Disclosures

Relevant Disclosures:

The Menopause Society Board of Directors

Consultant: Astellas

No conflicts of interest

References:

I will discuss clinical studies of off label use of pharmaceuticals for vasomotor symptoms.

This presentation references people born with ovaries. I may use the terms women, she, and her. These terms may not capture the diversity of all those experiencing menopause. We need more research to explore how diverse people experience menopause.

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Objectives

- Discuss symptom presentation of the genitourinary syndrome of menopause in cancer survivors
- Review consensus recommendations for treating the genitourinary syndrome of menopause in cancer survivors

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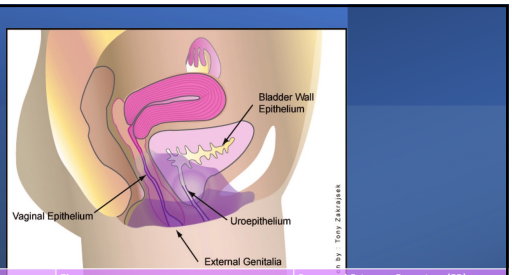

System	Tissues	Expressed Estrogen Receptors (ER)
Reproductive	Uterus, Vagina	ERα, ERβ, GPER
Urinary	Bladder, Urethra	ERβ
Gastrointestinal	Bowel, External Anal Sphincter	ERα, ERβ
Musculoskeletal	Pelvic Floor Muscles, Utero-sacral Ligaments	ERα, ERβ

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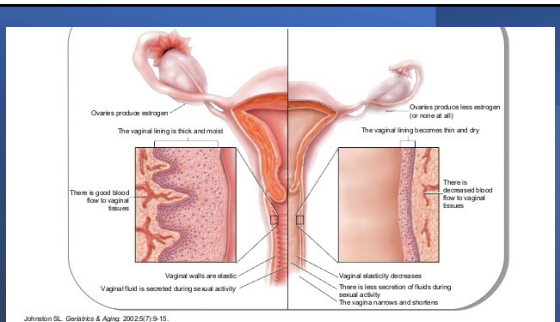

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Surgery: Oophorectomy, Vulvectomy, Hysterectomy

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Chemotherapy: ovarian toxicity and dysfunction, neuropathy

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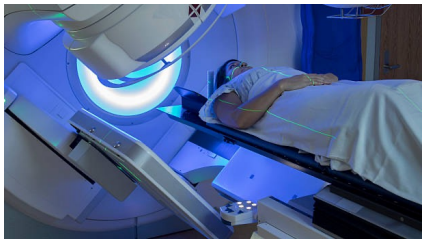

Pelvic Radiation: direct tissue damage, radiation vaginitis, vaginal fibrosis, mucositis, shortening, stenosis

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Tamoxifen: estrogenic effect, increased vaginal secretions

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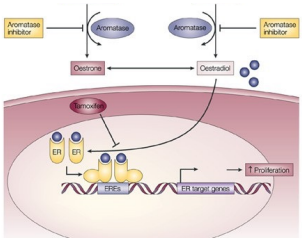

Aromatase Inhibitors :
marked vaginal dryness, vulvar thinning, sexual discomfort

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Immunotherapy: inflammation, GSM pain exacerbation

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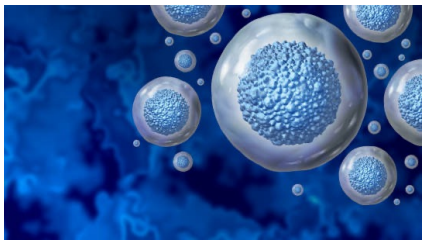

Stem Cell Transplant: GVHD: vulvovaginal dryness, pain, dyspareunia

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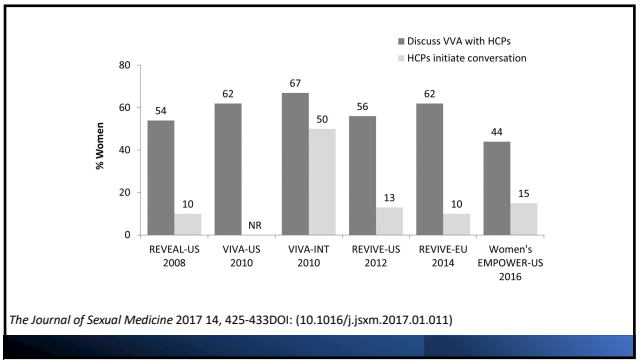

The Journal of Sexual Medicine 2017 14, 425-433DOI: (10.1016/j.jsxm.2017.01.011)

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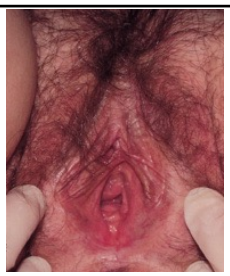
Symptoms

- Genital dryness
- Decreased lubrication with sexual activity
- Discomfort or pain with sexual activity
- Post-coital bleeding
- Decreased arousal, orgasm, desire
- Irritation/Burning/Itching of vulva or vagina
- Dysuria
- Urinary frequency/urgency



Signs

- Decreased moisture
- Decreased elasticity
- Labia minora resorption
- Pallor/Erythema
- Loss of vaginal rugae
- Tissue fragility/fissures/petechiae
- Urethral eversion or prolapse
- Loss of hymenal remnants
- Prominence of urethral meatus
- Introital retraction
- Recurrent urinary tract infections

Genitourinary Syndrome of Menopause

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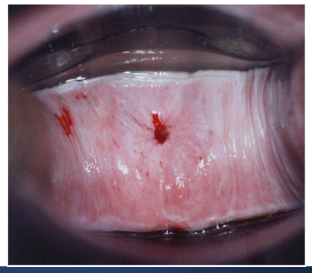
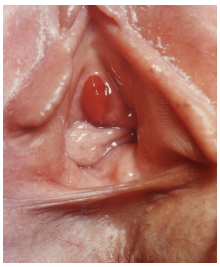

GSM in Cancer Survivors

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- Complete medical history
  - Symptom characterization, prior treatments
  - Review of vaginal irritants
- Sexual history
- Physical examination
  - Vaginal pH and wet prep as indicated
  - Vulvar/Vaginal cultures as appropriate
  - Biopsy white, pigmented, or thickened lesions

➢ Any vulvar lesion that does not respond to treatment should be biopsied

GSM: History and Evaluation

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- 41% of oncologists are refer patients with GSM to gynecologists
- Only 35% of oncologist manage symptoms independently
- Shared Decision making

GSM: Treatment

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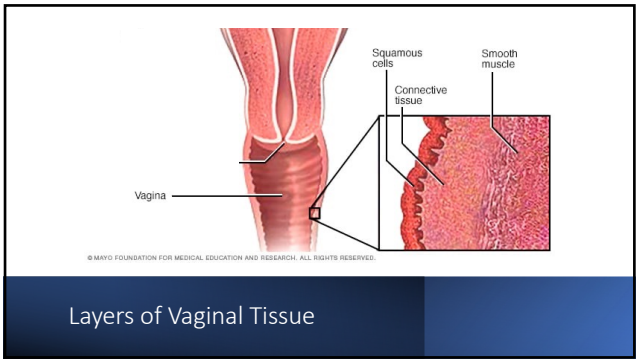

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Treatments for GSM: Lubricants

- Reduce friction
- Short term comfort
- One size does not fit all-encourage patients to try different formulations: water based vs. silicone
- Consider osmolality and pH
  - Ideal osmolality: of < 380 mOsm/kg,
  - Ideal pH>3.0
- Avoid additives irritating additives: parabens, glycerin, flavors, spermicides

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Treatments for GSM: Moisturizers

- Retain moisture
- One size does not fit all-encourage patients to try different formulations
- More frequent use compared to naturally menopausal women:
  - Consider daily use
  - Titrate to patient preference/tolerance

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Treatments for GSM: Lubricants and Moisturizers

Lubricants		Moisturizers
Water based Astroglide Liquid Astroglide Gel Liquid Astroglide Good Clean Love Just Like Me K-Y Jelly Pre-Seed Slippery Stuff Liquid Silk YES WB SYLK Sliquid	*Silicone based* Astroglide X ID Millennium K-Y Intrigue Pink Pjur Eros Uberlube Sliquid *Oil based* Elégance Women's Lubricants Olive oil YES OB	Replens Me Again Femenease K-Y SILK-Eluvena Revaree Silken Secret Hyalo-gyn

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Treatments for GSM: Kitchen cabinet?

- Natural oils: olive, coconut may be associated with vaginal infections
- Probiotics: could be helpful to microbiome, need comprehensive trials

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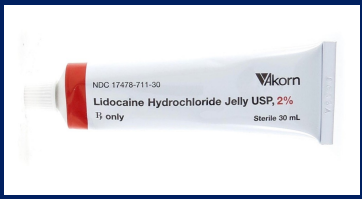
Treatments for GSM: Lidocaine

- Apply with cotton swab ~3 minutes before penetration



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Treatments for GSM: Vaginal Dilators

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Treatments for GSM: PFPT

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Treatments for GSM: Psychosocial Support

- Counseling
- Psychotherapy: CBT
- Support groups
- Group and individual education

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Treatment Options

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GSM Treatment Options: Vaginal Estrogen

10 mcg Estradiol hemihydrate vaginal tablet

17β Estradiol Vaginal ring

Estradiol or Conjugated Equine Estrogen Cream

4 or 10 mcg Estradiol vaginal insert

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Hormone Treatments: Low-dose Vaginal Estrogen

- Restores vaginal blood flow
- Decreases vaginal pH
- Improves thickness and elasticity of vulvovaginal tissues
- Many different formulations: vaginal ring, tablets, inserts, creams
- Improvements within a few weeks, full efficacy in 2-3 mo
- Serum levels typically in postmenopause range
- Large observational studies show no increased risk of endometrial cancer, breast cancer, or CVD
- Progestogen generally is not indicated
- Controversial data/guidance in hormone sensitive cancer survivors: Shared Decision-Making

Rahn DD, et al. *Obstet Gynecol*. 2014;124(6):1147-1156; Handa VL, et al. *Obstet Gynecol*. 1994;84(2):
215-218; Santen RJ. *Climacteric*. 2015;18(2):121-134; Crandall C, et al. *Menopause*. 2018;25(1):11-20; The NAMS 2020 Genitourinary Syndrome of Menopause Position Statement
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Local Estrogen Therapy

Women at high risk for breast cancer
- failed nonhormonal treatment

Women with ER positive breast cancers on tamoxifen
- persistent, severe symptoms with failed nonhormonal treatments and factors suggesting a low risk of recurrence

Women with ER positive breast cancers on AI
- persistent, severe symptoms with failed nonhormonal treatments and factors suggesting a low risk of recurrence
- consult with the oncologist to consider switching to tamoxifen

Women with triple negative breast cancers
- Theoretically reasonable data are lacking

Women with metastatic disease
- QoL, comfort, and intimacy may be a priority for many women with metastatic disease

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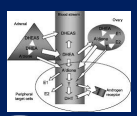
Hormone Treatments: Dehydroepiandrosterone (DHEA)

- 0.5%/6.5 mg DHEA vaginal suppository: Prasterone
- Indication: FDA approved for moderate to severe dyspareunia secondary to VVA
- Directions: inserted once daily at bedtime
- Phase 3 RCT showed significantly improved
  - Vaginal maturation index (VMI)
  - Vaginal pH
  - Signs of atrophy
  - Vaginal dryness
  - Dyspareunia
- Serum steroid levels remained within the normal postmenopause range
- Only adverse event (AE): vaginal discharge because of melting of the vehicle
- Safety: endometrial safety confirmed at 1 y



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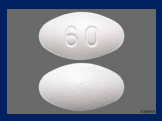
Hormone Treatments: Ospemifene

- **Oral** SERM: estrogen agonist/antagonist
- Indication: FDA approved for moderate to severe dyspareunia associated with VVA
- Dose: 60 mg/day
- Improves
  - — VMI
  - — Vaginal pH
  - — Symptoms of VVA
  - — May take 6 months to achieve full efficacy
- Safety
  - — No endometrial hyperplasia or cancer (at 52 w)
  - — Can increase VMS
  - — May increase the risk of venous thromboembolism (VTE)
- Antiestrogenic effects on breast but not approved for women with breast cancer
- NOT RECOMMENDED IN BREAST CANCER PATIES



Portman DJ, et al. *Menopause*. 2013;20(6):623-630; Bachmann GA, et al. *Menopause*. 2010;17(3):480-486; Simon J, et al. *Maturitas*. 2014;77(3):274-281; Soe LH, et al. *Int J Womens Health*. 2013;5:605-611; The NAMS 2020 Genitourinary Syndrome of Menopause Position Statement Editorial Panel. *Menopause*. 2020;27(9):976-992.

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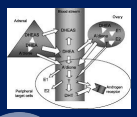
Hormone Treatments: Dehydroepiandrosterone (DHEA)

- 6.5 mg DHEA vaginal suppository: Prasterone
- Indication: FDA approved for moderate to severe dyspareunia secondary to VVA
- Directions: inserted once daily at bedtime
- Phase 3 RCT showed significantly improved
  - — Vaginal maturation index (VMI)
  - — Vaginal pH
  - — Signs of atrophy
  - — Vaginal dryness
  - — Dyspareunia
- Serum steroid levels remained within the normal postmenopause range
- Only adverse event (AE): vaginal discharge because of melting of the vehicle
- Safety: endometrial safety confirmed at 1 y
- CAN BE CONSIDERED IN BREAST CANCER PATIENTS



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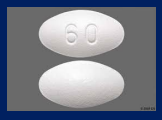
- **Oral** SERM: estrogen agonist/antagonist
- Indication: FDA approved for moderate to severe dyspareunia associated with VVA
- Directions: daily oral administration (60 mg)
- Improves
  - — VMI
  - — Vaginal pH
  - — Symptoms of VVA
  - — May take 6 months to achieve full efficacy
- Safety
  - — No endometrial hyperplasia or cancer (at 52 w)
  - — Can increase VMS
  - — May increase the risk of venous thromboembolism (VTE)
- Antiestrogenic effects on breast but not approved for women with breast cancer
- Favorable effects on bone



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Treatments for GSM: Laser

Laser therapy may be considered in women who prefer a nonhormonal approach; women must be counseled regarding lack of long-term safety and efficacy data

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Take Aways

- Load the Boat: Multidisciplinary Team Approach
- Reduce friction: Lubricants
- Retain moisture: Moisturizers
- Restore vaginal and urogenital tissues: Estrogen therapy
- Reduce pain: Lidocaine
- Maintain patency and caliber: Dilators
- Low threshold for PFPT
- Individualization and Shared Decision Making for all patients, especially those with hormone sensitive cancers using Ais:
  - Consult oncologic team
  - Evaluate patient preference, goals and concerns
  - Shared decision making with patient
  - Mitigate risk

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Local Estrogen Therapy

Women at high risk for breast cancer
- failed nonhormonal treatment

Women with ER positive breast cancers on tamoxifen
- persistent, severe symptoms with failed nonhormonal treatments and factors suggesting a low risk of recurrence

- Observational data do not suggest increased risk of breast cancer with systemic or local estrogen therapies beyond baseline risk

Women with ER positive breast cancers on AI
- persistent, severe symptoms with failed nonhormonal treatments and factors suggesting a low risk of recurrence
- consult with the oncologist to consider switching to tamoxifen

Women with triple negative breast cancers
- Theoretically reasonable data are lacking

Women with metastatic disease
QoL, comfort, and intimacy may be a priority for many women with metastatic disease

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