Genitourinary Syndrome of Menopause (GSM)

Estrogen and Beyond

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What is genitourinary syndrome of menopause?

- Constellation of symptoms and signs associated with decreased estrogen levels.
  - Vaginal or vulvar dryness.
  - Vaginal or vulvar burning.
  - Dyspareunia.
  - Lower urinary tract.
    - Dysuria.
    - Urgency.
    - Frequency.

Interference of Activities


Symptomatic GSM is a growing problem

- Increasing population of older postmenopausal women
- Declining use of systemic menopausal hormone therapy since the initial report of the WHI

Terminology GSM

- Consensus group: GSM is medically more accurate, all-encompassing, publicly acceptable, and less embarrassing than “vulvovaginal atrophy”.
- Some women may prefer to hear they have atrophy than a syndrome of menopause.
- Women with lichen sclerosis may fit into GSM and be treated with estrogen, not appropriate therapy.
- Rather then a leap forward, GSM terminology may be a backward approach.

GSM

- Half of postmenopausal women report symptoms.
- Negative effect on quality of life is substantial.
- 4-fold greater risk of sexual dysfunction if GSM symptoms present.
- Vasomotor symptoms tend to decrease over time.
- **GSM will not spontaneously resolve.**


How bothersome are vaginal dryness and sexual pain?

- First line therapies.
  - Nonhormonal lubricants and vaginal moisturizers.
  - Low-dose vaginal estrogen.
    - Significant improvement in QOL
    - Substantial number of women are undertreated.
- Second line therapy for women with moderate to severe dyspareunia who prefer non-vaginal therapy.
  - Transdermal or oral systemic estrogen.
  - Also for significant vasomotor symptoms.
  - Ospemifene (SERM)


Nonhormonal options for dyspareunia and vulvovaginal atrophy

**Moisturizers**
Used on a chronic maintenance basis to replace normal vaginal secretions

**Lubricants**
Designed to specifically reduce friction associated with sexual activity

Systemic Estrogen

- Significant reduction of vasomotor symptoms.
- Effectively alleviates atrophic vaginal and vulva symptoms.
- All low-dose systemic estrogen formulations are FDA-approved for treatment of atrophic vaginitis.
- Conjugated equine estrogen as low as 0.3mg/d and transdermal estradiol 12.5 mcg/d are effective.
- **NO data to suggest initial benefit for use of both systemic and local vaginal estrogen for severe atrophy.**

Local vaginal estradiol and conjugated equine estrogen

- Cream, ring and tab formulations highly effective
  - Even low dose tabs (10 mcg/d) of vaginal estradiol improve symptoms.
  - Ring preferred to cream for long term tx.
  - Comfort, ease of use, satisfaction.
- **Regimen: administered daily for 1-2 weeks as induction therapy and then used “indefinitely” at low doses for maintenance. (ACOG).**

Estring (vaginal estradiol ring)

- Should be inserted in upper third of vagina.
- Position not critical.
- Should be comfortable and not interfere with sex.
- If expelled, wash with water and reinsert.
- Left in place for 90 days.
Is progestin necessary with vaginal estrogen?

- Systematic Review 2014
  - Data insufficient to mandate endometrial surveillance or dictate frequency or means of surveillance.
  - Clinician vigilance for possible emergence of endometrial pathology.
- ACOG
  - “The addition of progestin for endometrial protection is not needed”
- Cochrane
  - “Does not require endometrial surveillance unless there is postmenopausal bleeding”

Cochrane 2006: local vaginal estrogen

- 19 trials of 4126 women: quality good.
- All local estrogen products had similar efficacy.
  - Creams, tabs, vaginal ring.
- As effective as systemic oral estrogen in relieving GSM symptoms.
  - 80-90% satisfaction compared to 75% using oral estrogen
- Conjugated equine estrogen cream.
  - Endometrial overstimulation (1 trial): hyperplasia but no atypia.
- Significant preference for ring.
  - Relief of symptoms: significant preference for any formulation compared to placebo and non-hormonal topical agents.

Reasons for discontinuing or not initiating estrogen therapy

- Boxed warning discourages clinicians from prescribing it and women from taking it.
  - “WARNING: endometrial and breast cancer, cardiovascular disorders, probably dementia”
- Derived from clinical trials of systemic hormone therapy (WHI) using substantially higher levels of estrogen.

Product labeling for vaginal estrogen

- Revision of labeling for vaginal estrogen
  - “Estrogen and progestin when given systemically have been linked to what is contained in the boxed warning.
  - However - the relevance to low-dose vaginal estrogen remains unknown.”
  - “Report any vaginal bleeding or spotting right away while using product.”
  - “Women with history of cancer of the breast or uterus or other hormone sensitive cancers are encouraged to consult their oncologist before use.”

Bioidentical hormones

- “Bioidentical” or “traditional hormones” carry the same risks and benefits if dosage and purity same.
- There is no scientific evidence that a different or “customized” dose of hormones would have changed results of WHI study.
- Endocrine Society supports FDA regulation.
  - Caution: Have no official labeling (package insert) because are not FDA-approved

What's natural and what's not....?

- All hormonal agents are derived from "CHEMICAL PLANTS" except those derived from horse urine.

- Conjugated equine estrogens (estrone, equilin + other compounds)
  = Premarin.

Endocrine Position Paper 2006
Bioidentical Hormones

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<th>Molecular structure</th>
<th>Traditional Hormones</th>
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<td>Yes</td>
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<td>Dosage</td>
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Osphena (Ospemifene) is a SERM

- Estrogen agonist-antagonist with tissue selective effects.
- One daily oral pill, no vaginal insert.
- FDA-approved for treatment of moderate to severe dyspareunia: no effect on urinary tract.
- Prescribing information same as estrogen and other SERMs such as risk for VTE.
- Women with breast cancer: No long term data.

Osphena

- Hot flashes most commonly reported adverse event.
- Placebo group: 2%; 60 mg Ospemifene: 7.2%

- Improves specific vaginal tissue that is painful.
- Thickens superficial cells of vagina.


Osphena effects on target tissue

**Endometrium**

- Agonist. 12 and 52 week trials. No endometrial cancer. One case hyperplasia, no atypia.

**Vagina**

- Agonist. 12 and 52 week trials. Significant increase in superficial cells.

Archer DF et al. Menopause 2014;22:786-796
Ospemifene effects on target tissue

- **Breast**
  - Neutral (limited data). No significant abnormalities on mammography.
  - No reports of cancer during trials.
  - Should not be used if breast cancer.

- **Bone**
  - Agonist (limited data).
  - 3 mo. RCT.
  - + effect of bone turnover on biomarkers

**Use a progestin with ospemifene?**

- **Use of progestin with ospemifene has not been evaluated in clinical trials.**
  - In all ospemifene trials conducted up to now, it was used as a single agent without progestin.
  - Industry data is not clear on whether a progestin should be given to women with a uterus.

**What is vaginal rejuvenation?**

- Proposed mechanism of microablative fractional CO2 laser occurs through an action that “stimulates tissue remodeling”.
- Activate fibroblasts to produce new collagen and stimulate endothelial growth factor to make new vessels with specific effects on epithelial tissue.
- Stimulates re-epithelization.
- Studies on skin of face, chest and neck.

**Small study (but about the only one!)**

- 5 women (aged 57-71) referred for anterior vaginal prolapse repair including vaginal hysterectomy.
- None of the women were using estrogen.
- RCT of CO2 laser-treated vaginal and untreated vaginal samples (other side of vagina).
- One side of the vagina treated with microablation fractional CO2 laser using different machine settings.
- 5 protocols were tested maintaining 30 w power but varying dot spacing.
- Treated and untreated vagina biopsied.

**Study details**

- Control side vagina confirmed atrophic mucosa.
- Protocol with most evident effects; 30W of DOT power, 1000 microm of DOT spacing
  - Demonstrated tissue remodeling which included activation of fibroblasts and collagen. (all 5 women)
  - “Reverse process toward restoration of a premenopausal state”.
  - No damage to surrounding tissue.

**Vaginal mucosa treated with laser**

Salvatore S et al. JNAMS 2015;22:845-849
Personal hx breast or endometrial cancer (or at high risk for either) + severe GSM symptoms

- Consider low-dose vaginal estrogen after informed consent of potential risks and balancing of individual preferences and needs.
- ACOG (Prac Bull 2014;123:202-216)
  - Nonhormonal methods considered first-line tx.
  - Short-term use of hormones may be considered in women with severe or refractory symptoms in whom other options have failed.

Desquamative Inflammatory Vaginitis (DIV)
(chronic inflammatory process)

- Typical patient – hypoestrogenic white woman.
  - Progestin-dominant contraception
  - Postpartum or breastfeeding
  - Perimenopausal*** or postmenopausal***
  - Abnormal vaginal discharge (yellow or brown).
  - Burning and severe dyspareunia.
  - Severe introital and vaginal erythema with copious vaginal discharge.

Criteria for DIV

1. Symptomatic women with at least one of the following complaints:
   - Profuse discharge, dyspareunia, pruritus, burning
2. Vaginal inflammation: spotted rash, erosions
3. Vaginal pH > 4.5
4. Wet prep with increased parabasal cells and leukocytes.
5. Reduced or absent lactobacilli


Desquamative Inflammatory Vaginitis (DIV) (chronic inflammatory process)

Important marker
Increased desquamation of the vaginal wall

Quantification of Parabasal Cells and Leukocytes

Increased desquamation of the vaginal wall

Leads to a brittle and thinned vaginal mucosa that can be sensitive and fragile.

Desquamatative Inflammatory Vaginitis

Cytologic and vaginal changes can look similar to atrophic vaginitis

H Haefner, MD, D Birenbaum, MD
(Used with permission)

Intravaginal Treatment of DIV

Anti-inflammatory Effect

- Clindamycin vaginal cream or suppository
- Hydrocortisone vaginal cream or suppository
- Median 3 weeks (range 1-19 weeks) for first follow up visit


DIV treatment outcomes

- Initial response to therapy is almost universal.
- Lack of response justifies reconsideration of dx.
- 80% controlled after initial treatment
- 1 year follow-up showed cures in 26%.
- 45-58% were asymptomatic but some required maintenance.
- 16% were only partially controlled.
- Both treatments relieved symptoms in 86% of patients.
- DIV can be managed effectively


Treatment for DIV
combination intravaginal clindamycin and hydrocortisone

- Made at compounding pharmacy
- Hydrocortisone 100 mg/gm in clindamycin 2% emollient cream base. Insert 5 gm (one applicator) in vagina every other night x 14 doses
Summary

- Recognize that GSM can significantly affect QOL.
- Try moisturizers and lubricants first.
- Try low-dose vaginal estrogen if no history of estrogen-dependent cancers.
- No progestin required.
- Consider less studied options such as ospemifene for severe dyspareunia.
- Laser rejuvenation not well tested yet.
- Diagnose DIV for what it is, not atrophy.

Thanks!