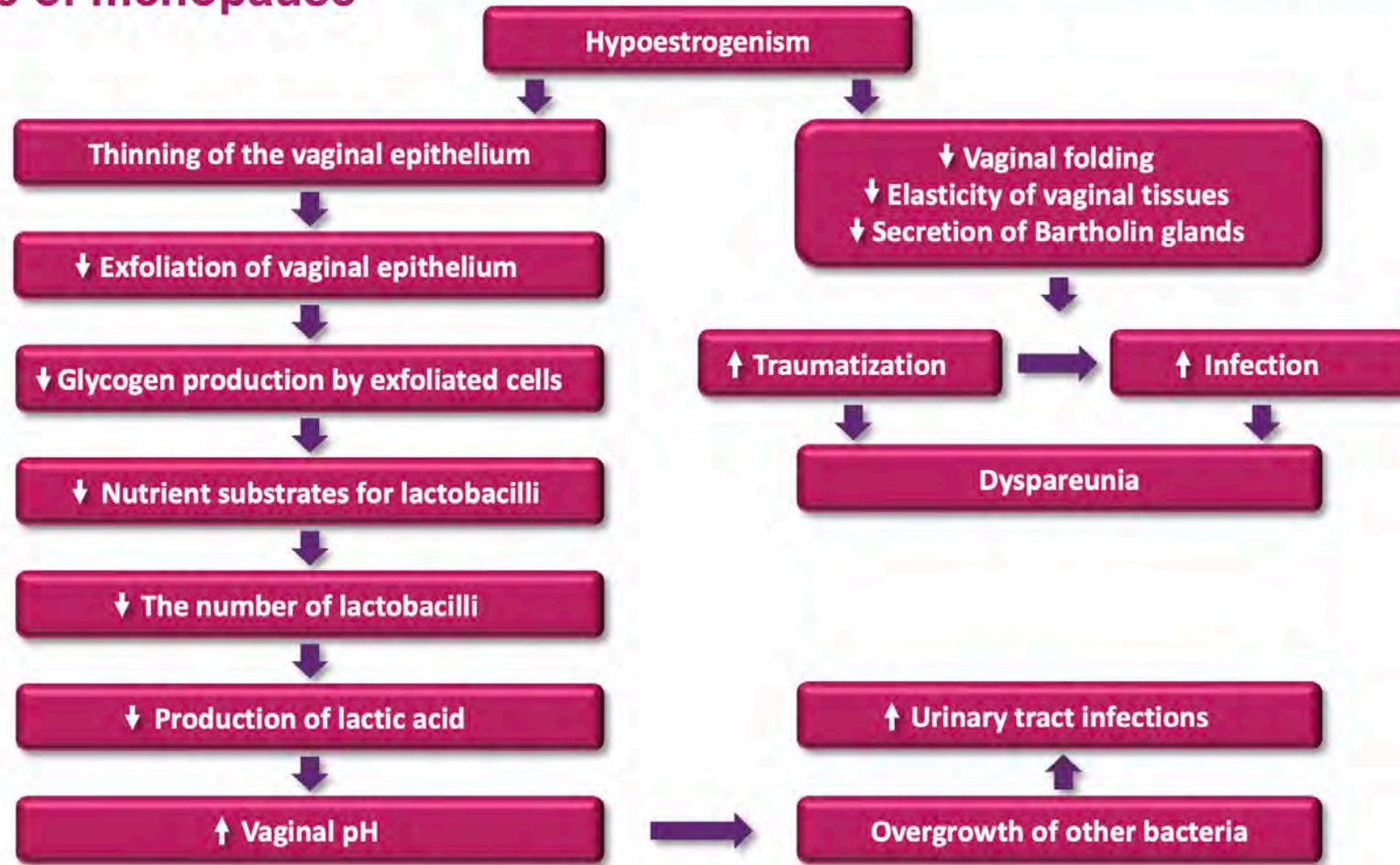
1. PREMARIN® Vaginal Cream Prescribing Information. Wyeth Pharmaceuticals Inc. 2. Drugs@FDA: FDA approved drug products: Premarin. FDA website. 3. Drugs@FDA: FDA approved drug products: Estrace. FDA website. 4. ESTRACE® Cream Prescribing Information. Allergan USA, Inc. 5. Drugs@FDA: FDA approved drug products: Estring. FDA website. 6. ESTRING® Prescribing Information. Pharmacia & Upjohn Co. 7. VAGIFEM® Prescribing Information. Novo Nordisk A/S. 8. Vagifem 1999 approval letter. 9. OSPHENA® Prescribing Information. Shionogi Inc. 10. INTRAROSA® (prasterone) Prescribing Information. AMAG Pharmaceuticals, Inc; 2018. 11. IMVEXXY™ Prescribing Information. Therapeutics MD, Inc.

Estrogen Receptors in the Vestibule



CURRENT VAGINAL THERAPIES: EFFICACY BASED ON PHYSIOLOGY

Multiple changes in the vulvovaginal environment lead to Genitourinary syndrome of menopause¹



CURRENT VAGINAL THERAPIES: EFFICACY BASED ON PHYSIOLOGY

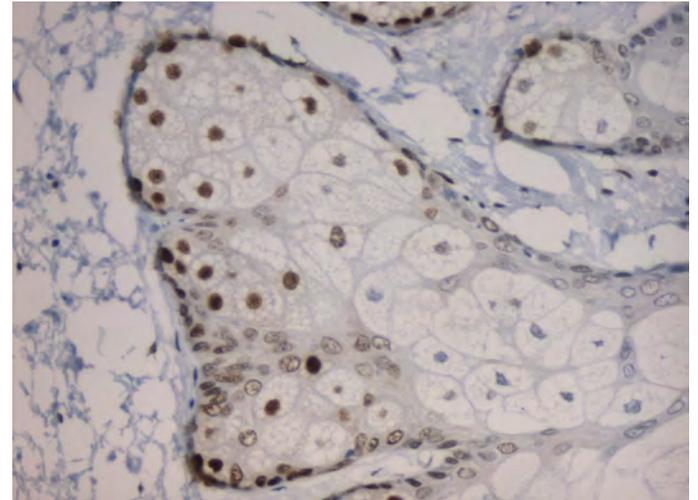
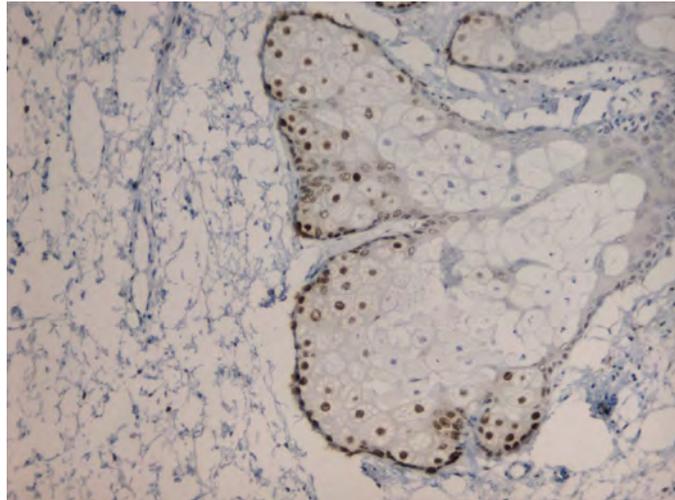
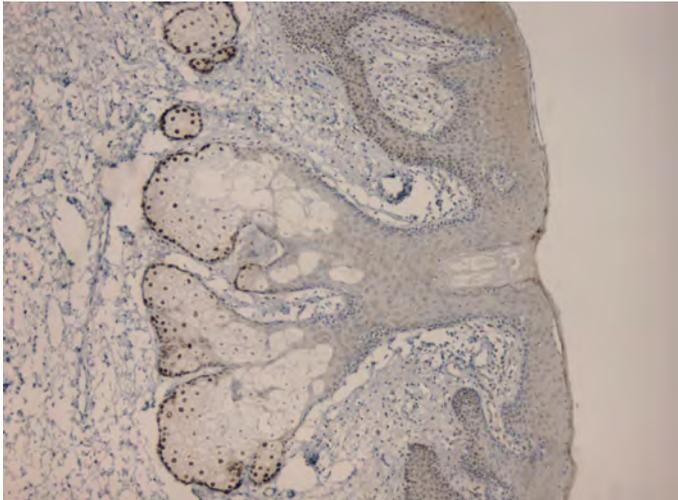
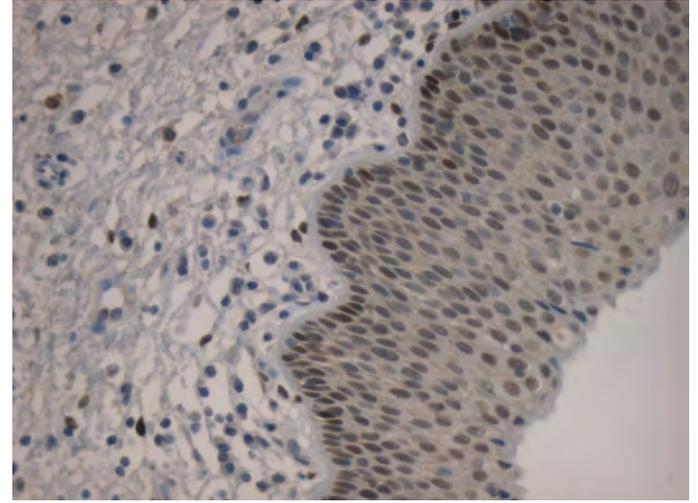
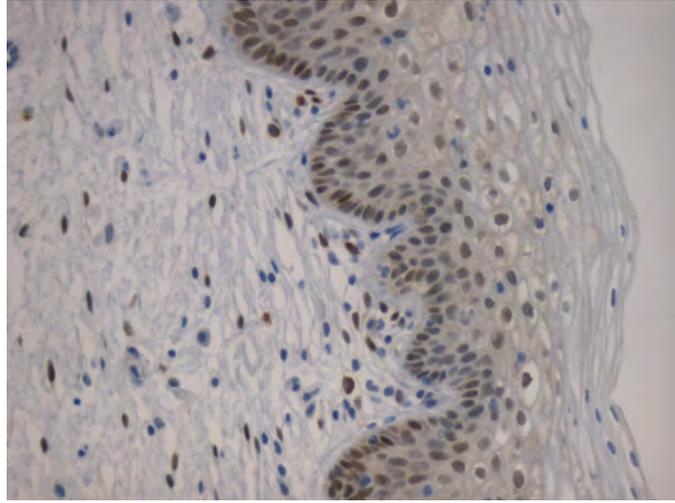
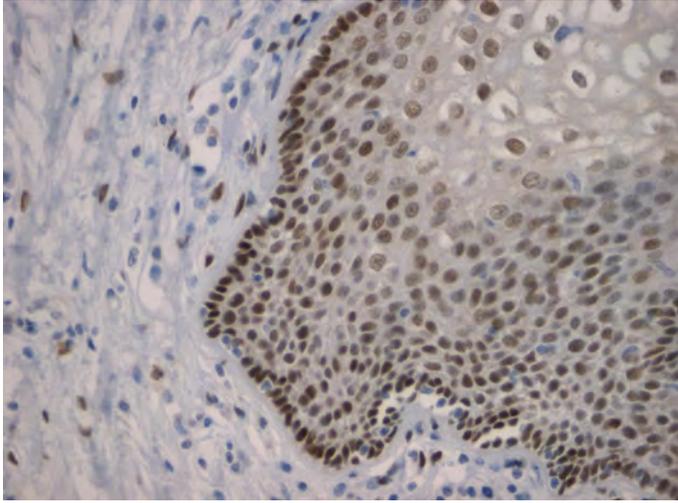
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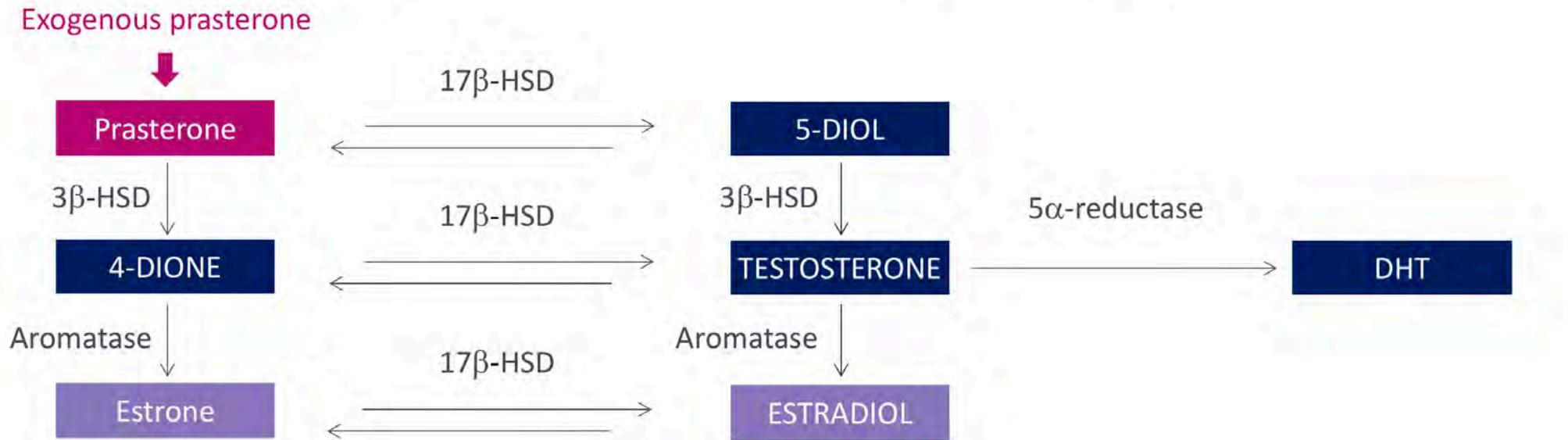
Androgen Receptors in the Vestibule



Intracellular Conversion of DHEA

Prasterone is a synthetic form of endogenous DHEA.^{2,3}

Human steroidogenic enzymes, such as hydroxysteroid dehydrogenases, 5 α -reductases, and aromatases, transform prasterone into androgens and estrogens.²

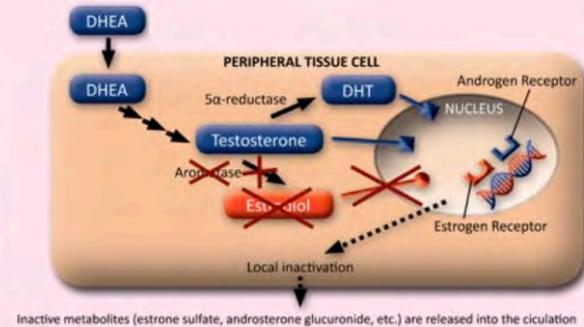
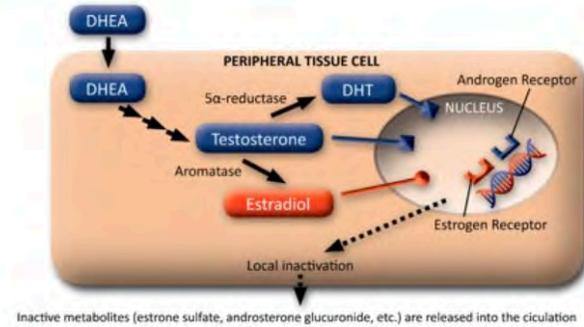
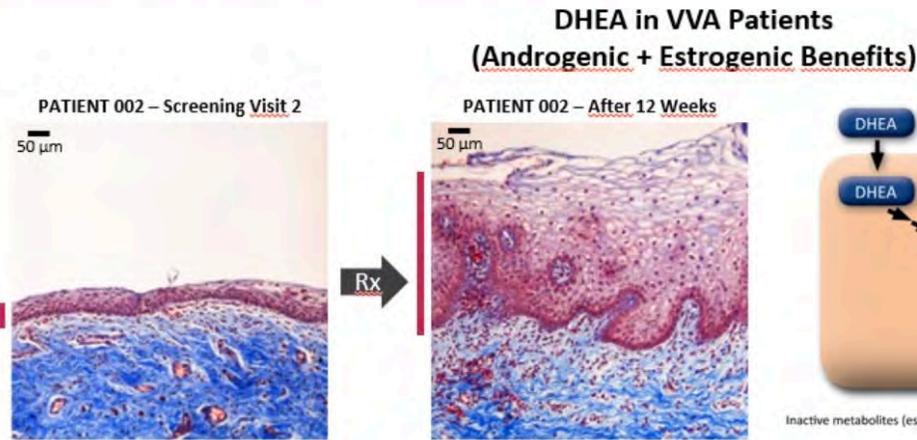
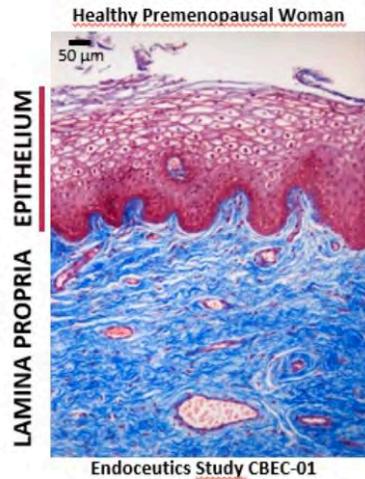


Are there androgen receptors in the vestibule (and vagina)

Effects of Prasterone on the Vaginal Histology of Breast Cancer Survivors Taking Aromatase Inhibitors and Suffering From VVA: Preliminary Results¹

Study qualified investigator: Dr Céline Bouchard (Qc, Canada)

Collection of **vaginal biopsies before and after 12 weeks** (± 7 days) of daily intravaginal prasterone (6,5 mg)

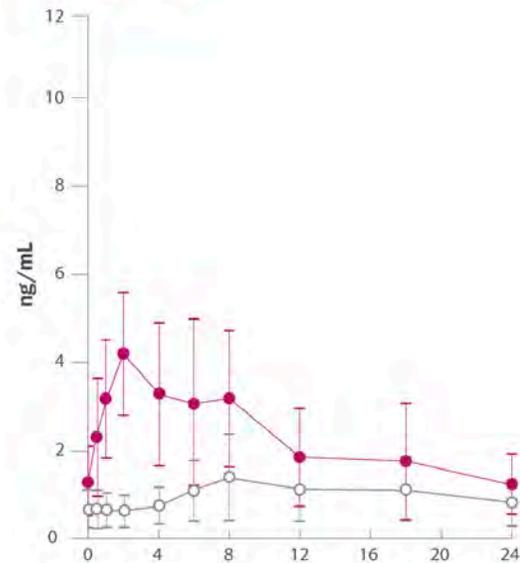


Pharmacokinetics

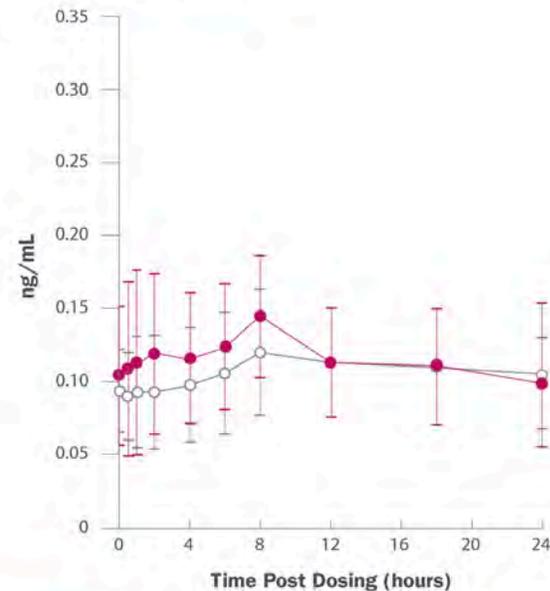
Serum Estradiol Concentrations Fall Within Postmenopausal Range^{1,2,*}



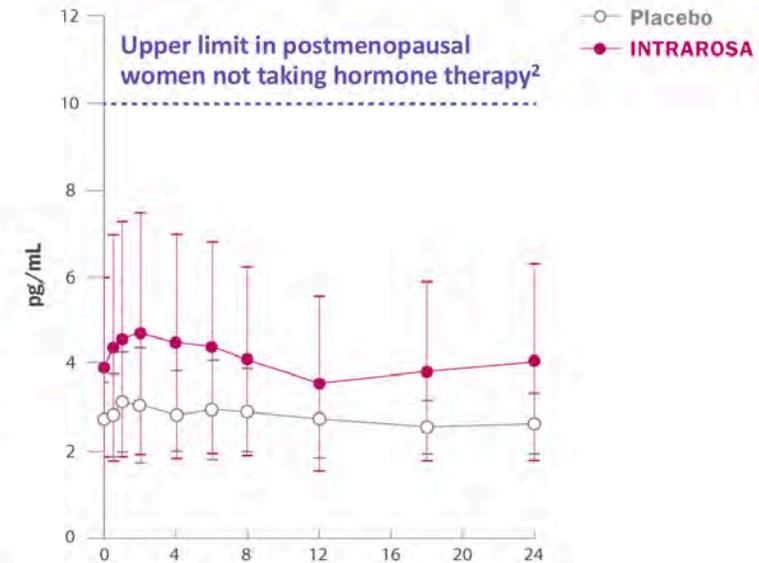
Prasterone



Testosterone



Estradiol (E₂)



In 2 primary efficacy trials, daily administration of INTRAROSA vaginal insert for 12 weeks increased mean serum C_{trough} of prasterone and its metabolites testosterone and estradiol by 47%, 21%, and 19% from baseline, respectively. This comparison based on C_{trough} may underestimate the magnitude of increase in prasterone and metabolites' exposure because it does not take into account the overall concentration-time profile following administration of INTRAROSA.

*Postmenopausal range is not from INTRAROSA clinical trials.²

C_{trough}=trough concentration.

1. INTRAROSA® (prasterone) Prescribing Information. AMAG Pharmaceuticals, Inc; 2018. 2. Test ID: EEST. Estradiol, serum. Mayo Clinic Medical Laboratories website. <https://www.mayomedicallaboratories.com/test-catalog/Clinical+and+Interpretive/81816>. Accessed September 20, 2018.

Mean Severity Score Decrease in Women Who Reported Moderate to Severe Dyspareunia as Their Most Bothersome Symptom of VVA (n=183)

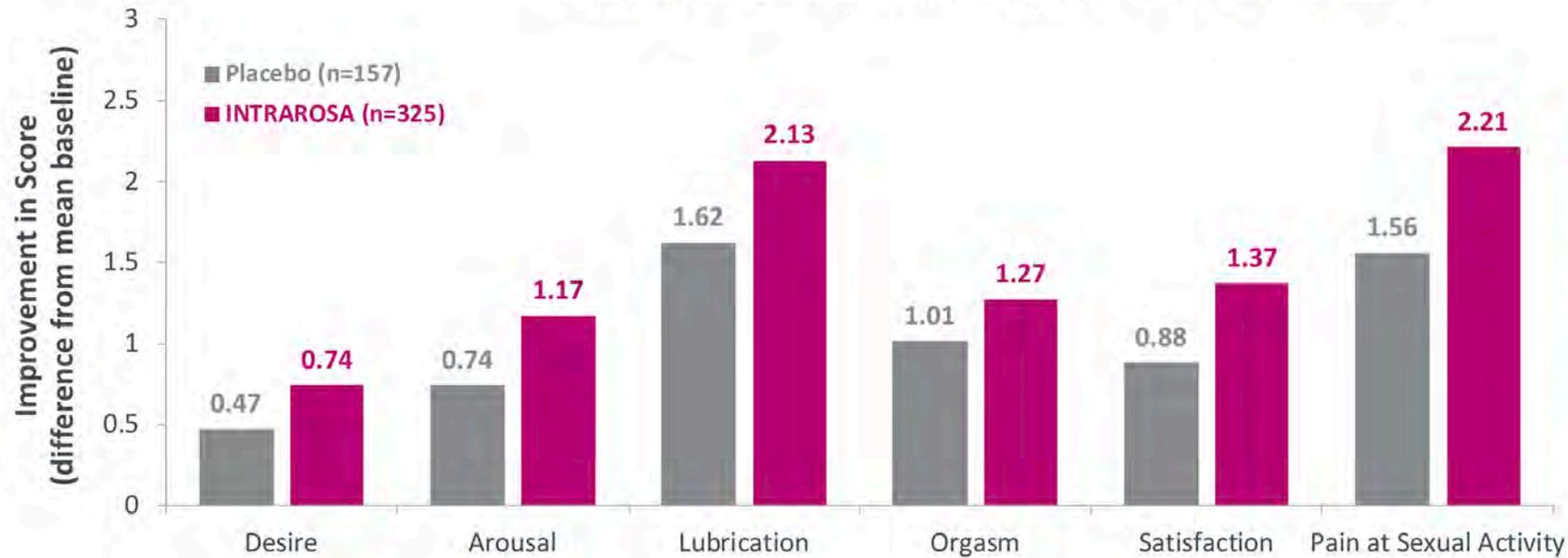


43.2% of women (n=79) **REPORTED NO PAIN** at Week 52³

*Secondary outcome measure.²

1. Labrie F, et al. *Maturitas*. 2015;81(1):46-56. 2. DHEA against vaginal atrophy - safety study of 12 months. ClinicalTrials.gov website. <https://clinicaltrials.gov/ct2/show/NCT01256671>. Updated October 18, 2017. Accessed September 20, 2018. 3. Data on File. Study Report for ERC-230. AMAG Pharmaceuticals. 2015.

At 12 Weeks, Survey Results Demonstrated the Following Improvements in Score From Baseline



Total score
IMPROVED
by **41.3%**
with INTRAROSA
vs placebo.

*INTRAROSA is not indicated for the treatment of sexual dysfunction.²

1. Labrie F, et al. *J Sex Med.* 2015;12(12):2401-2412. 2. INTRAROSA® (prasterone) Prescribing Information. AMAG Pharmaceuticals, Inc; 2018.

CURRENT VAGINAL THERAPIES: EFFICACY BASED ON PHYSIOLOGY

Basic facts about menopause

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**Can vaginal treatments safely and effectively
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METHODS

- 7 visits: screen, baseline, 4 weeks, 8 weeks, 12 weeks, 16 weeks, 20 weeks
- Vulvoscopic photography: blinded photographs assessed w/4 point Likert scale (lower scores = healthier appearance)
- Vestibular tissue appearance (VestTA): urethral meatal prolapse, introital stenosis, pallor, erythema, mucosa inflammation.
- Vaginal tissue appearance (VagTA): severity of loss of vaginal rugae
- Cotton-tipped swab test: 1:00, 3:00, 5:00, 6:00, 7:00, 9:00, 11:00
- Subject diaries at each sexual event: pain during foreplay, masturbation, oral sex, intercourse
- Prasterone 35 inserts dispensed at baseline, 4 weeks, 8 weeks, 12 weeks, 16 weeks

Urethral telescoping
Introital stenosis
Pallor
Erythema

Q-tip total = 11



Baseline

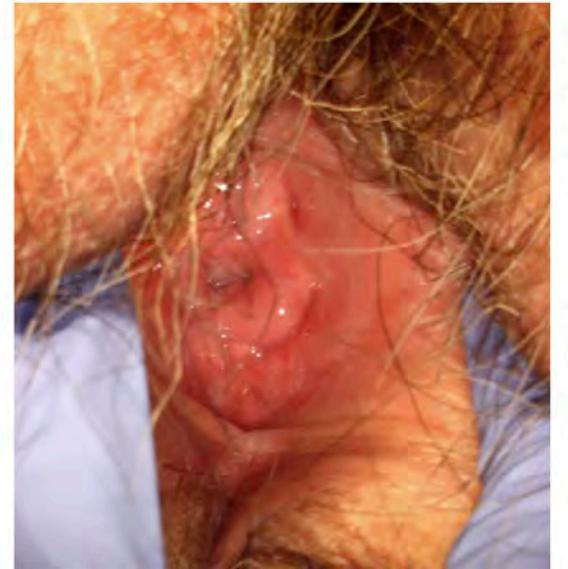


**Resolution of urethral
telescoping**
Resolution of pallor
Resolution of erythema

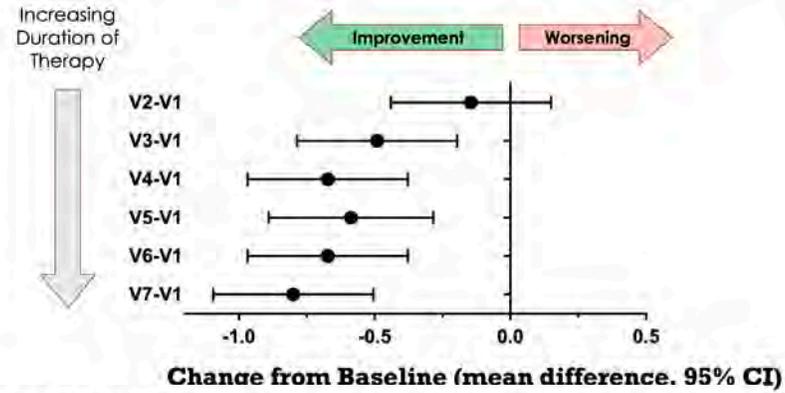
Q-tip total = 6



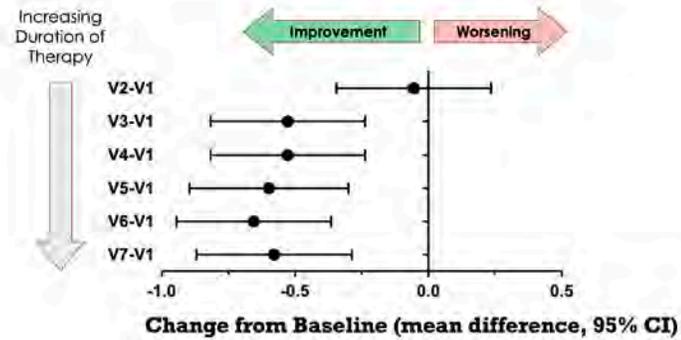
End of study



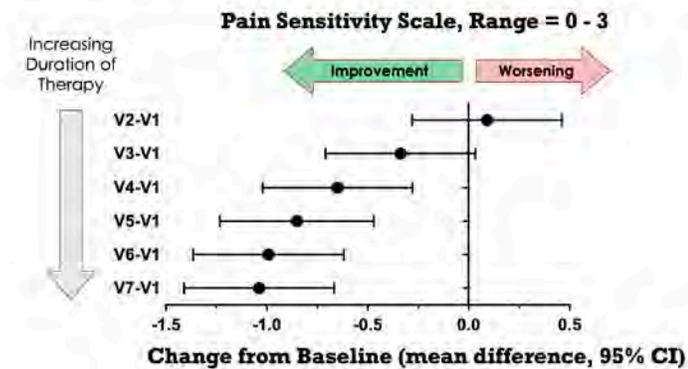
EFFECT OF PRASTERONE THERAPY ON VAGINA VISUAL SCALE



EFFECT OF PRASTERONE THERAPY ON VESTIBULE VISUAL SCALE



EFFECT OF PRASTERONE THERAPY ON COTTON SWAB TESTING



CONCLUSION

- First prospective vulvoscopic study to show intravaginal hormone therapy significantly improves VestTA and VagTA scores at 4 weeks
- First prospective vulvoscopic study to show intravaginal hormone therapy significantly improves vestibular pain at 8 weeks
- Vestibular improvement may explain robust lowering of dyspareunia in menopausal women with moderate to severe dyspareunia
- Proposed mechanism of action: discharge from intravaginal suppository reaches and acts on the vestibule

Take Home Message:

Menopause = ↓ estradiol blood test value, ↓ progesterone blood test value, ↑ FSH/LH and ↓ testosterone, ↓ calculated free testosterone, ↓ dihydrotestosterone

Do NOT treat some women with biologically identical hormones

These women usually not distressed by menopausal (especially sexual dysfunction) symptoms or usually view hormone risks greater than hormone benefits

Treat some women with biologically identical hormones

These women usually distressed by menopausal (especially sexual dysfunction) symptoms or usually view hormone benefits greater than hormone risks



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