

60 yo married white female, G₀, complains of severe pain with intercourse. The pain is described as searing and excruciating, especially upon penetration, and is not significantly improved with OTC lubricants. She has had an unremarkable and very satisfying sexual life in the past with no history of sexual abuse or trauma. The pain began approximately 6-8 weeks after the patient began taking an aromatase inhibitor (AI) for early stage and grade ductal carcinoma of the breast. Prior to beginning her AI, the patient had used estradiol vaginal cream (Estrace®; Allergan) to maintain her vaginal tissues. She has tolerated the pain until about 2 months ago and now, 6 months following her AI treatment, she seeks help

Disclosures 2016

Owner/Board of Directors: James A. Simon, MD, PC

Advisory Board/Consultant: Dr. James A. Simon has served (within the last year) or is currently serving as a consultant to or on the advisory boards of: AbbVie, Inc. (North Chicago, IL), AMAG Pharmaceuticals, Inc. (Waltham, MA), Amgen Inc. (Thousand Oaks, CA), Apotex, Inc. (Toronto, Canada), Ascend Therapeutics (Herndon, VA), JDS Therapeutics, LLC (Purchase, NY), Merck & Co., Inc. (Whitehouse Station, NJ), Noven Pharmaceuticals, Inc. (New York, NY), Novo Nordisk (Bagsværd, Denmark), Nuelle, Inc. (Mountain View, CA), Perrigo Company, PLC (Dublin, Ireland), Radius Health, Inc. (Waltham, MA), Regeneron Pharmaceuticals, Inc. (Tarrytown, NY), Sanofi S.A. (Paris, France), Sermonix Pharmaceuticals, Inc. (Columbus, OH), Shionogi Inc. (Florham Park, NJ), Sprout Pharmaceuticals (Raleigh, NC), Symbiotec Pharmed (Indore, India), TherapeuticsMD (Boca Raton, FL).

Speaker: He has also served (within the last year) or is currently serving on the speaker's bureaus of: Amgen Inc. (Thousand Oaks, CA), Eisai, Inc. (Woodcliff Lake, NJ), Merck (Whitehouse Station, NJ), Noven Pharmaceuticals, Inc. (New York, NY), Novo Nordisk (Bagsværd, Denmark), Shionogi Inc. (Florham Park, NJ).

Grants/Research: In the last year he has received or is currently receiving grant/research support from: AbbVie, Inc. (North Chicago, IL), Actavis, PLC. (Dublin, Ireland), Agile Therapeutics (Princeton, NJ), Bayer Healthcare LLC., (Tarrytown, NY), New England Research Institute, Inc. (Watertown, MA), Novo Nordisk (Bagsværd, Denmark), Palatin Technologies (Cranbury, NJ), Symbio Research, Inc. (Port Jefferson, NY), TherapeuticsMD (Boca Raton, FL).

Patent and Trademark Holder: U.S. Patent: 4,816,257, March 28, 1989: "Method for Producing an In Vivo Environment Suitable for Human Embryo Transplant.", U.S. Trademark: Reg. No. 3,446,895, Registered June 10, 2008: "You talk...I'll Listen. We'll Plan Together"., U.S. Trademark: Reg. No. 3,676,269, Registered September 1, 2009: U.S. Trademark: Reg. No. 3,760,080, Registered March 16, 2010: "Women's Health & Research Consultants & Design", U.S. Trademark Serial No.:86-714,153. "DR. SIMON SAYS" Registered February 2, 2016.

Stock Shareholder and/or other Financial Support: Dr. Simon is a stockholder (direct purchase) in Sermonix Pharmaceuticals (Columbus, OH).



Slide Courtesy of Murray Freedman, MD

Estrogen Receptor Concentrations in Select Adult Genital Tissues



Goals of VVA Treatment

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

Non-Rx Therapeutic Options

- ❖ Moisturizer: Long-term
 - Gel or cream
 - Used regularly
 - Maintains hydration; relieves dryness
- ❖ Lubricant: As needed (condom compatibility)
 - Moistens vaginal epithelium
 - Short duration of action
 - Facilitates medical exam or intercourse

Some Effects of Estrogen

- § Improve sensory perception
- § Increase central and peripheral nerve transmission
- § Increase lubrication
- § Reduce pH
- § Increase peripheral blood flow
- § Augment capacity to develop muscle tension
- § Increase vibratory sensation
- § Increase vaginal vault relaxation
- § Increase vaginal vault size
- § Increase tissue elasticity
- § Increase vaginal collagen content

Sarrel PM. Sexuality in the middle years. *Obstet Gynecol Clin North Am.* 1987; 14: 49-52.

Gescheider GA, Verillo RT, McCann JT, et al. Effects of the menstrual cycle on vibrotactile sensitivity. *Percept Psychophys* 1984; 36: 586-592.

Kow L, Pfaff D. Effects of oestrogen treatment on the size of receptive field and response threshold of the pudendal nerve in the female rat. *Neuroendocrinology* 1973; 13: 299-313.

Lara LA, et al. *J Sex Med.* 2009;6:30-39.

NIH State-of-the-Science Conference Statement on management of menopause-related symptoms. 2005:1-38.

FDA-Approved Products for Vaginal Changes of Menopause Include:

- ❖ Estradiol vaginal cream (Estrace[®]; Allergan)
- ❖ Conjugated estrogens vaginal cream (Premarin[®] Vaginal Cream; Pfizer)
 - Also indicated for dyspareunia
- ❖ Estradiol hemihydrate vaginal tablet (Vagifem[®]; Novo Nordisk)
- ❖ Estradiol vaginal rings
 - Can deliver a local (Estring[®]; Pfizer) or systemic dose (FemRing[®]; Allergan); systemic ring also indicated for vasomotor symptoms.
- ❖ Ospemifene (Osphena[®]; Shionogi)

Which Product to Use?

- ❖ Products are equally effective at doses recommended in labeling
 - Significant subjective symptom relief
 - Signs (pallor, dryness, friability, petechiae) also improved
- ❖ Clinician experience and patient preference drive choice of product
- ❖ In breast cancer patients, the focus is on little if any systemic absorption

How Soon Is Response Evident?

- ❖ Typically within a few weeks
 - May take up to 6 weeks (Label 12 weeks)
- ❖ 80% to 90% report subjective improvement

Estrogen Loss Increases UTI Susceptibility

- ❖ Estrogen-replete vagina:
 - Acidic—pH 4.5-6.5
 - Favors lactobacillus, discourages pathogens
- ❖ Estrogen-deprived vagina:
 - Alkaline—pH 6.5-7.0
 - Permits colonization by pathogens that can migrate to the urinary tract
 - Many patients have recurrent UTIs
- ❖ Local estrogen application can restore vaginal pH to ~5.5

Davila G, et al. *Am J Obstet Gynecol*. 2002;188:382-388.

Simunić V, et al. *Int J Gynaecol Obstet*. 2003;82:187-197.

Raz R. *Int J Antimicrob Agents*. 2001;17:269-271.

Vaginal Atrophy and Sexual Function

- ❖ Cross-sectional, population-based study of
 - 1,480 sexually active, postmenopausal women
 - 57% had vulvovaginal atrophy
 - 55% had female sexual dysfunction
 - Women with sexual dysfunction ~4X more likely to also have vulvovaginal atrophy
- ❖ Conclusion: Reducing symptoms of one condition may also relieve symptoms of the other

You May Need Vaginal Dilators

- ❖ In cases of extreme introital stenosis
- ❖ Vaginal agglutination
- ❖ Insertional dyspareunia



Use It or Lose It!

- ❖ Continued sexual activity via coitus or masturbation increases blood flow to pelvic organs



ORIGINAL ARTICLE

Current Overview of the Management of Urogenital Atrophy in Women with Breast Cancer

Sandhya Pruthi, MD,* James A. Simon, MD,[†] and Amy P. Early, MD[‡]

**Division of General Internal Medicine and Breast Diagnostic Clinic, Mayo Clinic, Rochester, Minnesota; [†]Department of Obstetrics and Gynecology, George Washington University, Washington, DC; and [‡]Department of Medical Oncology, University Buffalo School of Medicine, Buffalo, New York*

Pruthi S, Simon JA, Early AP. Current overview of the management of urogenital atrophy in women with breast cancer. *Breast J.* 2011 Jul-Aug;17(4):403-8. doi: 10.1111/j.1524-4741.2011.01089.x. Epub 2011 Jun 6.



Table 1. Estradiol Preparations and Maximum Annual Delivered Dose

Product name	Route/Type of administration	Typical regimen	Nominal daily delivery rate or administered lowest approved dose (mg/day)	Typical serum level (pg/mL)	Maximum annual delivered dose (mg) ¹
Vaginal estradiol					
Vagifem	Vaginal tablet	1 Tablet daily × 14 then 2 × weekly	10 μg	4.6	1.14
Estring	Vaginal ring	1 Ring vaginally q 3 months	7.5 μg	8.0	2.74
Estrace	Vaginal cream	1 g cream vaginally q week ²	variable ²	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	0.5 mg	55.4	182.5
Transdermal estradiol					
Divigel ³	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 ³	Spray	1.53 mg spray qd	0.021	19.6	7.67
Climara ⁴	Patch	1 Patch weekly	0.025	22	9.13
Menostar	Patch	1 Patch weekly	0.014	13.7	5.11
Vivelle-Dot ⁵	Patch	1 Patch twice weekly	0.0375	34	12.78

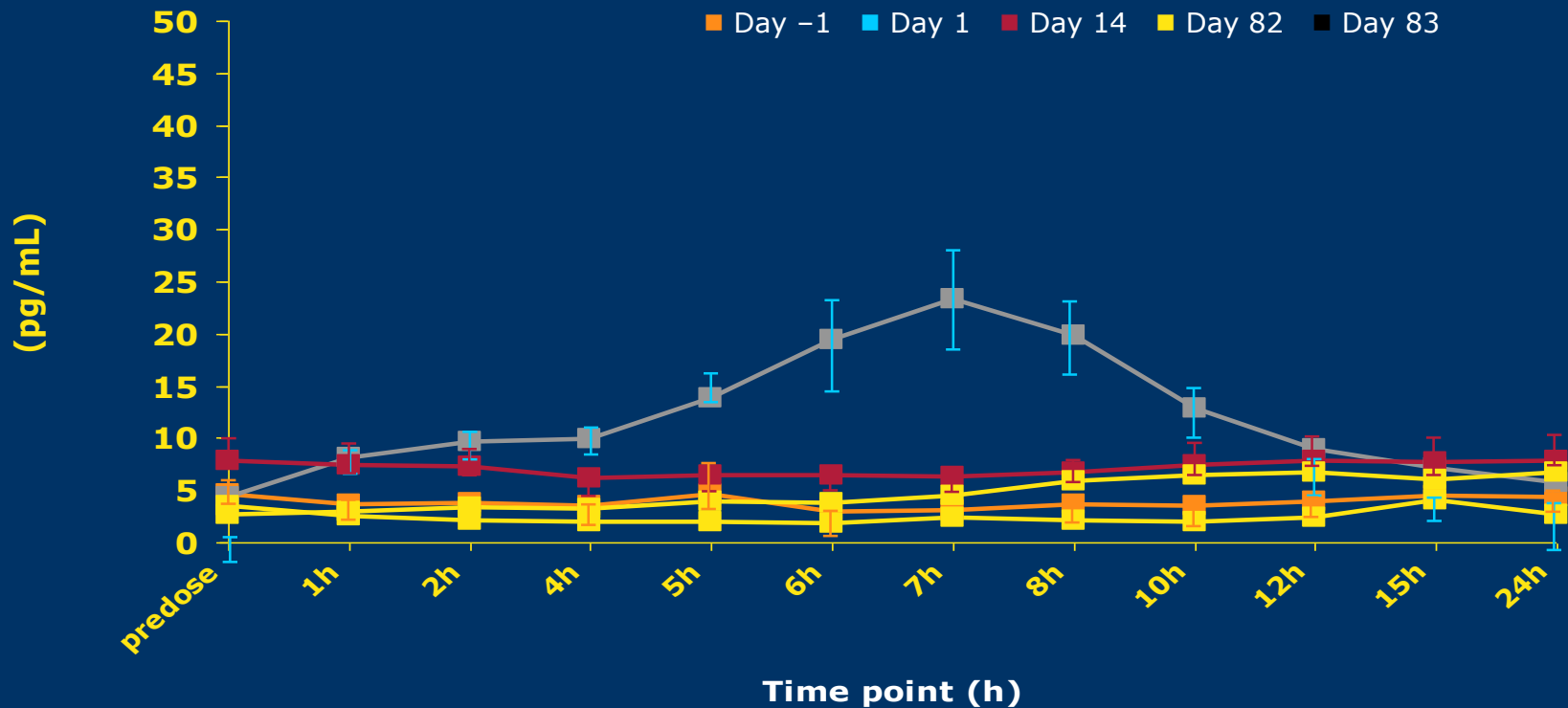
Support for the Contrary View (aka: “local is *not* local”)

- ❖ 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.

10µg E2 – mean* serum Estradiol concentrations at all time points



* Mean \pm SE

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

**Scientific Statement commissioned
by The Endocrine Society**

Journal of Clinical Endocrinology & Metabolism 95 (7 Suppl 1):s1-s66, 2010

Vaginal Issues

Overactive Bladder

Meta-analysis data

- ❖ Diurnal frequency diminished ($p=0.0011$)
- ❖ Nocturnal frequency diminished ($P=0.037$)
- ❖ Urgency decreased ($P= 0.043$)
- ❖ Incontinence episodes decreased ($P=0.0002$)
- ❖ First sensation to void improved ($P=0.0018$)
- ❖ Bladder capacity increased ($P=0.0018$)
- ❖ Urge incontinence improved (Cochrane review)
- ❖ Local superior to systemic estrogen therapy

Level of Evidence A

Recurrent Urinary Tract infection

- ❖ **Definition: three episodes of UTI within 12 months or two episodes within 6 months**
- ❖ **Cochrane review- no benefit of oral estrogens (RR 1.08 CI 0.88-1.33) level of evidence D**
- ❖ **Vaginal estrogen**
 - **Cream RR 0.25 CI 0.13-0.50**
 - **Vaginal ring RR 0.64-0.86**

Level of evidence A

Vaginal Atrophy

- ❖ **Estrogen therapy promotes vaginal cell growth, cellular maturation, fosters recolonization with lactobacilli, enhances vaginal blood flow, decreases vaginal pH, improves vaginal thickness and elasticity and vulvovaginal symptoms**
- ❖ **Vaginal preparations superior to oral**

Level of Evidence A

Endometrial effects of vaginal estrogen

- ❖ **Low dose vaginal estrogen probably does not require progestin administration to prevent uterine cancer but “no evidence based recommendations” for endometrial monitoring or progestogen dosing “**

Suckling J, Lethaby A & Kennedy R. Local oestrogen for vaginal atrophy in postmenopausal women. Cochrane Database Syst Rev 2006; (4). CD001500.

New Approaches to VVA Rx

- ❖ Estradiol-lower doses
- ❖ Estriol
- ❖ Tamoxifen vaginal
- ❖ SERMs (Ospemifene, Lasofoxifene, etc.)
- ❖ DHEA

Most Recently (THIS WEEK)



The American College of
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WOMEN'S HEALTH CARE PHYSICIANS

COMMITTEE OPINION

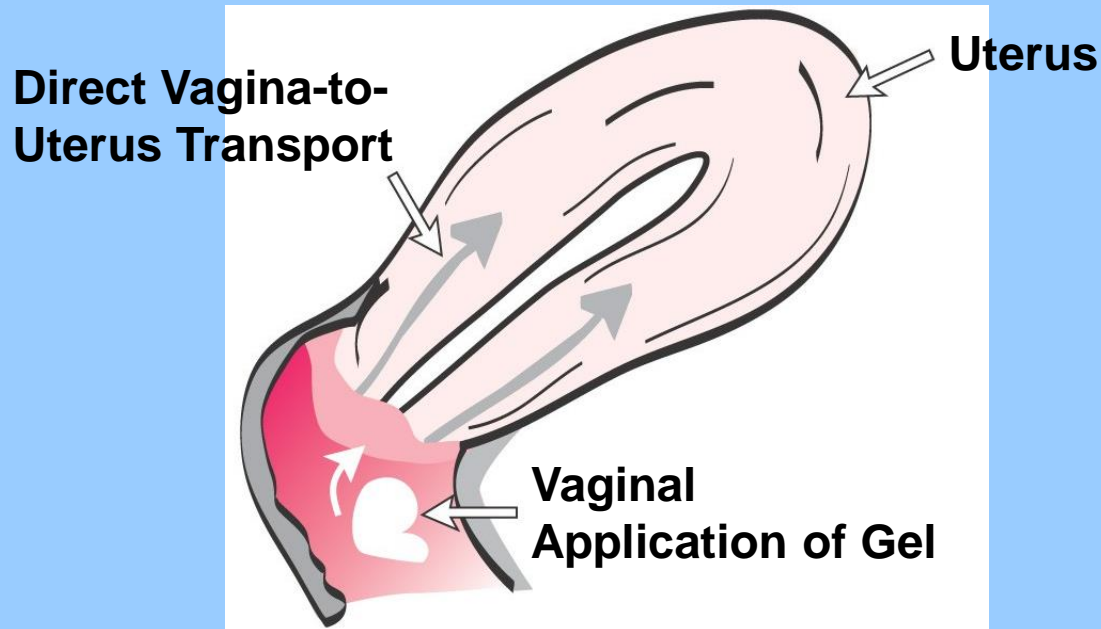
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Committee on Gynecologic Practice

This Committee Opinion was developed by the American College of Obstetricians and Gynecologists' Committee on Gynecologic Practice. Member contributors included Ruth Farrell, MD. This document reflects emerging clinical and scientific advances as of the date issued and is subject to change. The information should not be construed as dictating an exclusive course of treatment or procedure to be followed.

The Use of Vaginal Estrogen in Women With a History of Estrogen-Dependent Breast Cancer

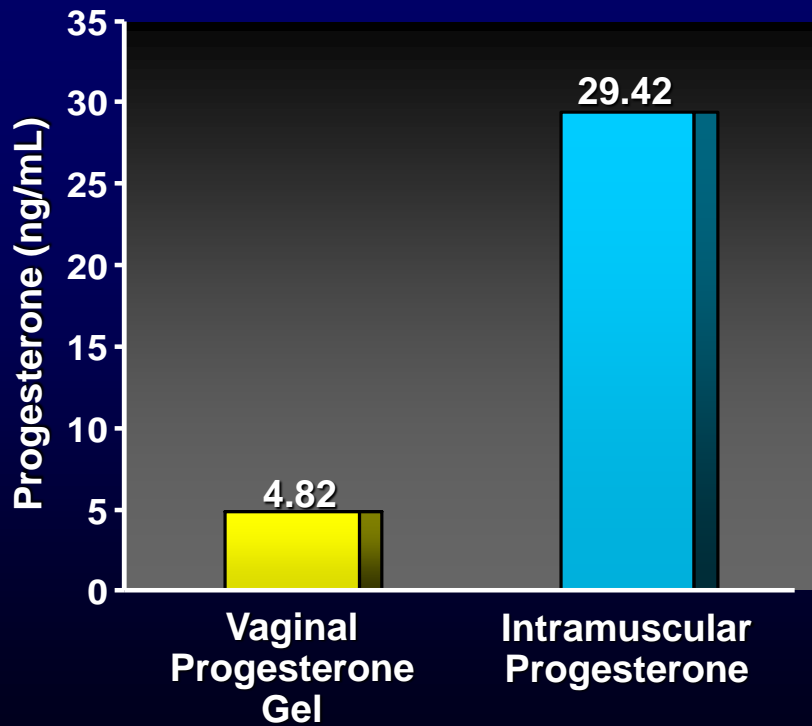
First Uterine Pass Effect



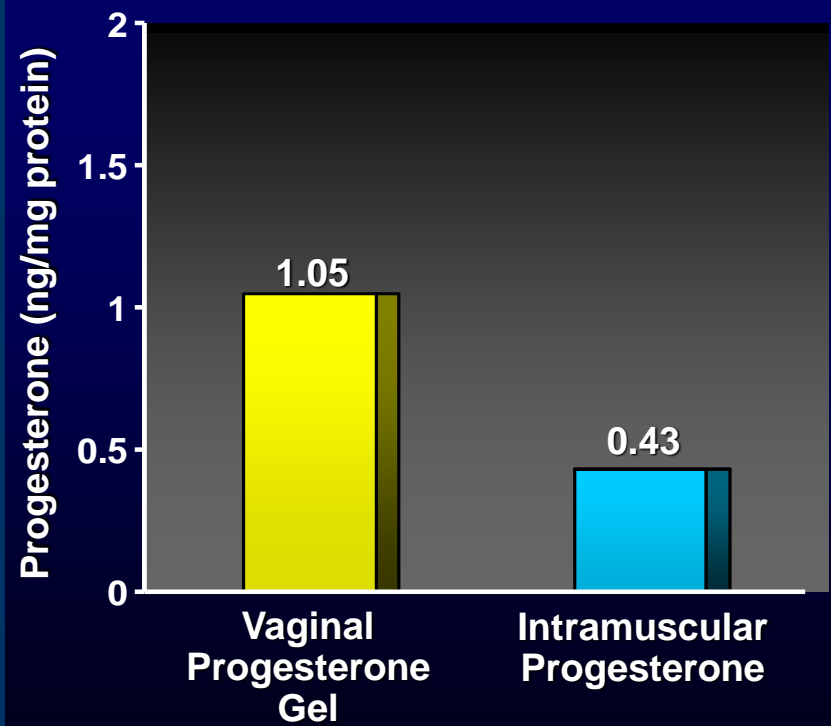
De Ziegler D, Bulletti C, De Monstier B et al. The first pass uterine effect.
Ann N Y Acad Sci 1997; 828: 291–299.

First Uterine Pass Effect: Study Results

Serum Progesterone



Endometrial Tissue Progesterone



Cicinelli E, de Ziegler D, Bulletti C, Matteo MG, Schonauer LM, Galantino P. Direct transport of progesterone from vagina to uterus. *Obstet Gynecol.* 2000 Mar;95(3):403-6.

Upper vs. Lower 1/3 Vaginal Placement

Cicinelli E, De Ziegler D, Morgese S, Bulletti C, Luisi D, Schonauer LM.
"First uterine pass effect" is observed when estradiol is placed in the upper
but not lower third of the vagina. Fertil Steril. 2004 May;81(5):1414-6.