GENITOURINARY SYNDROME OF MENOPAUSE:

New Terminology—Old Problem!

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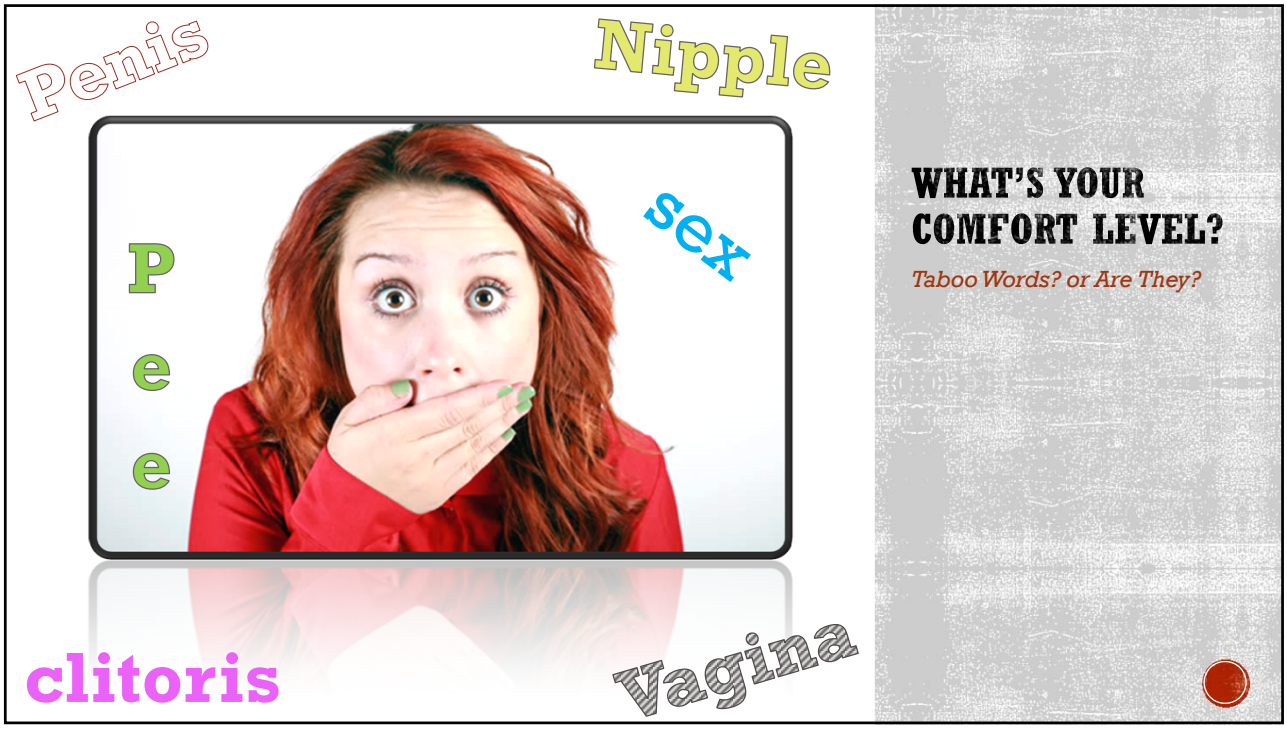
March 3, 2018

- Discuss the reason behind the development of this new terminology
- Review the Old Terminology for which Genitourinary Syndrome of Menopause (GSM) is replacing
- Outline a Primary Care physician (PCP) approach to GSM
- Assist the PCP in recognizing the clinical presentation of GSM
- *Explore* the step wise treatment options for GSM
- Empower the PCP to feel comfortable with initiating treatment for GSM

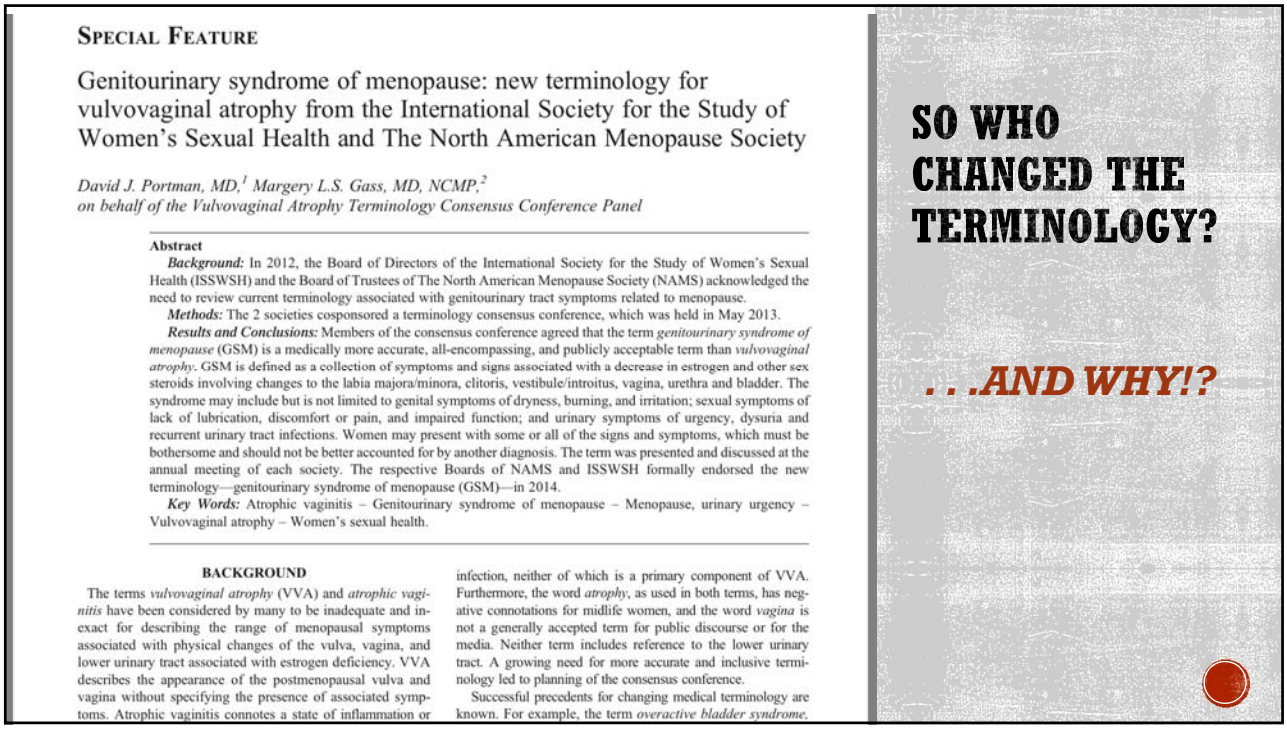


ORIGINAL TERMS:

VULVOVAGINAL ATROPHY (VVA)
ATROPHIC VAGINITIS

- So Why The Need to Change?
  - Vulvovaginal Atrophy is a term which describes a clinical appearance but does not include symptoms.
  - General public uncomfortable with using word "vagina" or "vaginal"

Who Changed It?. . .



SPECIAL FEATURE

Genitourinary syndrome of menopause: new terminology for vulvovaginal atrophy from the International Society for the Study of Women's Sexual Health and The North American Menopause Society

David J. Portman, MD,[1] Margery L.S. Gass, MD, NCMP,[2]
on behalf of the Vulvovaginal Atrophy Terminology Consensus Conference Panel

Abstract

Background: In 2012, the Board of Directors of the International Society for the Study of Women's Sexual Health (ISSWSH) and the Board of Trustees of The North American Menopause Society (NAMS) acknowledged the need to review current terminology associated with genitourinary tract symptoms related to menopause.

Methods: The 2 societies cosponsored a terminology consensus conference, which was held in May 2013.

Results and Conclusions: Members of the consensus conference agreed that the term *genitourinary syndrome of menopause* (GSM) is a medically more accurate, all-encompassing, and publicly acceptable term than *vulvovaginal atrophy*. GSM is defined as a collection of symptoms and signs associated with a decrease in estrogen and other sex steroids involving changes to the labia majora/minora, clitoris, vestibule/introitus, vagina, urethra and bladder. The syndrome may include but is not limited to genital symptoms of dryness, burning, and irritation; sexual symptoms of lack of lubrication, discomfort or pain, and impaired function; and urinary symptoms of urgency, dysuria and recurrent urinary tract infections. Women may present with some or all of the signs and symptoms, which must be bothersome and should not be better accounted for by another diagnosis. The term was presented and discussed at the annual meeting of each society. The respective Boards of NAMS and ISSWSH formally endorsed the new terminology—genitourinary syndrome of menopause (GSM)—in 2014.

Key Words: Atrophic vaginitis – Genitourinary syndrome of menopause – Menopause, urinary urgency – Vulvovaginal atrophy – Women's sexual health.

BACKGROUND

The terms *vulvovaginal atrophy* (VVA) and *atrophic vaginitis* have been considered by many to be inadequate and inexact for describing the range of menopausal symptoms associated with physical changes of the vulva, vagina, and lower urinary tract associated with estrogen deficiency. VVA describes the appearance of the postmenopausal vulva and vagina without specifying the presence of associated symptoms. Atrophic vaginitis connotes a state of inflammation or infection, neither of which is a primary component of VVA. Furthermore, the word *atrophy*, as used in both terms, has negative connotations for midlife women, and the word *vagina* is not a generally accepted term for public discourse or for the media. Neither term includes reference to the lower urinary tract. A growing need for more accurate and inclusive terminology led to planning of the consensus conference.

Successful precedents for changing medical terminology are known. For example, the term *overactive bladder syndrome*,

OVERVIEW OF THE ARTICLE

OBJECTIVES

3-FOLD

1. To review the basic and clinical science related to the genitourinary physical changes and resultant symptoms associated with menopause, & to identify key elements relevant to the terminology
2. To determine whether the term vulvovaginal atrophy should be revised and , if so, to develop a new term that more accurately and appropriately describes the condition for medical care, teaching and research
3. To generate a plan for disseminating recommendations and raising awareness of the new terminology among members of the broader health care community, including specialist, PCPs, researchers, and patients, as well as the public

PROCESS

- 5 person selection committee chose experts from the field of postmenopausal urogenital and sexual healthy fields.
- Chosen experts invited to attend a 2 day interdisciplinary consensus conference
- Experts evaluated the current terminology for symptomatic urogenital changes associated with menopause
- Upon completion of literature review, experts determined that a change in terminology was needed to:
  - Be more acceptable to women, educators, researchers, public, and media
  - Exploration of terms that would be descriptive, comprehensive, and suitable for all

TABLE 1. *Components used to develop new terminology*

Anatomy	Descriptors	Problem	Life Phase
Vagina	Vulvovaginal	Atrophy	Midlife
Vulva	Genital	Alterations	Aging
Labia	Gynecologic	Changes	**Menopause**
Vestibule	Reproductive	Condition	Perimenopause
Urethra	Sexual	Disease	Postmenopause
Bladder	Urogenital	Disorder	
	Genitourinary	Deficiency	
	Urinary	Dysfunction	
	Urologic	**Syndrome**	
		Vaginitis	

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

urogenital sinus tissue, as are the vulvar vestibule and the upper vagina.[29] Androgen receptors are also widely distributed in the vestibule and within its glands, making urogenital tissues responsive not only to estrogen but to androgens as well.[32] Urinary frequency and urgency are common midlife complaints; incontinence occurs in 15% to 35% of women

PROPOSED NEW TERMINOLOGY

OVERVIEW OF ARTICLE

Conclusion of Consensus Conference

- Final two proposed new terms where presented for an open discussion at 2 scientific meetings:
  - Annual Meeting of NAMS – October 2013
  - Annual Meeting of ISSWSH – February 2014

Conclusion of Scientific Meetings

- *New Terminology Approved:*

Genitourinary Syndrome Of Menopause

GENITOURINARY SYNDROME OF MENOPAUSE

(Formerly Known As Vulvovaginal Atrophy & Atrophic Vaginitis)

- "Chronic, progressive vulvovaginal, sexual, and lower urinary tract condition. . ."
- Involves multiple symptoms
- Due to hypoestrogenism secondary to the menopausal state
- > 50% of postmenopausal women affected

TABLE 1
External genital, urological, and sexual manifestations of genitourinary syndrome of menopause

External genital		Urological		Sexual
Signs and symptoms	Complications	Signs and symptoms	Complications	Signs and symptoms
Vaginal/pelvic pain and pressure	Labial atrophy	Frequency	Ischemia of vesical trigone	Loss of libido
Dryness	Vulvar atrophy and lesions	Urgency	Meatal stenosis	Loss of arousal
Irritation/burning	Atrophy of Bartholin glands	Postvoid dribbling	Cystocele and rectocele	Lack of lubrication
Tenderness	Intravaginal retraction of urethra	Nocturia	Urethral prolapse	Dyspareunia
Pruritus vulvae	Alkaline pH (5–7)	Stress/urgency incontinence	Urethral atrophy	Dysorgasmia
Decreased turgor and elasticity	Reduced vaginal and cervical secretions	Dysuria	Retraction of urethral meatus inside vagina associated with vaginal voiding	Pelvic pain
Suprapubic pain	Pelvic organ prolapse	Hematuria	Uterine prolapse	Bleeding or spotting during intercourse
Leukorrhea	Vaginal vault prolapse	Recurrent urinary tract infection	Urethral polyp or caruncle	
Ecchymosis	Vaginal stenosis and shortening			
Erythema	Introital stenosis			
Thinning/graying pubic hair				
Thinning/pallor of vaginal epithelium				
Pale vaginal mucous membrane				
Fusion of labia minora				
Labial shrinking				
Leukoplakic patches on vaginal mucosa				
Presence of petechiae				
Fewer vaginal rugae				
Increased vaginal friability				

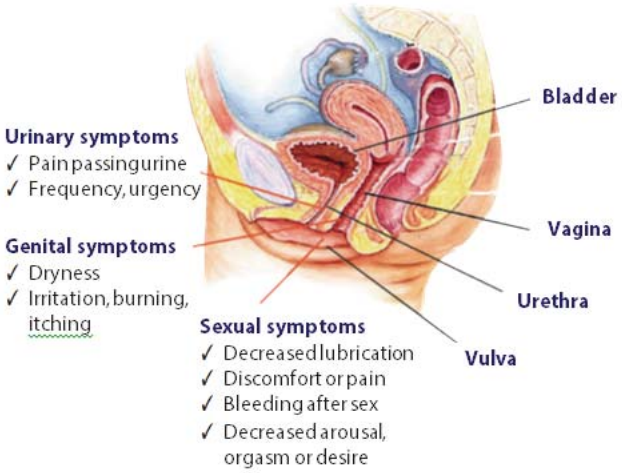
Gandhi. Genitourinary syndrome of menopause. Am J Obstet Gynecol 2016.

CLINICAL MANIFESTATIONS OF GSM

External Genitalia

Urological

Sexual



PATHOPHYSIOLOGY

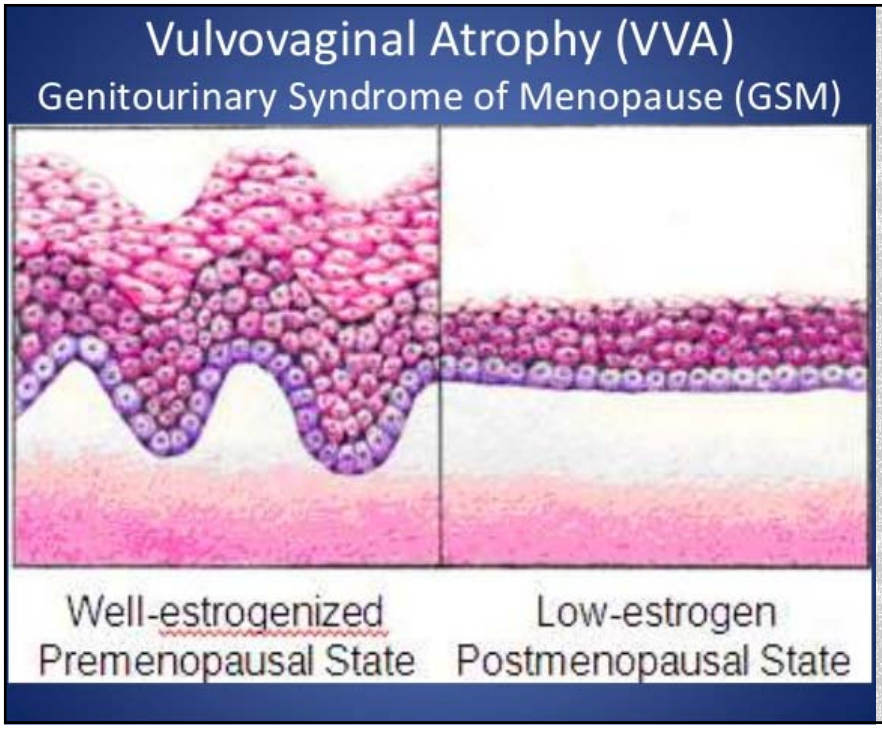
Embryonic Development:

Urogenital sinus

Mullerian duct = uterus and upper 4/5 of vagina once fused

Sinovaginal node (Muller tubercle)

Vaginal vestibule, and lower 1/5 of the vagina, urinary bladder, trigone, and urethra formed by all the above.



CHANGES IN VAGINAL TISSUE

Due to hypoestrogenic state

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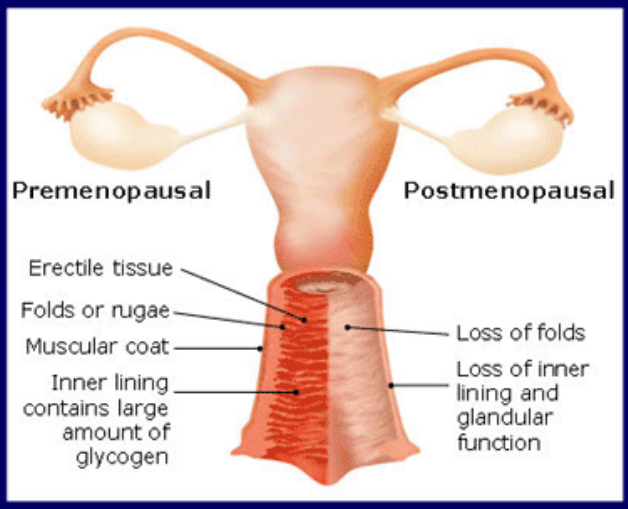
Postmenopausal Changes in the Vaginal Epithelium



Samsioe G. In: *A Profile of the Menopause*. Kent, UK: Wells Medical Limited; 1995:49 (Fig. 6.4).

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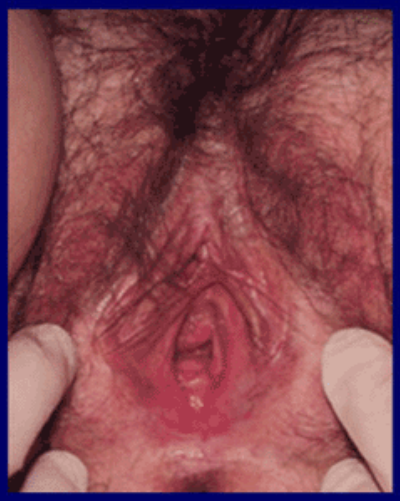
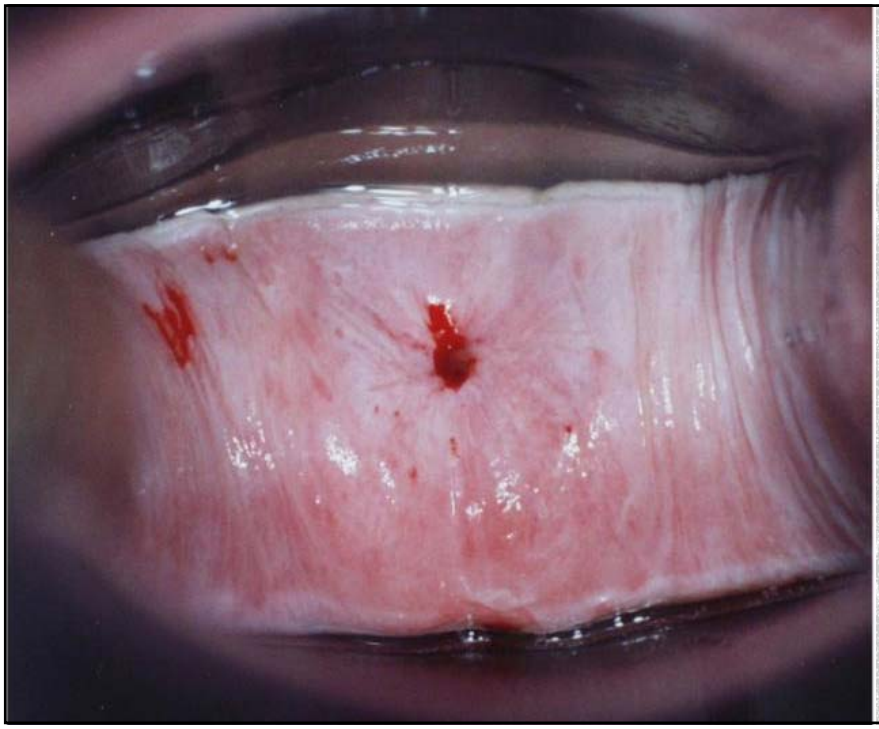
Atrophy: The Clinical Picture



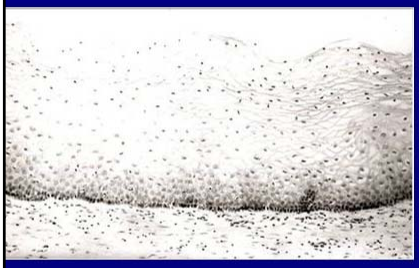
- 2 years since natural menopause
- No estrogen therapy
  - Loss of labial and vulvar fullness
  - Pallor of urethral and vaginal epithelium
  - Minimal vaginal moisture
  - Loss of urethral meatal turgor

Bachmann GA, Nevadunsky NS. Available at: http://www.aafp.org/afp/20000515/3090.html Accessed May 2004 & October 2006.



Vaginal histology

H & E, magnification × 10

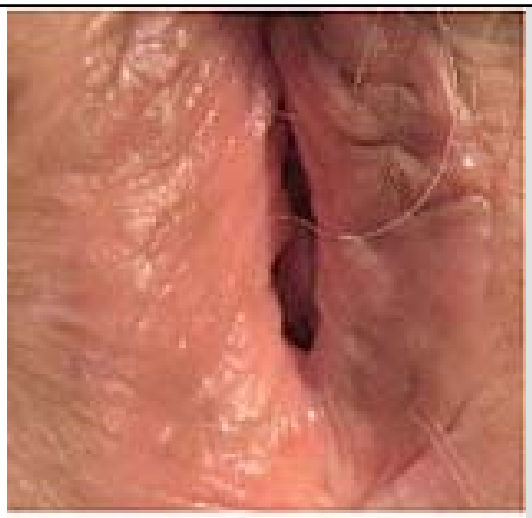


Premenopause

Well-estrogenized epithelium, multi-layered with good blood supply; superficial cells rich in glycogen

Postmenopause

Estrogen-deficiency atrophy with marked thinning of the epithelium, reduced blood supply and loss of glycogen



Severe vulvovaginal atrophy. Note loss of pubic hair and complete fusion of labia (labial agglutination). From: Goldstein I. Current management strategies of the postmenopausal patient with sexual health problems. *J Sex Med*. 2007;4 suppl 3:235-253.

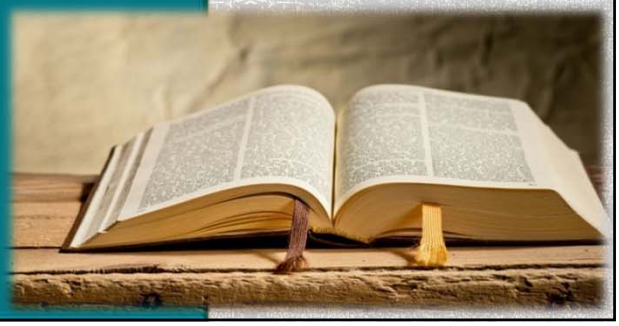
FUSION OF LABIA MAJORA AND MINORA

THE PRIMARY CARE PHYSICIAN'S APPROACH TO GSM

"You have not because you ask not." James 4:2

#SayQuotable

"YOU GOT TO ASK!"



"YOU GOT TO LOOK!"

- Inspect the external genitalia
  - Mons pubis
  - Clitoris
  - Labia majora & minora
  - Urethra meatus
  - Vestibule
  - Introitus
- Inspect the internal genitalia
  - Vaginal walls
  - Cervix

"YOU GOT TO TALK!"

- Discuss your findings:*
  - Patient focused
  - Care-giver focused
  - Patient & Care-giver focused
- Explain what your findings mean:*
  - Clinically (Diagnosis/Treatmemt0
  - Personally (for the patient)
- **Physician comfort and confidence important*

"YOU GOT TO DO!"

- Take Action
  - Expectant management
  - Conservative treatment
  - Medication administration
- Refer
  - Gynecologist
  - Physical Therapist
  - Oncologist

You Can Do It

STEP WISE APPROACH TO TREATMENT OF GSM

Laser/ Vaginal DHEA* — 5

Ospemifene — 4

Low Dose Vaginal Estrogen — 3

Mechanical Measures
Long Acting Vaginal Moisturizers
Nonhormonal Vaginal Lubricants — 2

Determine Severity of Symptoms — 1

TABLE 1. *Examples of nonhormonal therapeutic options for dyspareunia secondary to VVA*

Lubricants	Moisturizers
Water based	Replens
Astroglide Liquid	Me Again
Astroglide Gel Liquid	Vagisil
Astroglide	Feminease
Just Like Me	K-Y SILK-E
K-Y Jelly	Luvena
Pre-Seed	Silken Secret
Slippery Stuff	
Liquid Silk	
Silicone based	
Astroglide X	
ID Millennium	
K-Y Intrigue	
Pink	
Pjur Eros	
Oil based	
Elégance Women's Lubricants	
Olive oil	

Abbreviation: VVA, vulvovaginal atrophy.

TABLE 2. *Vaginal ET products for postmenopausal use in the United States and Canada*

Composition	Product name	FDA-approved dosage
Vaginal creams		
17β-estradiol	Estrace Vaginal Cream[a]	Initial: 2-4 g/d for 1-2 wk Maintenance: 1 g/1-3 times/wk[c] (0.1 mg active ingredient/g)
Conjugated estrogens	Premarin Vaginal Cream	*For VVA*: 0.5-2 g/d for 21 d then off 7 d[c] *For dyspareunia*: 0.5 g/d for 21 d then off 7 d, or twice/wk[c] (0.625 mg active ingredient/g)
Estrone	Estragyn Vaginal Cream[b]	2-4 g/d (1 mg active ingredient/g) Intended for short-term use; progestogen recommended
Vaginal rings		
17β-estradiol	Estring	Device containing 2 mg releases approximately 7.5 μg/d for 90 d (for VVA)
Estradiol acetate	Femring[a]	Device containing 12.4 mg or 24.8 mg estradiol acetate releases 0.05 mg/d or 0.10 mg/d estradiol for 90 days (both doses release systemic levels for treatment of VVA and vasomotor symptoms)
Vaginal tablet		
Estradiol hemihydrate	Vagifem	Initial: 1 tablet/d for 2 wk Maintenance: 1 tablet twice/wk (tablet containing 10.3 μg of estradiol hemihydrates, equivalent to 10 μg of estradiol; for VVA)

Abbreviations: ET, estrogen therapy; FDA, US Food and Drug Administration; VVA, vulvovaginal atrophy.
Products not marked are available in both the United States and Canada.
[a]Available in the United States but not Canada.
[b]Available in Canada but not the United States.
[c]Some FDA-approved dosages of conjugated estrogen and estradiol creams are greater than those currently used in clinical practice that are proven to be effective. Doses of 0.5-1 g of estrogen vaginal cream, used 1-2 times weekly may be adequate for many women.
From Estrace[116]; Premarin[117]; Estragyn[118]; Estring[119]; Femring[120]; Vagifem[121]; Bachmann G, et al.[122]

VAGINAL ESTROGEN BLACK BOX WARNING

- On all estrogen classed medications, including HT
  - No distinction between route
  - No distinction between dose
- Warning based on WHI trial & other studies specific to systemic ET or EPT
- Study findings not relevant to low dose vaginal estrogen
  - Minimal if any systemic absorption
  - Low PM blood estradiol levels compared to systemic estrogen

VAGINAL ESTROGEN BLACK BOX WARNING

- Observation studies and short term RCTs for low dose vaginal estrogen demonstrate:
  - No evidence of increased VTE risks, breast cancer, stroke, heart disease, or dementia
- Current box warning is inappropriate and based on extrapolated results from systemic MHT
- Health care providers and patients deterred from using, based on findings
- **VAGINAL ESTROGEN BLACK BOX REVISION RECOMMENDED!!!**

Vagifem
estradiol vaginal

Black Box Warnings

Estrogen Alone Tx Risk

Endometrial Cancer: unopposed estrogen use incr. endometrial CA risk in pts w/ intact uterus; adding progestin may decr. risk of endometrial hyperplasia, a possible precursor to endometrial CA; use adequate diagnostic measures such as endometrial sampling to rule out malignancy if undiagnosed persistent or recurrent abnormal genital bleeding; Cardiovascular and Probable Dementia: estrogen should not be used for cardiovascular dz or dementia prevention; incr. risk of stroke and DVT in postmenopausal women 50-79 yo (WHI estrogen-alone substudy regimen = conjugated estrogens 0.625 mg/day x7y); incr. risk of probable dementia in postmenopausal women 65 yo and older (WHIMS estrogen-alone substudy regimen = conjugated estrogens 0.625 mg/day x5y); risk unknown in younger postmenopausal women; other doses of conjugated estrogens or other estrogen dosage forms not studied, but assume similar risk; use lowest effective estrogen dose, shortest duration based on individual tx goals and risks

Estrogen Plus Progestin Tx Risk

Cardiovascular and Probable Dementia: estrogen + progestin tx should not be used for cardiovascular dz or dementia prevention; incr. risk of MI, stroke, and PE/DVT in postmenopausal women 50-79 yo (WHI estrogen/progestin substudy regimen = conjugated estrogens 0.625 mg/day w/ medroxyprogesterone 2.5 mg/day x6y); incr. risk of probable dementia in postmenopausal women 65 yo and older (WHIMS estrogen/progestin substudy regimen = conjugated estrogens 0.625 mg/day w/ medroxyprogesterone 2.5 mg/day x4y); risk unknown in younger postmenopausal women; Breast Cancer: estrogen + progestin tx may incr. risk of invasive breast CA in postmenopausal women (WHI estrogen/progestin substudy regimen = conjugated estrogens 0.625 mg/day w/ medroxyprogesterone 2.5 mg/day x6y); other doses or estrogen/progestin combos not studied, but assume similar risk; use lowest effective estrogen dose, shortest duration based on individual tx goals and risks

from JoAnn V. Pinkerton, MD, NCMP, Executive Director

NAMS
The North American Menopause Society

NAMS Citizen's Petition and FDA Response
June 7, 2018

The North American Menopause Society (NAMS) has received a disappointing response to the citizen's petition submitted by the Working Group on Women's Health and Well-Being in Menopause and NAMS asking FDA to "modify the label for low-dose vaginal estrogen products approved for treating symptoms of vulvovaginal atrophy (VVA)."

Our requests were

1. To remove the black box warning in the Warnings and Precautions section of the labeling but retain the text (in regular font) about the risks identified in the Women's Health Initiative (WHI) trials of oral systemic (higher dose) hormone therapy.
2. To highlight in the Warnings and Precautions section of the labeling as it relates to the use of low-dose vaginal estrogen products for the treatment of VVA symptoms that
   a. Genital bleeding is a concern because bleeding may be a sign of endometrial cancer. Report any bleeding or spotting without delay.
   b. Women with estrogen-sensitive breast cancer should consult with their oncologists before use of the product.

In their denial of our petition, FDA sent a 22-page letter in which they reconfirmed that all estrogen products will have the black box warning ("class labeling") and that "the prescribing information should state that the lowest effective doses of estrogens (with or without progestins) should be prescribed for the shortest duration consistent with the treatment goals and risks for the individual patient."

NAMS continues to believe that the black box warning for low-dose vaginal estrogen, defined as dosed appropriately such that blood levels remain within the normal postmenopause range, unnecessarily frightens women and keeps them from much-needed treatment.[1] The genitourinary syndrome of menopause (GSM) is chronic and progressive and can have many medical consequences including increased urinary tract infections and risk for vaginal infection and may affect relationships, quality of life, daily activities, and enjoyment of sex. The recent report from the WHI observational study by Crandall and associates[2] did not find a significantly increased risk of breast or endometrial neoplasia for women using low-dose vaginal estrogen therapy nor any increased risk of cardiovascular disease, total cancer, or all-cause mortality. This supports our understanding that low-dose vaginal estrogens have primarily local vaginal estrogen effects without significant endometrial or systemic effect because minimal absorption occurs.[3]

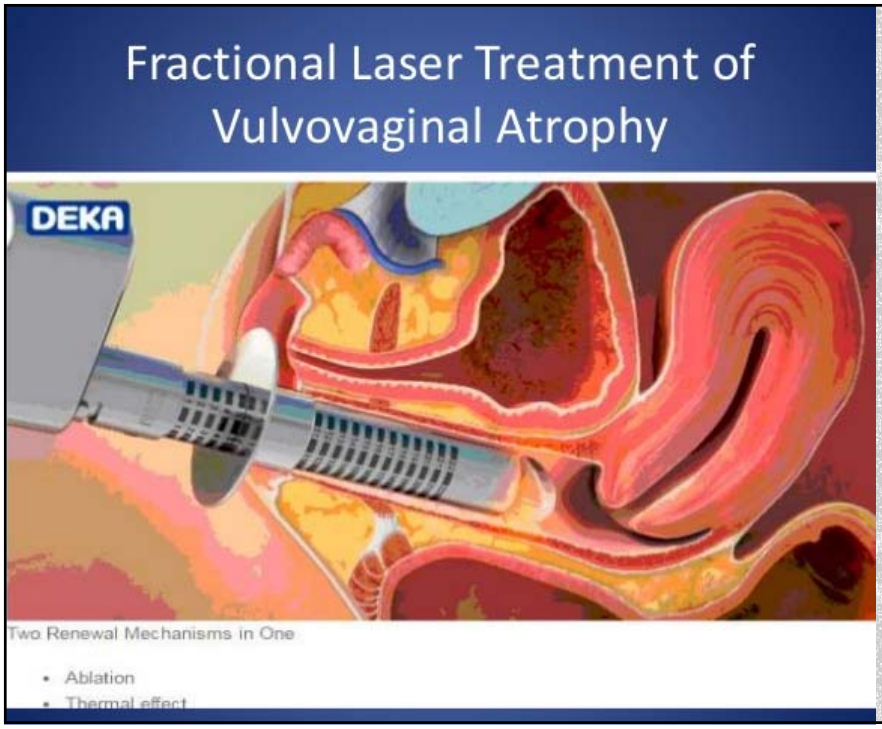
There are low-dose vaginal estrogen options available, including vaginal 10-µg estradiol tablets, estradiol 7.5-mg ring, the new 4- and 10-mg vaginal soft gel inserts, and both vaginal creams (conjugated estrogen and estradiol) that can be dosed at 0.5 g. Postmenopausal bleeding, if it occurs, should be evaluated to rule out endometrial neoplasia. Use in women with prior breast cancer needs to be individualized and involve the woman's oncologist. There is more concern for women on aromatase

BLACK BOX REVISION DENIED!

- A citizen's petition filed in 2016
- 600 signatures – clinicians, patients, medical & professional organization representatives
- "FDA reconfirmed that ALL estrogen products will have black box warning"

SELECTIVE ESTROGEN RECEPTOR MODULATOR

Oral treatment for vulvovaginal atrophy and dyspareunia



Innovative treatment option for GSM

- Discuss the reason behind the development of this new terminology
- Review the Old Terminology for which Genitourinary Syndrome of Menopause (GSM) is replacing
- Outline a Primary Care physician (PCP) approach to GSM
- Assist the PCP in recognizing the clinical presentation of GSM
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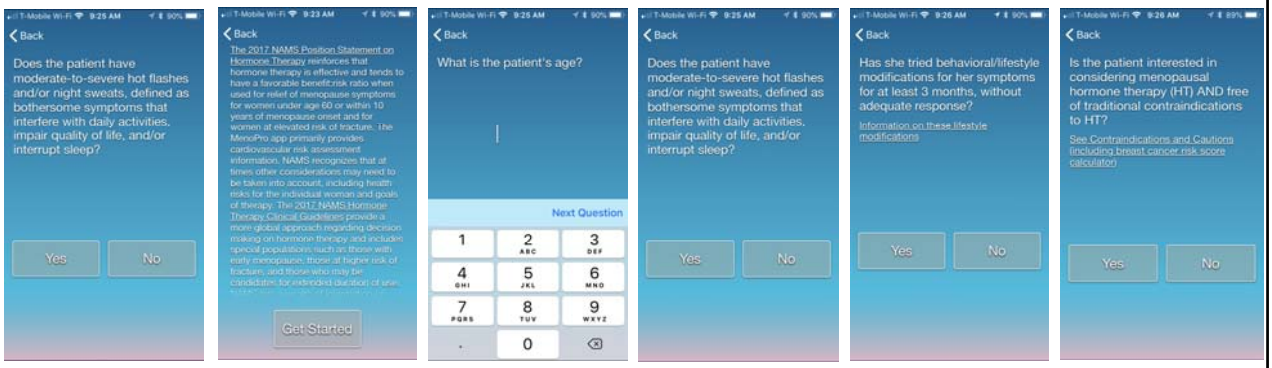
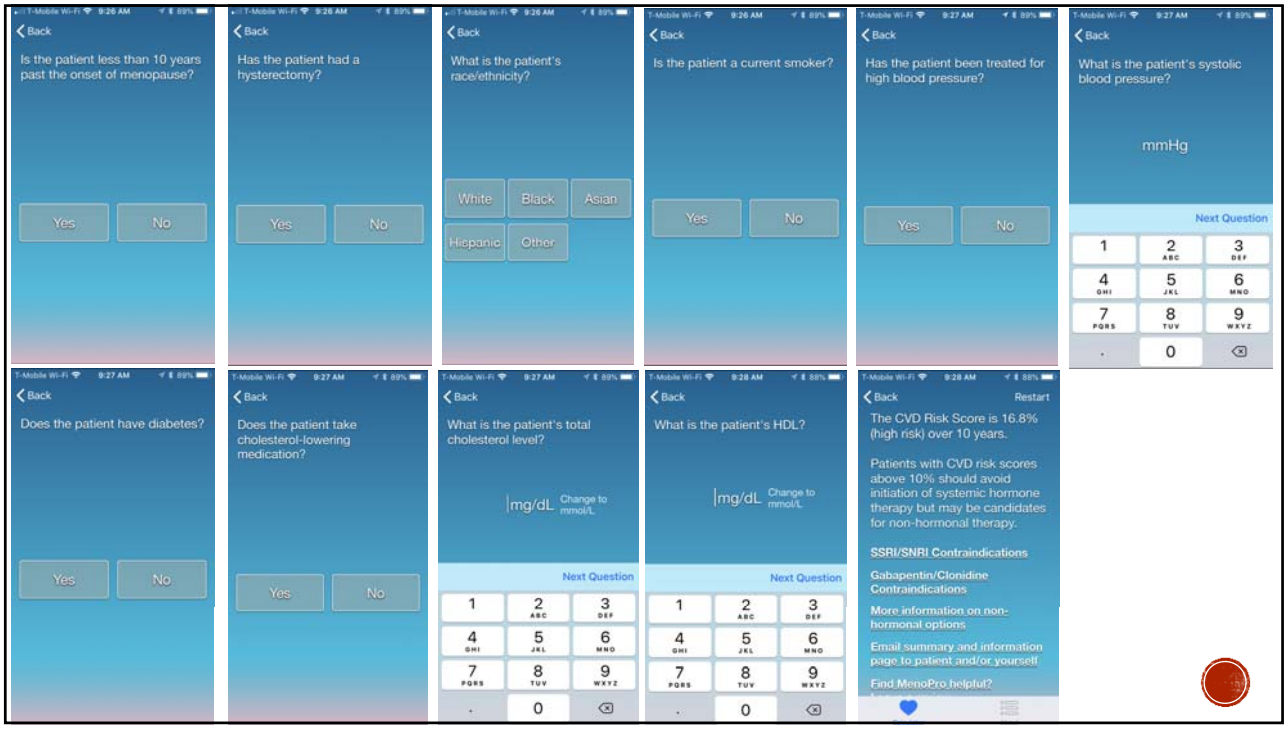
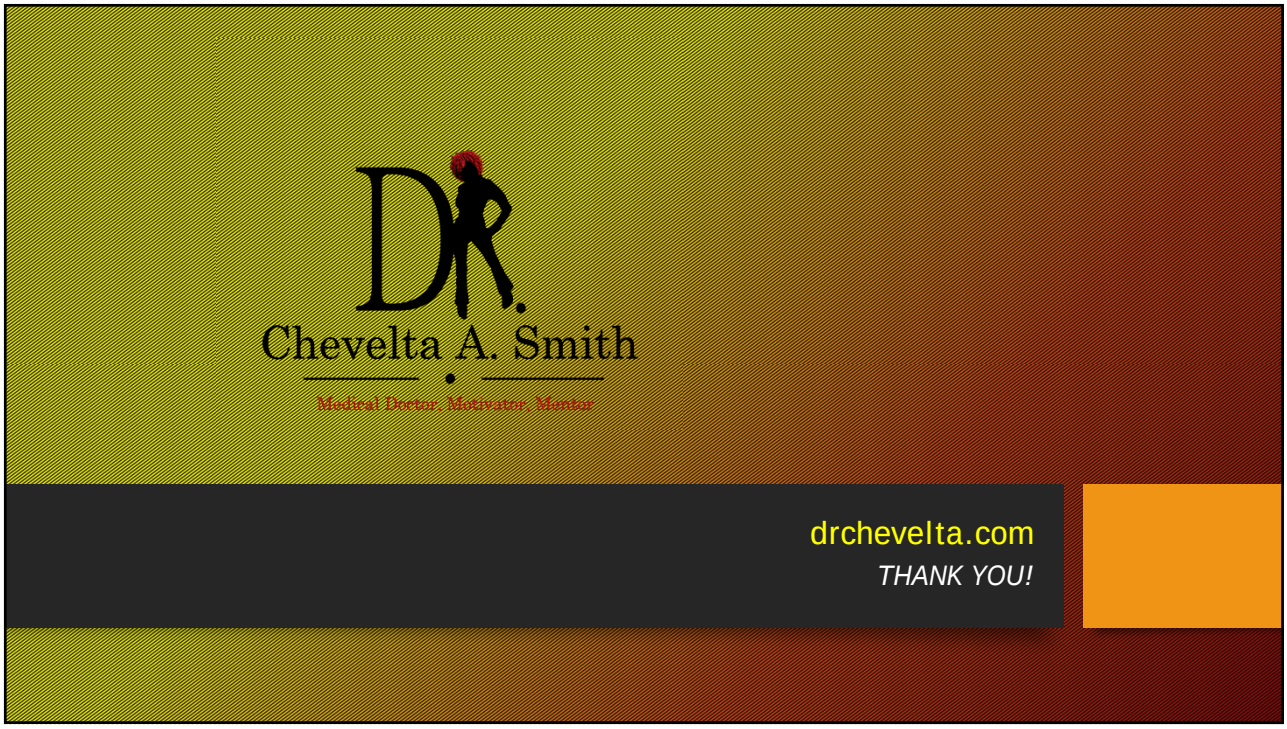
MENOPRO | NAMS APP




Back
Is the patient less than 10 years past the onset of menopause?
Yes
No
Back
Has the patient had a hysterectomy?
Yes
No
Back
What is the patient's race/ethnicity?
White
Black
Asian
Hispanic
Other
Back
Is the patient a current smoker?
Yes
No
Back
Has the patient been treated for high blood pressure?
Yes
No
Back
What is the patient's systolic blood pressure?
mmHg
Next Question
Back
Does the patient have diabetes?
Yes
No
Back
Does the patient take cholesterol-lowering medication?
Yes
No
Back
What is the patient's total cholesterol level?
mg/dL
Change to mmol/L
Next Question
Back
What is the patient's HDL?
mg/dL
Change to mmol/L
Next Question
Back
Restart
The CVD Risk Score is 16.8% (high risk) over 10 years.
Patients with CVD risk scores above 10% should avoid initiation of systemic hormone therapy but may be candidates for non-hormonal therapy.
SSRI/SNRI Contraindications
Gabapentin/Clonidine Contraindications
More information on non-hormonal options
Email summary and information page to patient and/or yourself
Find MenoPro helpful?


Chevelta A. Smith
Medical Doctor. Motivator. Mentor
drchevelta.com
THANK YOU!