Genitourinary Syndrome of Menopause (GSM)

Estrogen and Beyond

Barbara S. Apgar, MD, MS

Professor of Family Medicine

University of Michigan Medical Center

Ann Arbor, Michigan

ASCCP2016

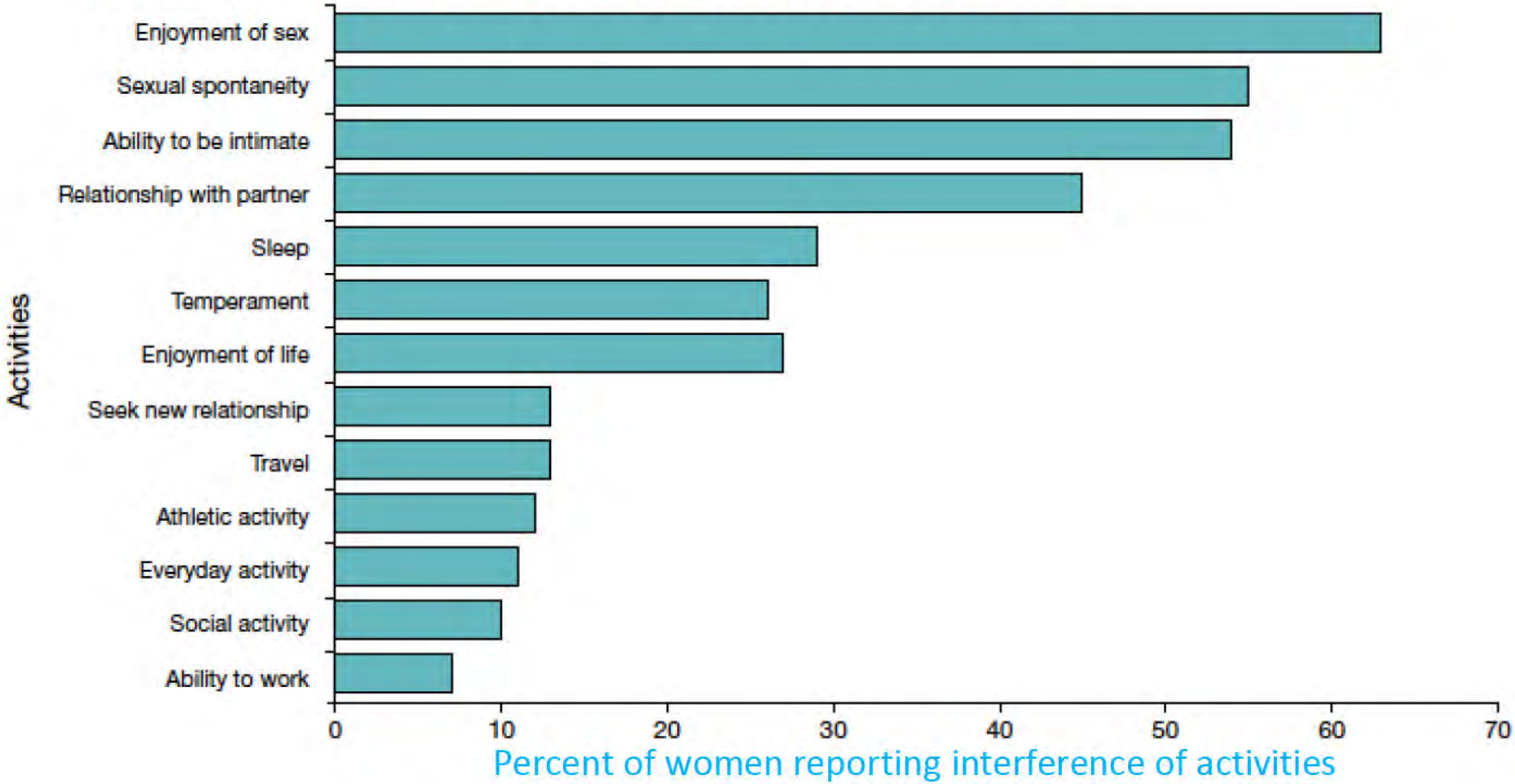
- Disclosure: nothing in regards to this topic.

- Images: Apgar, Brotzman, Spitzer. Integrated Text and Atlas of Colposcopy, 2008.
- Laser rejuvenation image pending permission

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



Kingsberg SA et al. J Sex Med 2013;10:1790-9.

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 felt that GSM is medically more accurate, all- encompassing, publicly acceptable, and less embarrassing than “vulvovaginal atrophy”.
- Term endorsed by Int Soc for Study of Women’s Sexual Health and North American Menopause Soc in 2014.
- Some women may prefer to hear they have atrophy rather 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.

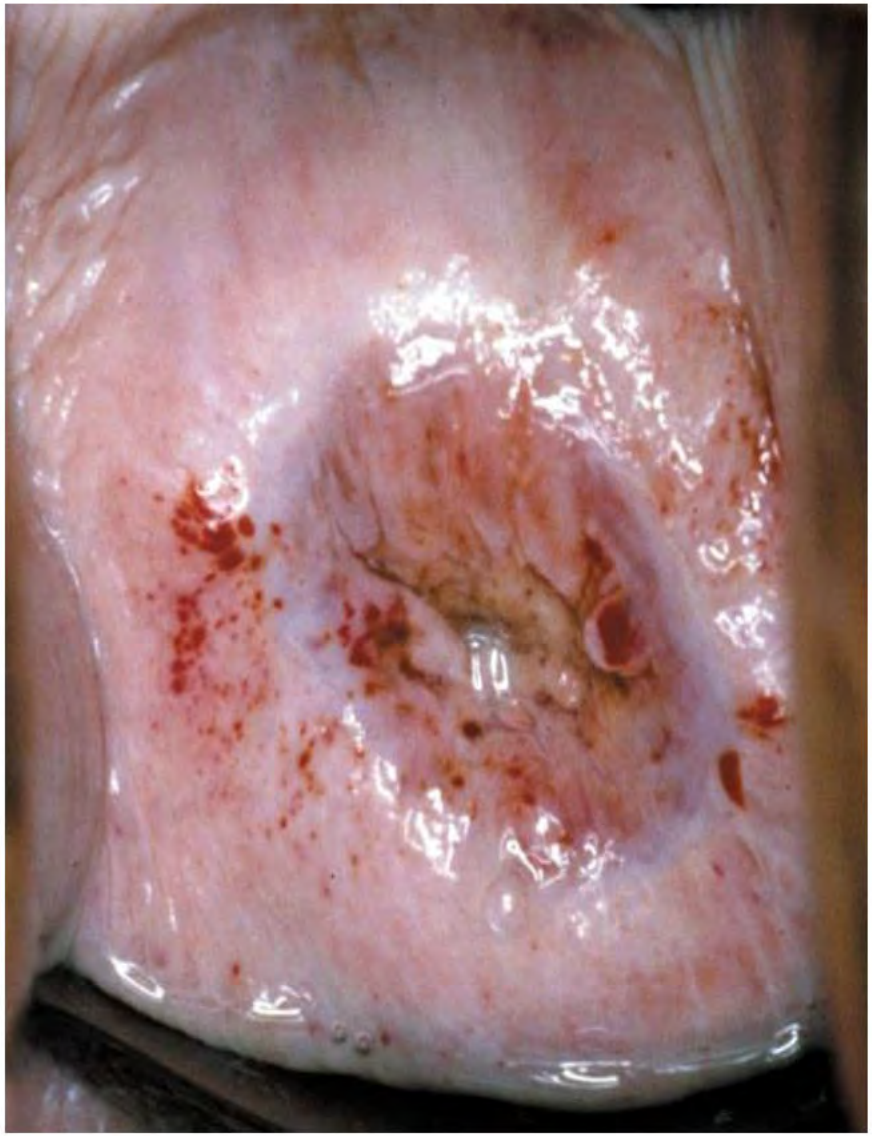
Portman DJ et al. Maturitas 2014;79:349-54.

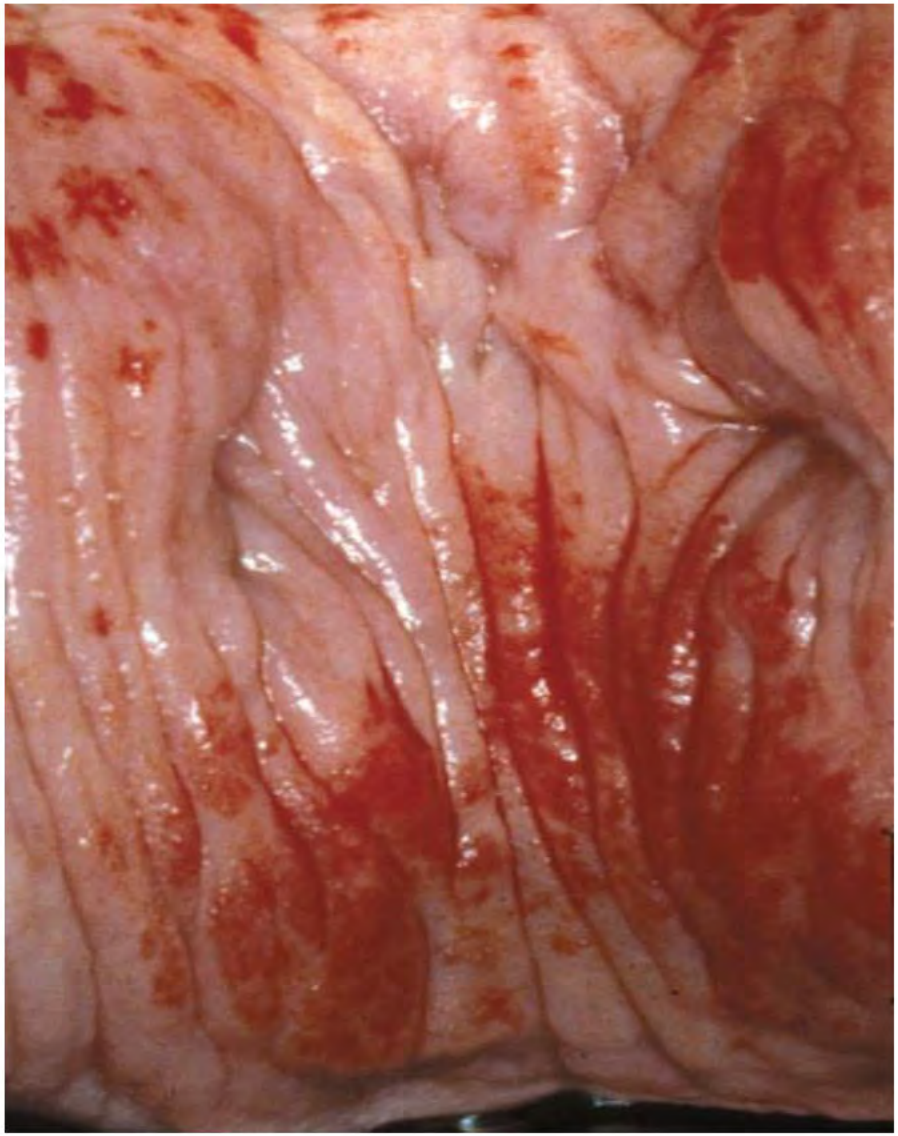
Vieira-Baptista P et al. JLGTD 2015;19:362-363.

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*.

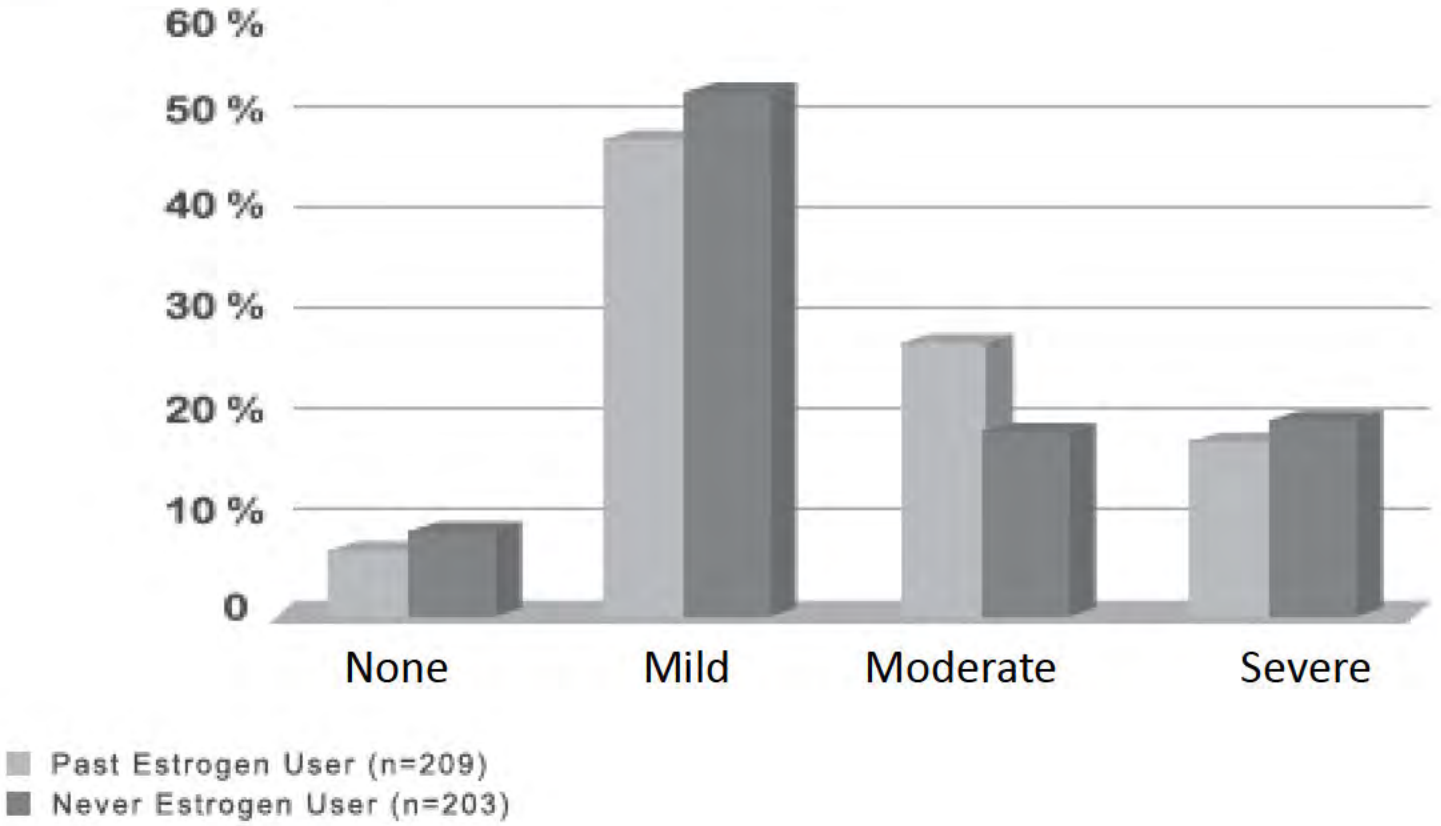
NAMS Position Statement. Menopause 2013;20:888-902.
Kingsberg SA et al. J Sex Med 2013;10:1790-9.
Rahn DD et al. Obstet Gynecol 2014;124:1147-1156





Apgar, Brotzman, Spitzer

How bothersome are vaginal dryness and sexual pain?



Santoro et al. J Sex Med 2009;6:2133-42.

GSM and quality of life

- *First line therapies.*
  - Nonhormonal lubricants and long-acting vaginal moisturizers.
  - Low-dose vaginal estrogen (no contraindications).
    - Significant improvement in QOL.
    - Substantial number of women are undertreated.
- *Second line therapy* for moderate to severe dyspareunia who prefer non-vaginal therapy.
  - Transdermal or oral systemic estrogen.
    - Also for significant vasomotor symptoms.
  - Oral estrogen agonist/antagonist ospemifene.
    - NAMS 2013 Position Statement. Menopause 2013;20:888-92

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

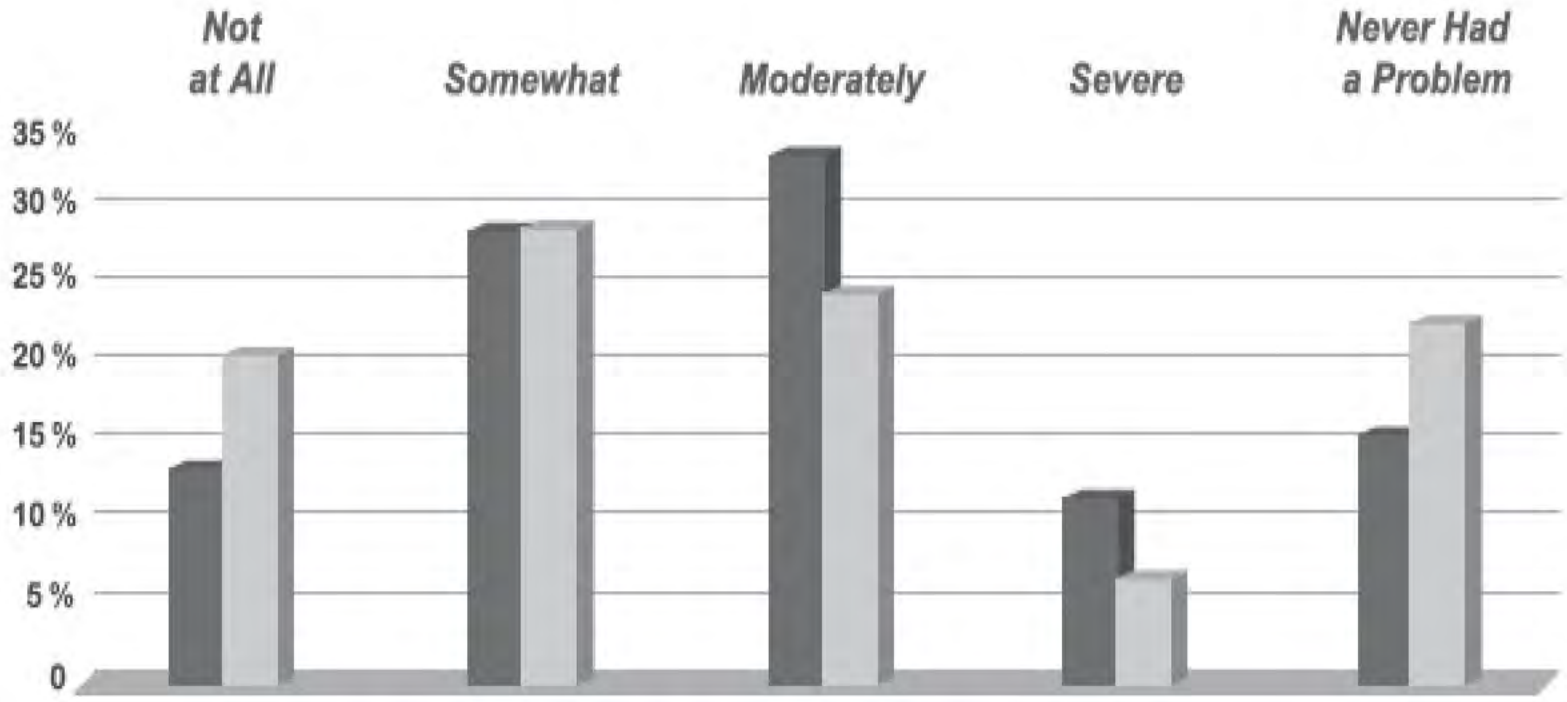
Nonhormonal options for dyspareunia and vulvovaginal atrophy

- *Lubricants (before sex)*
  - Water based
    - Astroglide Gel, Liquid
    - K-Y jelly
  - Silicone based
    - Astroglide S
    - K-Y Intrigue
    - ID Millennium
  - Oil based
  - Olive oil
  - Elegance
- *Moisturizers (2x week)*
  - Replens
  - Vagisil
  - KY Silk-E
  - Luvena
  - Silken Secret
  - Summer's Eve

Regular sexual activity (partner, device, solo)

NAMS Position Statement. Management of symptomatic vulvovaginal atrophy 2013;20:888-902

Current estrogen uses – Impact of vaginal dryness on QOL prior to hormone therapy



Santoro et al. J Sex Med 2009;6:2133-42.

How does estrogen work to reverse vulvovaginal atrophy?

- Promotes vaginal cell growth and cell maturation.
- Enhances vaginal blood flow.
- Fosters lactobacilli recolonization.
- Decreases vaginal pH.
- Increases vaginal epithelial thickness and elasticity.

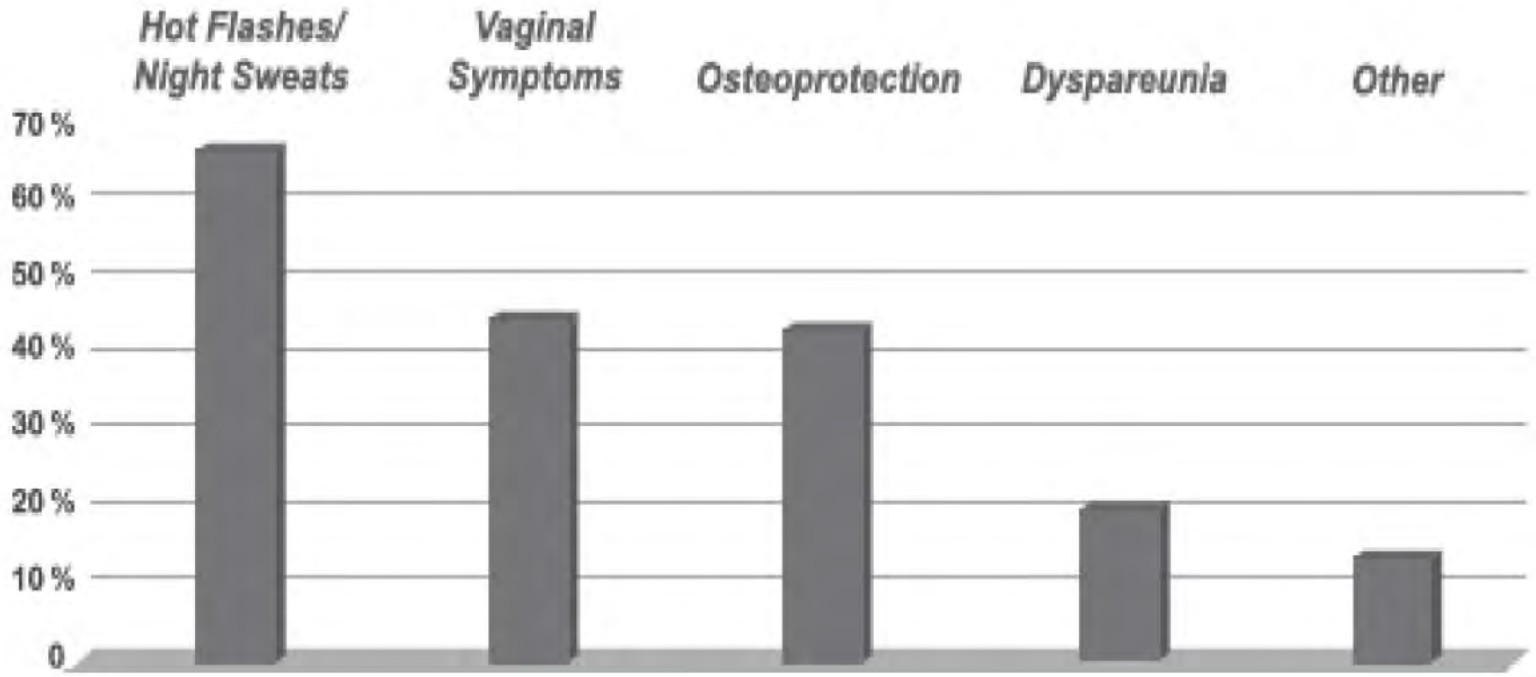
Pinkerton JA V et al. Menopause 2013;21;309-319

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.*

CURRENT Estrogen Users (n=332):

For what reasons do you mainly use hormone therapy?



J Sex Med 2009;6:2133–2142

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).*

ACOG Prac Bull No.141. Obstet Gynecol 2014;123: 202-216.

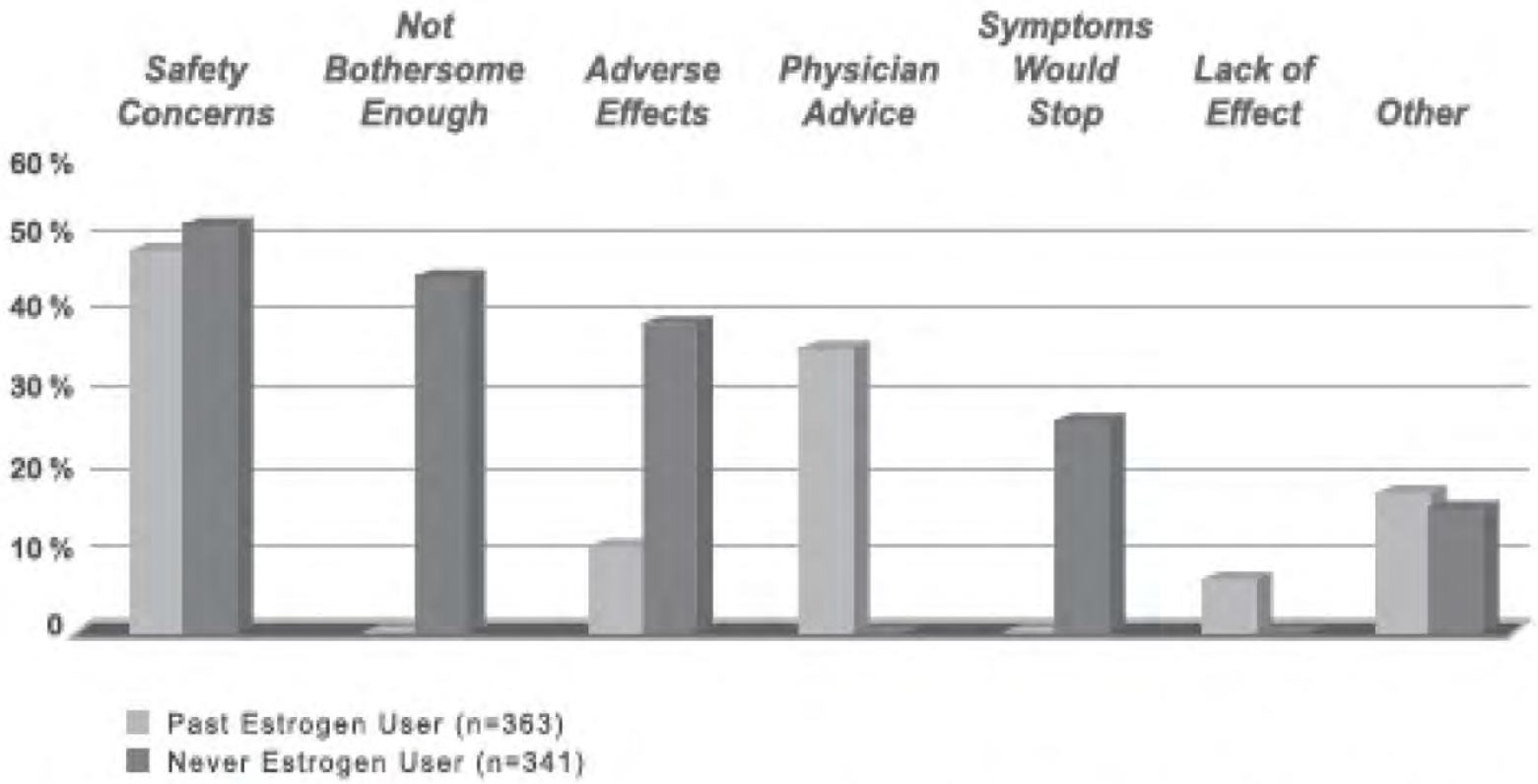
Uterus treated with vaginal estrogen

- Systematic Review 2014
  - Data insufficient to mandate endometrial surveillance or dictate frequency or means of surveillance.
  - Clinician vigilance for possible emergence of endometrial pathology. (s)
- 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.
- Conjugated equine estrogen cream.
  - Endometrial overstimulation (1 trial): HP but no atypia.
- As effective as systemic oral estrogen in relieving GSM symptoms.
  - 80-90% satisfaction compared to 75% using oral estrogen.
- 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



Santoro et al. J Sex Med 2009;6:2133-42.

Product labeling for vaginal estrogen

- Revision encouraged by NAMS, ACOG, Endocrine Soc, Am Soc Reprod Med, Int Soc Study of Women's Sex Health.
- 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.
    - Manson JE et al. Menopause 2014;21:911-916

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."**

Manson JE et al. Menopause 2014;21:911-916

Bioidentical hormones

- Bioidentical hormones are either FDA-approved or formulated by compounding pharmacies.
- There is no scientific evidence that a different or "customized" dose of hormones would have changed results of WHI.
- "Bioidentical" or "traditional hormones" carry the same risks and benefits if dosage and purity same.
- Society supports FDA regulation and oversight.

  - Endocrine Society Position Statement. Bioidentical Hormones. Oct 2006

Pharmacy compounded bioidentical hormones

- Caution: Have no official labeling (package insert) because are not FDA-approved.
- Caution in prescribing compounded hormones when FDA-approved alternatives exist.
  - 17 beta estradiol (transdermal or oral)
  - Estrone sulfate (active ingredient in naturally – occurring and synthetic conjugated equine estrogen.

ACOG Comm Opinion No 532. Obstet Gynecol 2012;120(2):411-15.

Ospemifene (SERM)

- FDA-approved for treatment of moderate to severe dyspareunia (level A): effect on urinary tract known.
- Prescribing information same as estrogen and other SERMs such as risk for VTE.
- Women with breast cancer: No long term data.
- Hot flashes most commonly reported adverse event.
  - Placebo group: 2%; 60 mg Ospemifene: 7.2%
    - Tan O et al. Menopause 2012;19:109-117

Ospemifene effects on target tissue

- **Endometrium**
  - Partial agonist. 12 and 52 week trials. Slight increase in thickness from baseline by TVUS.
- Vagina
  - Agonist. 12 and 52 week trials. SS 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.
- **Bone**
  - Agonist (limited data).
  - 3 mo. RCT.
  - + effect of bone turnover on biomarkers

Use a progestin with ospemifene?

- Prescribing information.
  - 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.
  - No endometrial cancer cases were reported up to 52 weeks of ospemifene 60 mg daily.
  - One case of endometrial hyperplasia without atypia.

Letter to the Editor. Menopause 2015;22:916.

Tissue-selective estrogen complexes

- Pairing of estrogen with a SERM.
- Goal?
  - Provide clinical benefits of each component with improved tolerability.
- Therapeutic profile of TSEC.
  - Relief of hot flashes, treatment of vulvovaginal atrophy.
  - Prevention of bone loss.
  - Safety for endometrium and breast.

Tissue-selective estrogen complexes

- TSEC in development (not FDA-approved):
  - *Bazedoxifene* (prevention and treatment of postmenopausal osteoporosis) and *conjugated estrogens* (prevention and treatment of hot flashes and vulvovaginal atrophy).
- 2-year phase III trial.
  - Significantly more effective than placebo in improving vaginal atrophy and reducing dyspareunia.
  - Well tolerated with safety profile similar to placebo.

Lobo RA et al. Fertil Steril 2009;92:1025-1038

What is vaginal rejuvenation?

- Proposed mechanism of microablative fractional CO2 laser occurs through an action that “stimulates tissue remodeling”.
  - Activating fibroblasts to produce new collagen and stimulating 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.

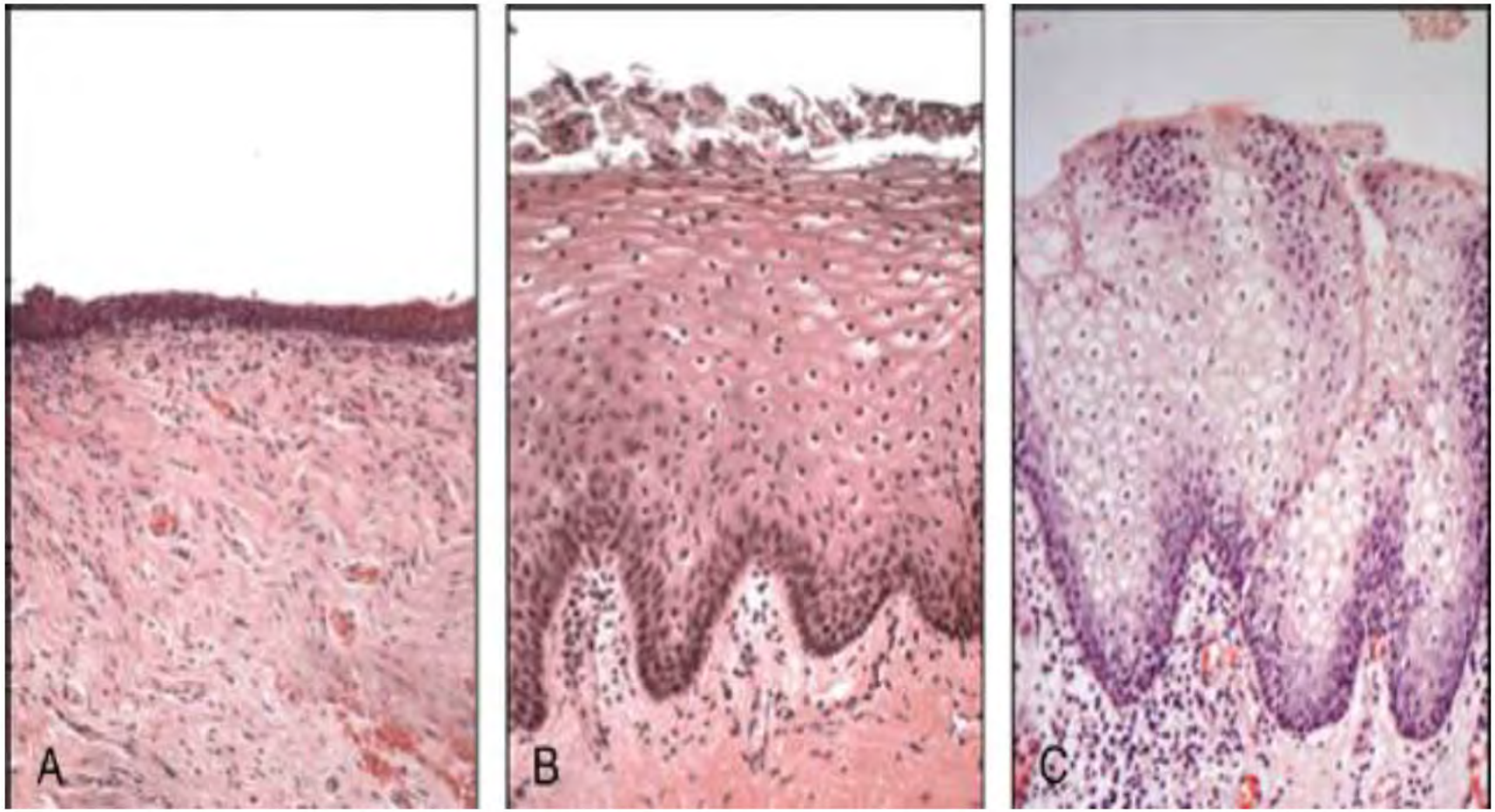
Salvatore S et al. JNAMS 2015;22:845-849

Study details

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

Salvatore S et al. JNAMS 2015;22:845-849

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

- Primary nonhormonal moisturizer. (s)
- Consider low-dose 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.

Clinical Practice Guidelines for GSM

One urogenital atrophy (UGA) complaint.	Non-hormonal agents or vaginal estrogen (s) 2C
Multiple UGA complaints.	Vaginal estrogen (s) 2C
Multiple UGA complaints + urge urinary incontinence.	Vaginal estrogen –ring and tablet studied (r) 1B
Multiple UGA complaints + stress urinary incontinence	Vaginal estrogen (s) 2C
Recurrent UTI with or w/o UGA complaints.	5. Vaginal estrogen-ring and estriol studied (R) 1B

Rahn DD et al. Vaginal estrogen for GSM. Systematic Review. Obstet Gynecol 2014;124:1147-56.

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.
- Systematic estrogen rarely adds more symptom reduction.

ASCCP2016