Genitourinary Syndrome of Menopause:

Novel Term for Common Conditions

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NAMS 2016

Disclosures

Research, Consultant, and/or Speaker

Allergan, AMAG Pharma, Amgen Inc., Azure, FORE/American Bone Health, Heptares Therapeutics, Illumigyn, JDS Therapeutics, Juniper Pharma, Menck, Noven, Novo Nordisk, Own the Bone Advisory Board of the American Orthopedic Association, Palatin Technologies, Pfizer, Radius Health, Shionogi Inc., Sprout, Therapeutics MD, Valeant

Objectives

• Historical review for the change in terminology, GSM vs. VVA
• Review incidence, signs, symptoms and pathophysiology of GSM
• Discuss the impact of GSM on quality of life from major surveys
• Review current therapeutic options for GSM
• Describe the Day-to-Day Impact of Vaginal Aging (DIVA) questionnaire

ISSWSH-NAMS CONSENSUS CONFERENCE

MAY 17 – 19, 2013
Chicago, IL
**ISSWSH-NAMS Conference Objectives**

Review basic and clinical science evidence on VVA and define key factors that influence diagnosis, treatment, and patient management.

Determine and develop a new/revised lexicon and nomenclature for VVA to enhance medical care, teaching and research.

“Atrophy” offensive and “Vagina” not for public use.

VVA- Vulva and Vagina, BUT what about the lower urinary tract.

Other examples: ED and OAB.

Generate an action plan to disseminate recommendations and raise awareness among members of the healthcare community and public.

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**Publication and Sponsorship Strategy**

May 2013

Manuscript submission plan...Success!

**Components Used to Develop New Terminology**

<table>
<thead>
<tr>
<th>Anatomy</th>
<th>Descriptors</th>
<th>Problem</th>
<th>Life Phase</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vagina</td>
<td>Vulvovaginal</td>
<td>Atrophy</td>
<td>Midlife</td>
</tr>
<tr>
<td>Vulva</td>
<td>Genital</td>
<td>Alterations</td>
<td>Aging</td>
</tr>
<tr>
<td>Labia</td>
<td>Gynecologic</td>
<td>Condition</td>
<td>Menopause</td>
</tr>
<tr>
<td>Vestibule</td>
<td>Reproductive</td>
<td>Disease</td>
<td>Postmenopause</td>
</tr>
<tr>
<td>Urethra</td>
<td>Sexual</td>
<td>Deficiency</td>
<td>Dysfunction</td>
</tr>
<tr>
<td>Bladder</td>
<td>Genitourinary</td>
<td>Urinary</td>
<td>Vaginitis</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Urologic</td>
<td></td>
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</tbody>
</table>

Terms in bold are the words selected by the panel to develop new nomenclature.

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**ISSWSH-NAMS Conference Objectives**

Create a standardized, practical assessment tool clinicians can use to facilitate identification and staging of "VVA" (now called GSM).

Current ongoing project sponsored by NAMS, NERI, MGH and others, to develop new validated GSM PRO (patient reported outcome) instruments to use for research and clinical practice. **STAY TUNED**
Genitourinary Syndrome of Menopause: GSM

- Comprehensive term that includes symptomatic VVA as well as lower urinary tract symptoms related to low levels of estrogen and other sex steroids
- Includes changes to the labia majora/minora, clitoris, vestibule/introitus, vagina, urethra and bladder
- GSM is highly variable and women may present with all or few of the signs and symptoms of this condition
- Not attributable to another diagnosis
- Unlike the vasomotor symptoms of menopause, GSM symptoms may worsen over time unless treated
- Symptoms are NOT limited to sexually active women

Differential Diagnosis

- Candidiasis
- Bacterial vaginosis
- Desquamative inflammatory vaginitis
- Contact dermatitis (irritant or allergic)
- Lichen sclerosis
- Lichen planus
- Lichen simplex chronicus
- Vulvar intraepithelial neoplasm
- Vulvar cancer
- Other benign and malignant tumors
- Other medical disorder (e.g., diabetes, lupus)
- Psychological causes
- Trauma/Foreign body
- "Vulvodynia"

GSM Symptoms and Signs

<table>
<thead>
<tr>
<th>Symptoms</th>
<th>Signs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Genital dryness</td>
<td>Decreased moisture</td>
</tr>
<tr>
<td>Decreased lubrication with sexual activity</td>
<td>Decreased elasticity</td>
</tr>
<tr>
<td>Discomfort or pain with sexual activity</td>
<td>Labia minora retraction</td>
</tr>
<tr>
<td>Post-coital bleeding</td>
<td>Painless Erythema</td>
</tr>
<tr>
<td>Decreased arousal, orgasm, desire</td>
<td>Loss of vaginal rugae</td>
</tr>
<tr>
<td>Irritation/Burning/Itching of vulva or vagina</td>
<td>Tissue fragility/Inflamed/petechiae</td>
</tr>
<tr>
<td>Dysuria</td>
<td>Urethral erosion or prolapse</td>
</tr>
<tr>
<td>Urinary frequency/urgency</td>
<td>Loss of hymenal remnants</td>
</tr>
<tr>
<td></td>
<td>Prominence of urethral meatus</td>
</tr>
<tr>
<td></td>
<td>Introversal retraction</td>
</tr>
<tr>
<td></td>
<td>Recurrent urinary tract infections</td>
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</tbody>
</table>

Supportive findings: pH >5, increased parabasal cells on maturation index, and decreased superficial cells on wet mount or maturation index

Menopause and pH

Vaginal pH (lateral outer third of the vagina) is useful, effective, and inexpensive for screening for menopause

- The normal vaginal wall pH of a reproductive-aged woman is 3.8 to 4.5
- pH > 5.0 is consistent with menopause
  - pH in the 5.0 to 6.5 range suggests either bacterial pathogens or decreased serum estradiol
  - In the absence of bacterial pathogens, a pH of 6.0 – 7.5 is strongly suggestive of menopause
**Vaginal Maturation Index**

Postmenopausal vaginal epithelium:

Superficial cells **decreased**

Parabasal cells **increased**

**Premenopause ➔ Postmenopause**

<table>
<thead>
<tr>
<th>Superficial cells</th>
<th>Intermediate cells</th>
<th>Parabasal cells</th>
</tr>
</thead>
<tbody>
<tr>
<td>15%</td>
<td>80%</td>
<td>1%</td>
</tr>
<tr>
<td>5%</td>
<td>60%</td>
<td>39%</td>
</tr>
</tbody>
</table>

Freedman M. Menopause 2008;17:9-13

**Vagina: Mature vs. Atrophic**

Folds or rugae

Erectile tissue

Muscular coat

Inner mucous lining contains large amount glycogen

Premenopausal Postmenopausal

Loss of folds

Loss of inner mucous lining and glandular function

Samsioe G. A profile of the Menopause 1995; 49 (Fig. 6.4)

**Vaginal Histology**

**Premenopause**

Epithelium well-estrogenized, multilayered 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

**Overview of GSM**

- Women have an increase in life expectancy. By 2020, there will be more than 50 million women in the U.S older than 51 years[^1].
- GSM symptoms will affect at least 50% of postmenopausal women at some point in their lives.
  - Prevalence increases with menopausal stage:
    - 4% during perimenopausal transition and 47% 3 years post FMP.[^2]
  - GSM: chronic, progressive, and symptoms do not improve without treatment.
- Many women remain unaware that vulvar and vaginal changes can be a direct result of the menopausal transition.
- Communication challenges/barriers exist for both HCPs and patients.
- Significant under-diagnosis, under-treatment or delays in seeking treatment.

[^1]: NAMS, Menopause Practice: A Clinician’s Guide. 5th edition. 2014
[^3]: Sturdee DW, Panay N. Climacteric 2010;13:509-22

[^4]: Freedman M. Menopause 2008;17:9-13
**Real Women's Views of Treatment Options for Menopausal Vaginal Changes (REVIVE survey)**

- Largest US survey: 3,046 postmenopausal women (45-75yrs) with VVA symptoms - dryness, dyspareunia, irritation
- 44% never discussed VVA symptoms with an HCP
  - Only 13% stated an HCP initiated the VVA conversation
  - 40% expected the HCP to initiate the conversation
- 24% of women attributed VVA symptoms due to menopause. If aware “natural part of aging”
- 19% of HCPs addressed their sexual lives
- VVA affected sex, sleep, enjoyment of life and temperament


**Vaginal Health: Insights, Views & Attitudes (VIVA)**

Online international questionnaire
3520 postmenopausal women, aged 55-65 years

45% reported vaginal discomfort: (only 4% knew this was VVA)
- 83% vaginal dryness & 42% pain during intercourse

75% of women felt that vaginal atrophy would have negative impact on life:

When asked how do they think vaginal discomfort affects women’s lives in general:
- 65% negative consequences on sex life
- 49% negative consequences on marriage/relationship
- 36% lowers quality of life
- 31% makes them feel old
- 26% negative impact on self-esteem
- 13% negative impact on social life

**Women’s Voices in the Menopause**

International computer-assisted web interviews on vaginal atrophy
4246 postmenopausal women, aged 55-65 years
5 countries (US, Canada, Finland, Sweden, UK)

Of women who had been prescribed treatment for menopause-related vaginal discomfort:
- 67% reported positive effects:
  - 25% improvements in everyday life
  - 27% sex life returning to normal
  - 26% better quality of life

Nappi RE, Kokot-Kierepa M. Climacteric 2012;15(1) 19-23

**Vulvovaginal Atrophy Strongly Associated with Female Sexual Dysfunction**

Menopause Epidemiology Study –
cross-sectional, population-based study
1480 sexually active postmenopausal US women aged 40-65 years

Prevalence of VVA: 57%
Women with FSD were 3.8 (CI 3.9-4.9) times more likely to have VVA than women without FSD

FSD: female sexual dysfunction


Premenopause Postmenopause
Therapeutic Options

• Nonmedical - Regular Sexual Activity
• Nonprescription therapies
  • OTC lubricants and moisturizers
  • Herbal products
• Prescription therapies
  • Systemic estrogen
  • Local low-dose vaginal estrogen
  • Ospemifene

Vaginal Lubricants and Moisturizers

FDA APPROVED AS “COSMETICS”

• Approval process less rigorous
• Data often limited, few studies
• Lack of scientific trials for determining efficacy, safety and side effects

Lubricants and Moisturizers

• Lubricants are considered for short-term relief of vaginal dryness during sexual activity
  • Short duration of action
  • Must be applied frequently
  • Sexual aid
• Vaginal moisturizers are considered for long-term relief of vaginal dryness
  • Continuous use; several times a week
  • Everyday aid

Herbal Products

• The Herbal ALTeratives for Menopause Study (HALT)
  • Randomized, double blind, placebo 1 year trial
  • 351 women, high retention for all regimens
  • Dietary supplements:
    - Black Cohosh, “other herbs”, soy
  • No beneficial effect on VVA as compared to placebo

**Prescription Therapies**

- FDA Approved
- Investigational and Off Label

**FDA January 2003 guidelines for vulvar and vaginal studies for VVA assessment**

- 3 co-primary endpoints
  - Cytological (maturation index-parabasal and superficial cells)
  - Vaginal pH
  - Severity of patient-assessed MBS

**FDA guidance: Assessment of VVA**

- MBS
  - Patient-assessed symptom at baseline
    - Vaginal dryness
    - Pain with intercourse
    - Itching/irritation
    - Bleeding associated with sexual activity
    - Soreness
  - Rated on a 3 or 4 point scale (none, mild, moderate, severe)
  - One symptom rated as moderate or severe and followed until the end of study

**Estrogen Treatment and VVA**

- Estrogen lowers vaginal pH, increases subepithelial capillary growth, thickens epithelium
- Raises level of vaginal secretions
- VMI increases reflecting higher percentage of superficial cells relative to parabasal cells
- Estrogen therapy alleviates subjective vaginal symptoms
  - Dryness, soreness, irritation, pruritus, and dyspareunia
Low-Dose Vaginal Estrogen Therapy

- Preferred to systemic ET if GSM symptoms are the main complaint
- Cochrane review of 30 efficacy trials, 6,235 women—all local estrogen products tested alleviated symptoms of VVA with similar efficacy (2016)
- Thin atrophic vaginal epithelium absorbs locally applied estrogen faster than after the epithelium has been estrogenized—important to use as studied
- Progestogen is generally not indicated, but only 1 year safety data
- Elimination of first-pass effect by hepatic enzymes may account for reduced risks of adverse events including thrombosis (local and lower doses)
- Recent ACOG committee opinion endorsed for use in breast cancer survivors
  - Use if unresponsive to non-hormonal remedies

Systemic Estrogen Therapy

- Menopausal symptoms
- Prevent Bone loss
- VVA
  - 10%-15% of women on systemic HT for symptoms may also need local low-dose estrogen therapy
  - Approved lower systemic doses may lack efficacy
- Risks/benefits—see MenoPro App

Low-dose vaginal estrogen except for Femring®

Table 2: NAMS Position Statement. Menopause 2013;20(9):888-902

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### Onset of Action of Vaginal Estrogens

- Improvements in VMI reported as early as 2 to 4 weeks after initiation of vaginal CEE cream or estradiol vaginal tablets
- Vaginal pH falls to lowest levels by 3rd week of vaginal estrogen treatment (number of superficial cells in the vagina has already increased by that time)
- Superficial cells continue to increase during 12-weeks of therapy

CEE, conjugated equine estrogen.

### Ospemifene

Ospemifene is the only SERM approved for the treatment of moderate to severe dyspareunia a symptom of vulvovaginal atrophy due to menopause (February 2013)

- Daily 60mg oral tablet
- Two 12-week efficacy clinical trials that met all co-primary endpoints
- A 52-week efficacy and safety extension study showed sustained improvements and no VTE, endometrial hyperplasia or carcinoma
- VMS were the most common AE 7.2% vs 2% in placebo
- Preclinical data reveal antiestrogen effects on breast tissue and agonistic effects on bone
- Current ongoing Phase 3 trial with primary endpoint of vaginal dryness

Bachmann GA, Komi JO. Menopause 2010;17:480-486
Portman DJ, Bachman GA, Simon JA. Menopause 2013;20:623-630

### Investigational and Off-Label Therapies

- TX-004HR estradiol vaginal softgel capsule — Therapeutics MD
- Generic estradiol vaginal tablet, 10 mcg—Amneal
- Intravaginal DHEA — EndoCeutics
- Lasofoxifene oral systemic — Sermonix
- Lasofoxifene local vaginal — Azure
- Testosterone Vaginal Cream (U.S. pilot studies – breast cancer patients) often used compounded in US
- Estriol Vaginal Gel/Pessaries — (Europe)
- Vaginal Oxytocin (vagitocin) — (Europe)
- Fractional CO2 Laser Treatments

### Day-to Day Impact of Vaginal Aging Questionnaire (DIVA)

- Multidimensional self-report questionnaire: 23 items in 4 domain scales
  1. activities of daily living
  2. emotional well-being
  3. sexual functioning
  4. self-concept and body image
- Designed to facilitate evaluation of the impact of GSM symptoms on QOL for women of diverse backgrounds
- Valid for researchers and clinicians