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Genitourinary Syndrome of Menopause

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Changing the narrative

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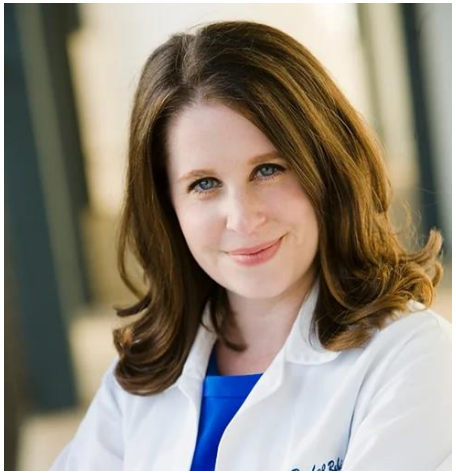

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Disclosures

- Sprout, Materna Medical (RR)
- No applicable disclosures (MK, UL)

Acknowledgements

- American Urological Association
- You

Objectives

- Review the epidemiology, pathophysiology, evaluation, and treatment of GSM
- Engage in case-based scenarios to illustrate and integrate knowledge regarding GSM performed in a role play format to longitudinally follow a patient journey and address real world questions
- Empower providers to provide a patient-centered evidence-based experience for counseling and treatment of GSM

Objectives

- Remove barriers to treatment for our patients!

Why are we here?

- Confusing landscape of historical terminology
  - Vaginal atrophy
  - Atrophic vaginitis
  - Urogenital atrophy
  - Vulvovaginal atrophy
- To advocate for our patients and improve their quality of life

Clarity

- Genitourinary Syndrome of Menopause
  - Consensus panel NAMS, ISSWSH
  - Improves medical accuracy, public acceptance
  - Decreases social stigma

Portman DJ et al. 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. *Climacteric*. 2014;17(5):557-63.

GSM

- Collection of broad array of signs and symptoms
  - Dryness, burning, irritation, dyspareunia, pain, impaired function, urgency, dysuria, recurrent urinary tract infections
- Involves labia, clitoris, vestibule, vagina, urethra, bladder
- Associated with imbalances in estrogen, sex steroids

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Table 3 Genitourinary syndrome of menopause (GSM): symptoms and signs

Symptoms	Signs
Genital dryness	Decreased moisture
Decreased lubrication with sexual activity	Decreased elasticity
Discomfort or pain with sexual activity	Labia minora resorption
Post-coital bleeding	Pallor/erythema
Decreased arousal, orgasm, desire	Loss of vaginal rugae
Irritation/burning/itching of vulvar or vagina	Tissue fragility/fissures/petechiae
Dysuria	Urethral eversion or prolapse
Urinary frequency/urgency	Loss of hymenal remnants
	Prominence of urethral meatus
	Introital retraction
	Recurrent urinary tract infections

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

Portman et al, The Journal of Sexual Medicine 11.12 (2014): 2865-2872.

GSM

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Demographics

- Prevalence in post-menopausal women from 13% - 87 %
  - Inaccurate measurements
  - Underreported
  - Low levels of spontaneous symptom reporting
  - Vasomotor symptoms abate, GSM tends to increase with age

Mili N PS, et al. Genitourinary syndrome of menopause: a systematic review on prevalence and treatment. Menopause. 2021;28(6):706-16.

Demographics

- Also consider peri-menopausal women
- Other patient populations
  - Women on systemic estrogen
  - Young women on OCP
  - Breastfeeding
  - Hypothalamic amenorrhea from disorders or eating, excessive exercise
  - GnRH for endometriosis, fibroids
  - Surgical oophorectomy
  - Cancer treatments – pelvic surgeries, radiation, chemotherapy, endocrine, aromatase inhibitors

Quality of life impact

- Reduced global quality of life
- Sexual function
- Interpersonal relationships

Moral E DJ, et al. The impact of genitourinary syndrome of menopause on well-being, functioning, and quality of life in postmenopausal women. Menopause. 2018.

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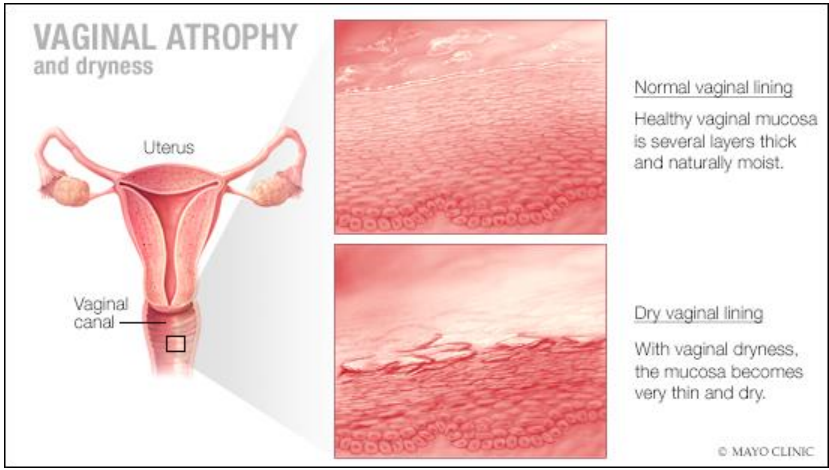
Diagnosis of GSM

Una J. Lee, MD

Vulvo-vaginal atrophy

- Common, underreported condition
- Thinning, drying, and inflammation of the vaginal and vulvar surfaces due to decreased estrogenization
- Can cause daily symptoms, dyspareunia, urinary symptoms, and vulnerability to UTIs

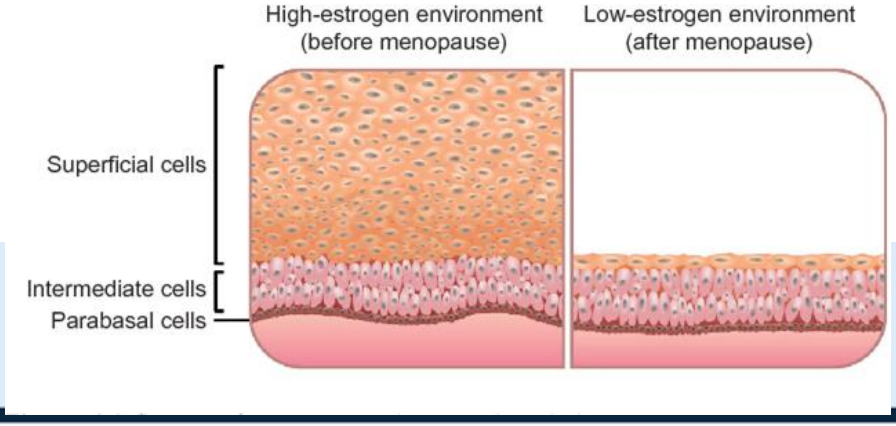


Terminology

- Vaginal atrophy
- Atrophic vaginitis
- Urogenital atrophy
- Post menopausal atrophic vaginitis (ICD-10)
- Vulvovaginal atrophy (VVA)
- Genitourinary syndrome of menopause (GSM), established 2014

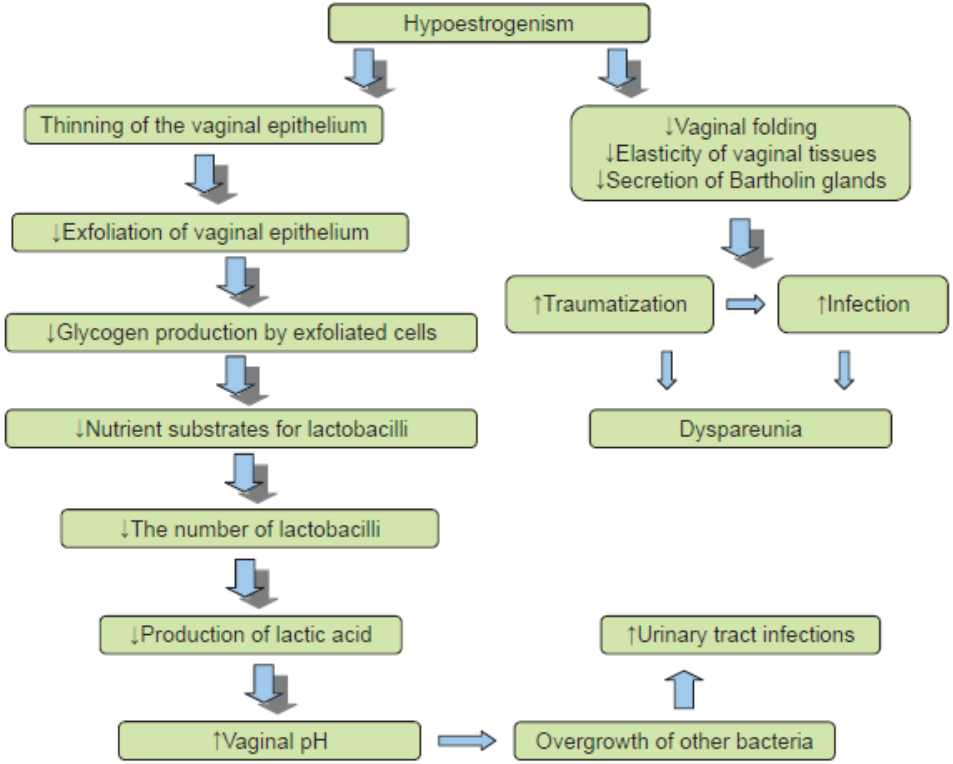
Pathogenesis

- The vagina is composed of – stratified squamous epithelium, middle muscular layer (vaginalis muscularis), and adventitia
- Estrogen is a dominant regulator of vaginal physiology
- Estrogen-receptor is present in the vaginal tissues of premenopausal and postmenopausal women



Cascade effects

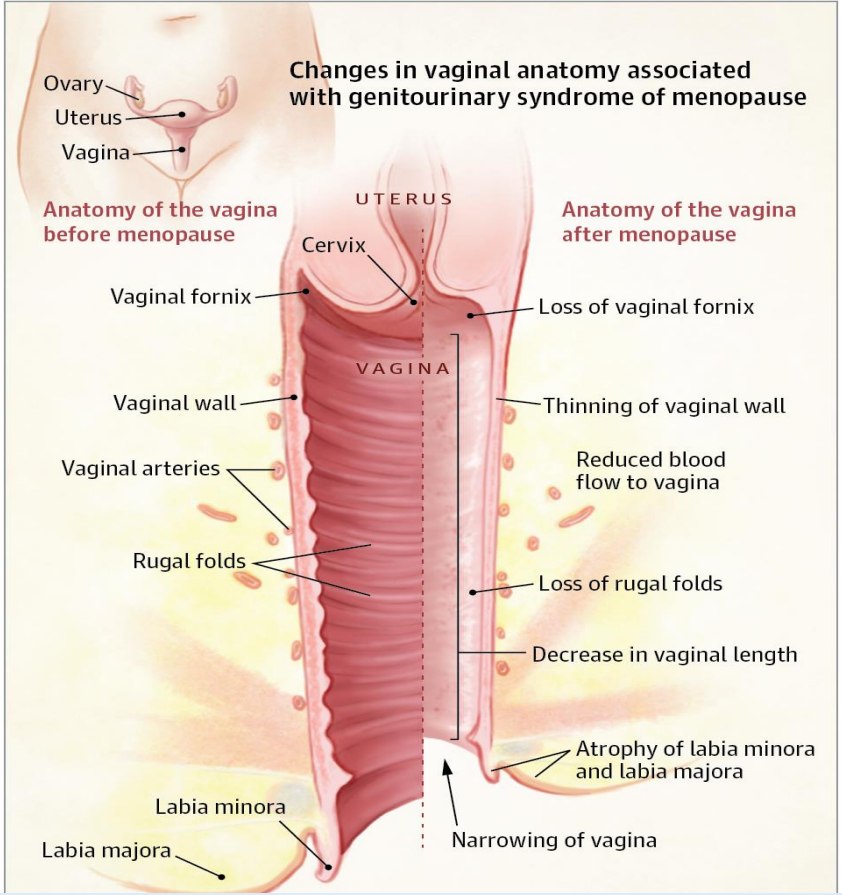
- Importance of microbiota in vaginal health cannot be underestimated
- The dominant constituent is lactobacillus
- Production of lactic acid, as a result of the vital activity of these bacteria, ensures the maintenance of the optimum low pH of the vaginal fluid
- Thus protecting from infections of the urogenital tract



I Naumova. *Int J Women's Health*, 2018

Changes in anatomy

- Loss of vaginal fornix
- Thinning of vaginal wall
- Reduced blood flow to vagina
- Loss of rugal folds
- Decrease in vaginal length
- Atrophy of labia minora and labia majora
- Narrowing of vagina



Prevalence/Epidemiology

- Occurs in majority of women, not all are symptomatic
- Most often in peri- and post-menopausal women
- 20-40% of mid-life and older women (range: 27-60%)
- VVA can be progressive and less likely to resolve without intervention

Other patient populations with GSM

- Women on systemic estrogen
- Breastfeeding women (due to high prolactin causing negative feedback on estrogen)
- Young women on OCPs
- Hypothalamic amenorrhea caused by excessive exercise, disordered eating
- Women on GnRH agonists for endometriosis or fibroids
- Women after surgical oophorectomy
- Women undergoing cancer treatments (surgery, pelvic radiation, chemotherapy, endocrine therapy)
    - Aromatase inhibitors are clearly associated with VVA due to the profound estrogen deficient state

Signs and symptoms of VVA/GSM

- Vaginal dryness (55%)
- Pain during intercourse/dyspareunia (44%)
- Vaginal irritation/discomfort (37%).
- Itching, pain during exercise, tenderness, and bleeding related to intercourse
- Urinary tract symptoms: urgency, dysuria, **recurrent urinary tract infections**, urge incontinence, stress incontinence

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

Normal vaginal pH ranges **between 3.8 and 5.0**, which is moderately acidic. A lower pH value (more acidic) in the vagina than the blood or interstitial fluids can protect vaginal mucosa from pathogenic organisms

- Premenopausal pH 4.5-6, 6.5 before ovulation
- Menopausal 6.5-7
- With vaginal estrogen 5.5

Portman et al. *J Sex Med* 2014;11:2865–2872.

Diagnosis

- Clinical history/Signs/Symptoms
- Questionnaires
  - Vaginal health index (VHI)
  - Day-to-Day Impact of Vaginal Aging (DIVA)
- Physical examination
  - Visual inspection: pale, fragile epithelium, petechiae, thinning, erythema
- Microscopy
  - Increased vaginal pH (>5.0; normal pH is 3.8-4.5) and fresh wet mount (change in maturation index toward basal cells)

Patient perspective

- Low awareness of women about the vaginal/vulvar symptoms post-menopause
- Unwillingness/embarrassment to discuss the symptoms of an intimate character
- 75% of women with signs/symptoms of VVA do not seek help from specialists

A WEALTH OF KNOWLEDGE AND PASSION: PATIENT PERSPECTIVES ON VAGINAL ESTROGEN AS EXPRESSED ON REDDIT

Sabrina Stair, Shreeya Popat, Una Lee, Virginia Mason Franciscan Health, Seattle, WA

Qualitative analysis
67 unique threads with a total of 1101 responses analyzed.
Themes and illustrative quotes were identified

- Medication usage
- Medication alternatives
- Frustration with the healthcare system
- Validation of shared experiences.

> Now if only they could make the cream applicator less of a medieval torture device with razor edges and un-cleanable crevices, that would be great!

> We're all different and just need to do trial and error until hitting upon the formula that works best. Appreciate your support and guidance!

“Vagina” is not a bad word

Historical and contemporary censorship of the word “vagina”

Virginia Mason Franciscan Health™

Cedars Sinai

Shreeya Popat, MD, Rainey Horwitz, MS, Karyn Eilber, MD, Una Lee, MD

Introduction/Objective

- Word “vagina” first used in 1680
- For over 350 years, the word “vagina” has been avoided in the media, print, and society in general despite being the anatomically accurate medical term for female reproductive canal
- Objective: characterize instances of censorship of word “vagina” to better understand perceptions and behaviors surrounding the word

Methods/Materials

- Internet/database search (PubMed, Academic OneFile, Proquest, Health Business Elite, etc.) for “vagina,” “censor,” and related wildcard terms
- Articles filtered by 3 independent reviewers, reviewed for common themes

Examples of censorship of the word “vagina” across multiple platforms

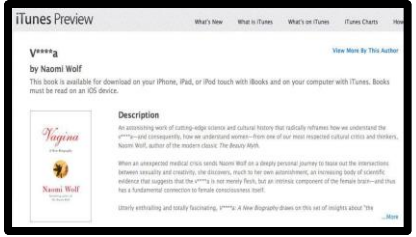
Education

Date	Example
March 2007	New York High school students suspended for saying "vagina" in Vagina Monologues performance
February 2008	Grover Cleveland High school newspaper La Sabre Vagina Day specialty issue confiscated, and associated T-shirts penalized
April 2016	Michigan substitute art teacher said "vagina" in reference to Georgia O’Keefe posters in classroom, was fired for not following the district art curriculum

Miscellaneous

Date	Example
September 2012	Apple censored book titled “Vagina” by Naomi Wolf in iTunes (Figure 1)
July 2014	Apple policy prohibits engraving the word "vagina" or "clit" on devices but allows "penis" and related terms
October 2018	A hygiene product for new moms called "Momwasher" had to change "vagina" to "body" in ads in several cities

Figure 1: Book title “Vagina” censored on iTunes



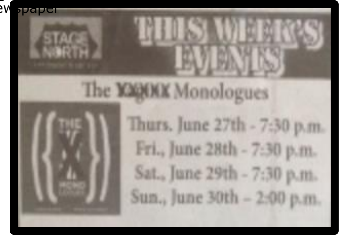
Social Media

Date	Example
November 2016	“Legalize Vagina” movement: video removed by Facebook
March 2019	Facebook blocks ads for vaginal lubricant Pulse
September 2019	Jen Gunter, OBGYN and author of The Vagina Bible, had to omit title and "your vaginal health" in ads for her book on Facebook and Twitter
September 2019	UK Vagina Museum: only 1/7 proposed Facebook ads accepted

Arts

Date	Example
June 2013	Wisconsin newspaper Ashland Daily Press censors "vagina" in ad for Vagina Monologues performance (Figure 2)
June 2013	Australian photographer Philip Werner held an exhibition in Sydney titled 101 Vagina, police demanded that signage be covered/removed

Figure 2: “Vagina Monologues” censored in local newspaper



Politics

Date	Example
June 2012	Michigan state rep. Lisa Brown barred from speaking on the house floor after she made a speech to protest proposed abortion bills in which she said "vagina"

Television & Film

Date	Example
October 2007	Season 2 Grey’s Anatomy episode: producers requested the word "vagina" be omitted. Showrunner Shonda Rhimes coined "vajayjay" for a surgeon to use about her labor/delivery
March 2010	Kotex couldn’t advertise on 3 TV networks until it changed “vagina” to “down there”
December 2012	MTV censored "vagina" when airing Mean Girls
October 2019	Delta airlines removed dialogue and scenes featuring the word "vagina" from the movie Booksmart
January 2020	Family Guy couldn’t say vagina, so they made up “cleeman.” Ironically, several years later, they were barred from using "cleeman."
August 2020	Food Network censors "vagina" on Amy Schumer Learns to Cook

Themes derived from analysis of instances of censorship of the word “vagina”

1. Policies are unclear: Censoring parties respond vaguely, do not explicitly identify language or elements of concern.
2. Policies are highly variable: on same platform, some companies use word “vagina” in ads while others blocked.
3. Differing standards between male and female anatomic terms: “penis” is allowed while “vagina” is not
4. Objections call use of “vagina” overtly sexual, profane. However, there is no biologically accurate alternative.

Conclusions

- The word “vagina” is censored on multiple platforms: print, TV, film, social media, politics, education, etc.
- Patients turn to internet/media as accessible sources of health information
- Censorship of “vagina” forces inaccurate, over-generalized, ambiguous references to female genitalia
- Ongoing, pervasive censorship perpetuates ignorance and shame about women’s pelvic health

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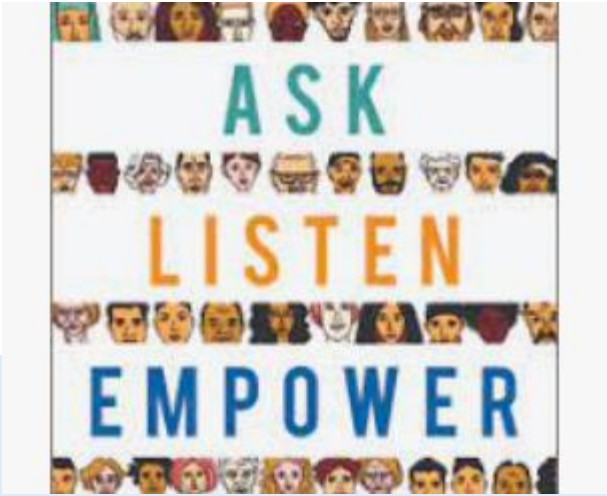
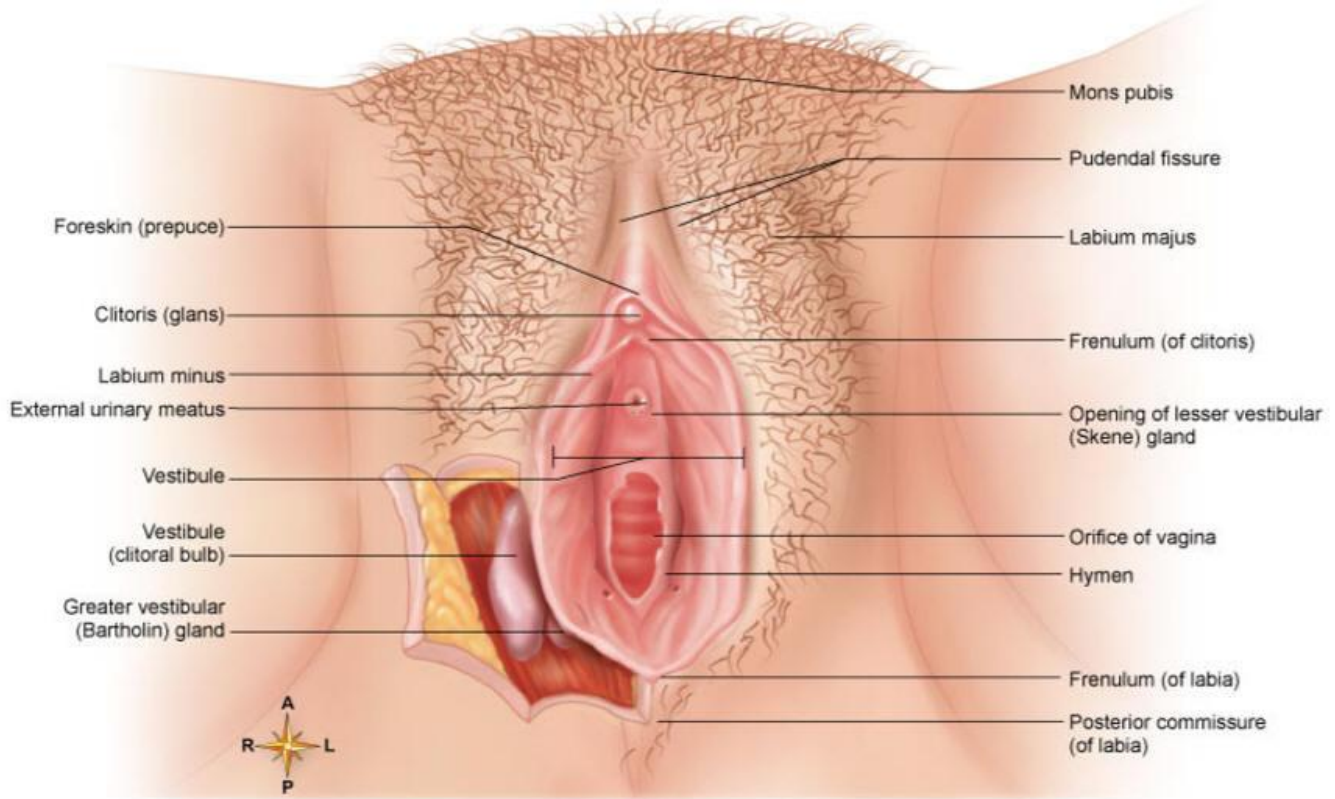
Clinical Evaluation

- Starts with Increased awareness of this condition
- Screening- asking patients about their GU symptoms
- Including GSM on the differential diagnoses
- Physical Exam

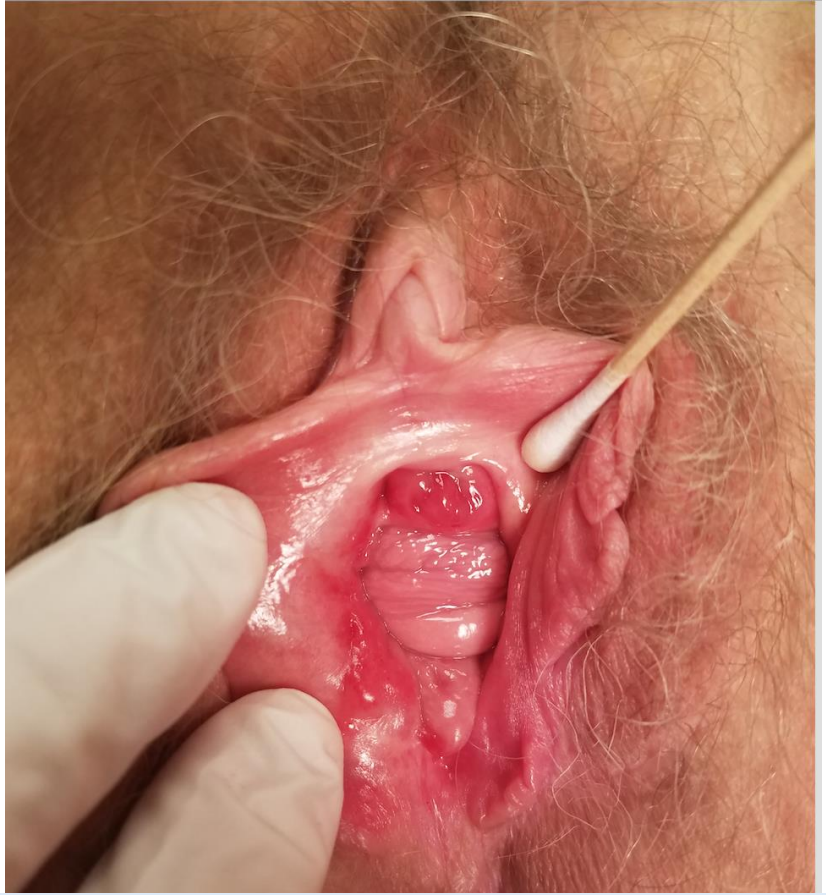


Female GU Anatomical Structures



Pelvic exam

- Gentle pelvic exam with visualization and palpation
- External female genitalia/Vulvar tissues
- Assessment of GU skin
- Urethra and periurethral tissues
- Clitorus and clitoral hood
- Vainal introitus and vaginal canal
- Pelvic floor muscles
- Perineum and anus
- Bimanual exam
- Rectal exam
- Use of a mirror to show and educate patient on their anatomy and findings



Differential Diagnosis of VVA/GSM

- Dermatologic, allergic, inflammatory conditions
  - Contact dermatitis (irritant vs allergic), lichen sclerosus, lichen planus, lichen simplex chronicus
- Infections
  - Genital/STDs, urinary tract infection, skin (vulvovaginal candida)
- Trauma/foreign bodies
  - surgical mesh, permanent sutures
- Malignancy
  - Vulvar, skin, GYN, Pagets
- Pre-neoplastic disorders
  - Vulvar intraepithelial neoplasia (VIN)
- Pain disorders
  - vulvodynia/vestibulodynia, chronic pelvic pain, vaginismus
- Overactive bladder

Contact dermatitis

- **Irritant contact dermatitis** (immediate; peaks then heals)
  - Risk factors: obesity, humidity, incontinence, skin care products/antiseptics/contraceptive products, skin sensitivity
  - Women with VVA have impaired barrier function and less protection from irritants

Contact dermatitis

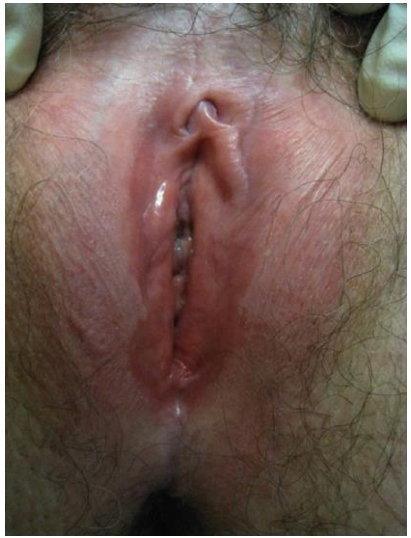
- **Allergic contact dermatitis** (24-48 hr post-exposure; crescendo timing)
  - Ingredients of topical medications and popular remedies played the most important role as sensitizers in the genital area.
  - The most important allergens were active ingredients like local anesthetics, antibiotics, corticosteroids, and herbal extracts

Vulvar Lichen Sclerosus

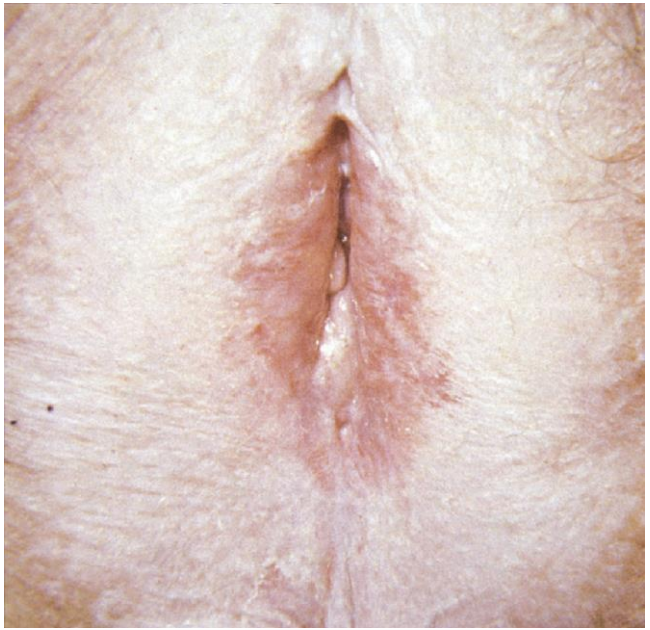
- Chronic inflammatory skin disorder of the vulva
- Intractable burning and **pruritus**, dyspareunia, soreness, dysuria (some women are asymptomatic)
- Benign
  - some develop squamous cell carcinoma (SCC) of the vulva and some women have concomitant SCC when initially diagnosed with LS
- Skin is whitish, thin
  - Can lead to agglutination/stenosis
- Diagnosis: clinical diagnosis +/- punch biopsy
- Treatment: Use of high-potency topical corticosteroids
  - 0.05% clobetasol propionate is the recommended therapy.
  - Minimal amount applied twice daily for one month, followed by once daily at bedtime for 1 month , then 2x/week for 3rd month (30 g supply for 3 months). Maintenance 2x/week PRN

Vulvar Lichen Sclerosus

Thin, whitish vulvar skin



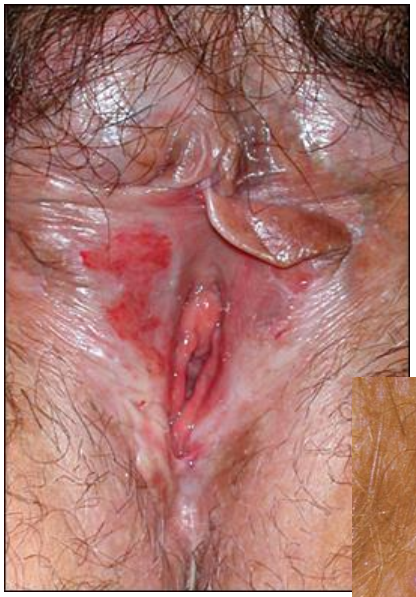
Loss of labia minora

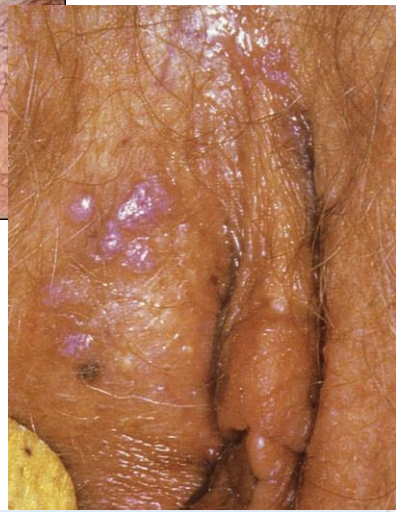


Loss of architecture with the agglutination
The skin has pigment changes and a “parchment paper” crinkled appearance

Vulvar Lichen planus

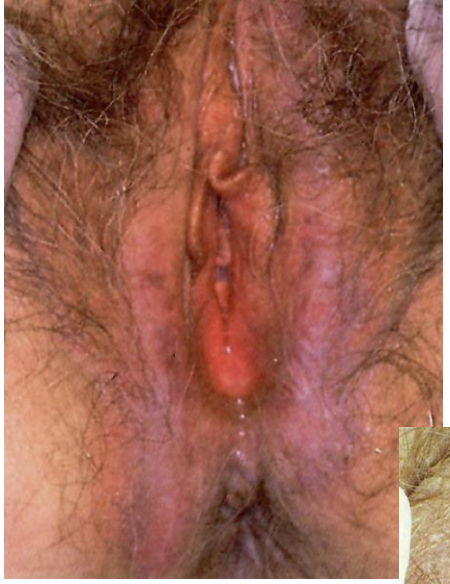
- Inflammatory autoimmune disorder that can affect the vulva and the vagina
- Peak incidence between ages 30 and 60
- There are three clinical variants of lichen planus affecting the vulva: erosive, papulosquamous, and hypertrophic
- Rare compared to Lichen sclerosis
- Diagnosis: vulvar biopsy
- Treatment: high-potency topical corticosteroid (clobetasol propionate 0.05% ointment)

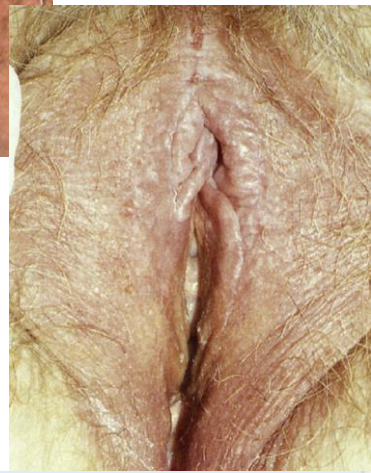




Lichen simplex chronicus

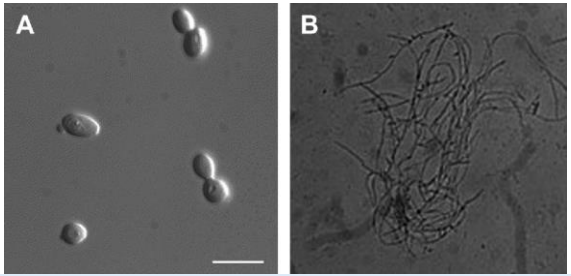
- Chronic eczematous disease characterized by intense and unrelenting itching and scratching
- Skin can progress to a thick leathery appearance
- Treatment is through education and behavioral techniques to prevent scratching and topical corticosteroids and antihistamines





Vulvovaginal Candidiasis

- Caused by *C. albicans* or other *Candida* sp. or yeasts
- Typical symptoms: pruritus, vaginal soreness, dyspareunia, external dysuria, and abnormal vaginal discharge
- Signs: vulvar edema, fissures, excoriations, and thick curdy vaginal discharge
- Diagnosis can be made by clinical signs and symptoms
- Can be aided by
  1. wet prep (saline, 10% KOH) or Gram stain with budding yeasts, hyphae, or pseudohyphae
  2. a culture with positive result for a yeast species.
- Rx with short course topical formulations
  - Alternative: diflucan oral 1 dose
  - -azole drugs more effective than nystatin



Vulvar Intraepithelial Neoplasia (VIN)

- Premalignant high grade squamous lesions of the vulvar skin
- 50% asymptomatic; vs. nonspecific pruritis burning or pain
- Untreated VIN may regress, progress to SCC, or remain dormant
- Appearance varies
  - Visible lesions: flat to elevated
  - Color: white, gray, red, brown, black
- Diagnosis is by visual inspection followed by confirmation by histopathology
- Need excisional biopsy for diagnosis

Perineal care and prevention measures

- Barrier creams
  - Aquaphor
  - Diaper cream with active ingredient Zinc oxide (triple paste, A&D, Desitin)
- Natural remedies: organic cold pressed coconut oil, olive oil
- Clothing/bathing/toileting/sexual activity recommendations for avoiding irritation
- Tobacco cessation (smoking assoc with anti-estrogenic effects; lower proportion of vaginal *Lactobacillus* spp.)
- Pelvic floor muscle training if also has urinary incontinence

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APR 28-MAY 1

Treatment of GSM

Rachel S. Rubin, MD

Education is ESSENTIAL for adherence

GSM treatment does not work if:

It’s too expensive for the patient to pick up

It’s too gooey and the patient doesn’t use it

It sits in the bathroom drawer unopened

It doesn’t get re-filled

The patient reads the boxed label and assumes you are trying to kill her

Most Bothersome Symptom (MBS--FDA)

- **Vaginal dryness**
- **Dyspareunia**
- Vaginal/vulvar irritation
- Vaginal soreness
- Dysuria
- Bleeding associated with sexual activity

FDA Guidance for Industry: Estrogen and Estrogen/Progestin Drug Products to Treat Vasomotor Symptoms and Vulvar and Vaginal Atrophy Symptoms — Recommendations for Clinical Evaluation. U.S. Department of Health and Human Services Food and Drug Administration Center for Drug Evaluation and Research (CDER). January 2003

ISSWSH
International Society for the Study of Women's Sexual Health, Inc.

Goals of GSM/VVA Treatment

- Relieve symptoms
- Reverse anatomic changes
- Improve sexual function and quality of life

North American Menopause Society. *Menopause.* 2007;14:357-369.

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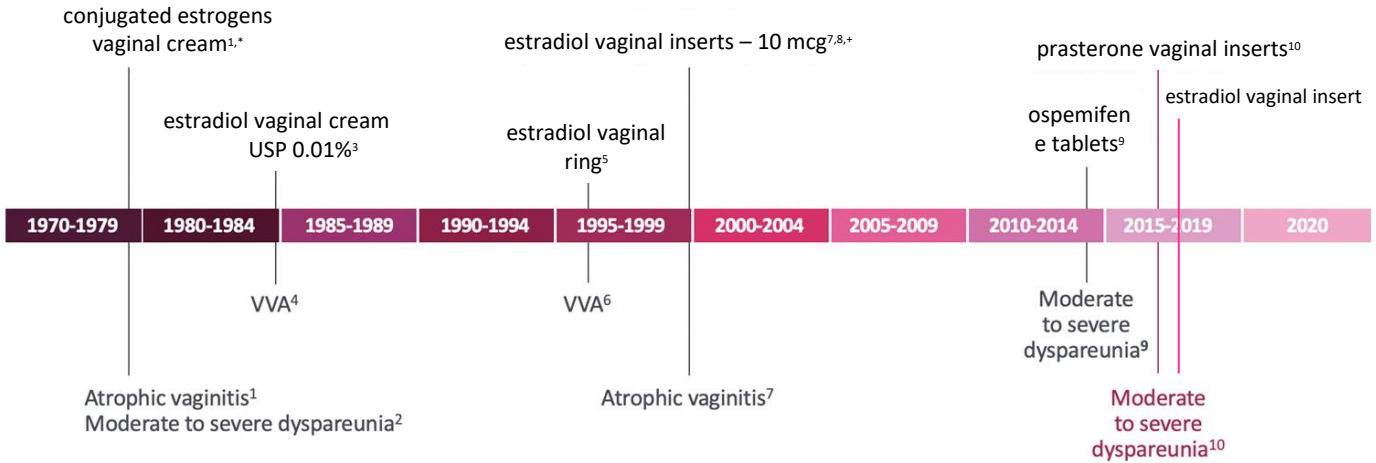
FDA Approved Treatment Options



*Atrophic vaginitis indication approved in 1978; dyspareunia indication approved in 2008.[2]
†25 mcg dosage approved in 1999; 10 mcg dosage approved in 2009.[7,8]
Premarin, Estrace, Estring, Vagifem, and Osphena are registered trademarks of their respective owners.
INTRAROSA is a registered trademark of Endoceutics, Inc.

1. PREMARIN® Vaginal Cream Prescribing Information. Wyeth Pharmaceuticals Inc. 2. FDA. Drugs@FDA: FDA approved drug products: Premarin. 3. FDA. Drugs@FDA: FDA approved drug products: Estrace. 4. ESTRACE® Cream Prescribing Information. Allergan USA, Inc. 5. FDA. Drugs@FDA: FDA approved drug products: Estring. 6. ESTRING® Prescribing Information. Pharmacia & Upjohn Co. 7. VAGIFEM® Prescribing Information. Novo Nordisk A/S. 8. Vagifem 1999 approval letter. 9. OSPHENA® Prescribing Information. Shionogi Inc. 10. INTRAROSA® (prasterone) Prescribing Information. AMAG Pharmaceuticals, Inc; 2018.

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Treatment	Product Name	Dose
Vaginal Cream		
17-beta- estradiol cream	Estrace, generic	1gm daily for 2 weeks then 1gm 2x per week
Conjugated estrogens cream	Premarin	1gm daily for 2 weeks then 1gm 2x per week
Vaginal Inserts		
Estradiol	Vagifem, Yuvafem,	10mcg inserts daily for 2 weeks and then 2x per week
17-beta-estradiol soft gel caps	Imvexxy	4 OR 10 mcg inserts daily for 2 weeks and then 2x per week
DHEA (prasterone)	Intrarosa	6.5mg capsules daily
Vaginal Ring		
17-beta-estradiol ring	Estring	1 ring inserted every 3 months
SERM		
Ospemifene	Osphena	60mg oral tablet daily

Treatment	Product Name	Dose
Vaginal Cream		
17-beta- estradiol cream		laily for 2 weeks then 0.5- er week
Conjugated estrogens c		for 2 weeks then 0.5- k
Vaginal Inserts		
Estradiol		ily for 2 weeks and k
17-beta-estradiol s		rts daily for 2 weeks eek
DHEA (prasterone)		daily
Vaginal Ring		
17-beta-estradiol ring		rted every 3 months
SERM		
Ospemifene	Osphena	60mg oral tablet daily

A DAB OF ESTROGEN CREAM IS NOT ENOUGH!

For _____

Address _____ Date _____

℞

Estradiol 0.01% cream or conjugated estrogen vaginal cream 1 gram nightly in vagina for 2 weeks and then 1 gram 2x per week

Dispense 3 month

Refill: forever

REFILL _____ TIMES

_____, M.D.

Address _____

Dr. R Tips:

- Applicator is re-used. Don't let them throw it away

GoodRx

CostPlus DRUG COMPANY

<$10/month
Cost Plus Drugs
Online Mark
Cuban Pharmacy

For _____

Address _____ Date _____

℞

Estradiol vaginal tablets 10mcg
1 tablet vaginally daily for 2 weeks
then twice per week
Dispense: 3 month supply
Refill: forever

REFILL _____ TIMES _____, M.D.

DEA NO. _____ Address _____

GoodRx

~40-50/month
Cost Plus Drugs
Online Mark
Cuban Pharmacy

Reps will sample

For _____

Address _____ Date _____

Rx

Vaginal DHEA 6.5mg
1 suppository in the vagina nightly
Dispense 3 month
Refill: forever

REFILL _____ TIMES _____, M.D.

Dr. R Tips:

- Use the applicator to decrease discharge
- Only 2 ingredients palm oil and DHEA for your ‘natural folx’
- $85/mo at Costco

For _____

Address _____ Date _____

℞

Estradiol 4 or 10mcg soft gel caps
1 insert vaginally daily for 2 weeks
then twice per week
Dispense: 3 month supply
Refill: forever

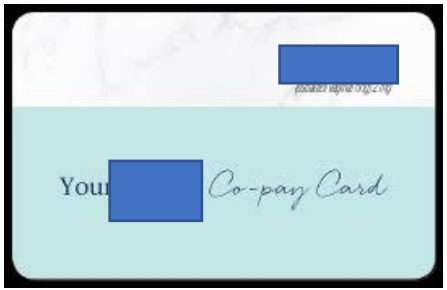
REFILL _____ TIMES _____, M.D.

DEA NO. _____ Address _____

Dr. R Tips:

- 4mcg for very nervous patients
- No applicator! Good for environment

Reps will sample



For _____

Address _____ Date _____

℞

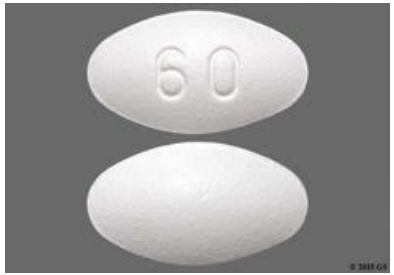
Estradiol 2mg ring
1 ring in vagina for 3 months
Dispense: 1 ring
Refill: forever

REFILL _____ TIMES _____, M.D.

DEA NO. _____ Address _____

Dr. R Tips:

- Great for patients with poor dexterity or dementia
- May fall out if prolapse



Only oral option!

For _____

Address _____ Date _____

℞

Ospemifene 60mg
1 tab po daily
Dispense: 90
Refill: forever

REFILL _____ TIMES _____, M.D.

DEA NO. _____ Address _____

Dr. R Tips:

- Only oral option
- Since oral SERM more possibility of systemic side effects and benefit

Dr. R Tips:

- Nobody tries and fails vaginal hormones. You may need to change delivery system.

- Vaginal hormones are the foundation. Doesn’t matter how pretty the furnishings are if the foundation is weak

- PATIENCE! It takes time to start working. Tissue doesn’t regenerate over night. Encourage them to wait 2 months for maximal benefit

Dr. R Tips:

- How long do I need to take this?
    - EASY! Forever! Til Death Do you part
        - When do you stop brushing your teeth?
        - When do you stop washing/moisturizing your face?
        - When do you stop wearing your seat belt?

Dr. R Tips:

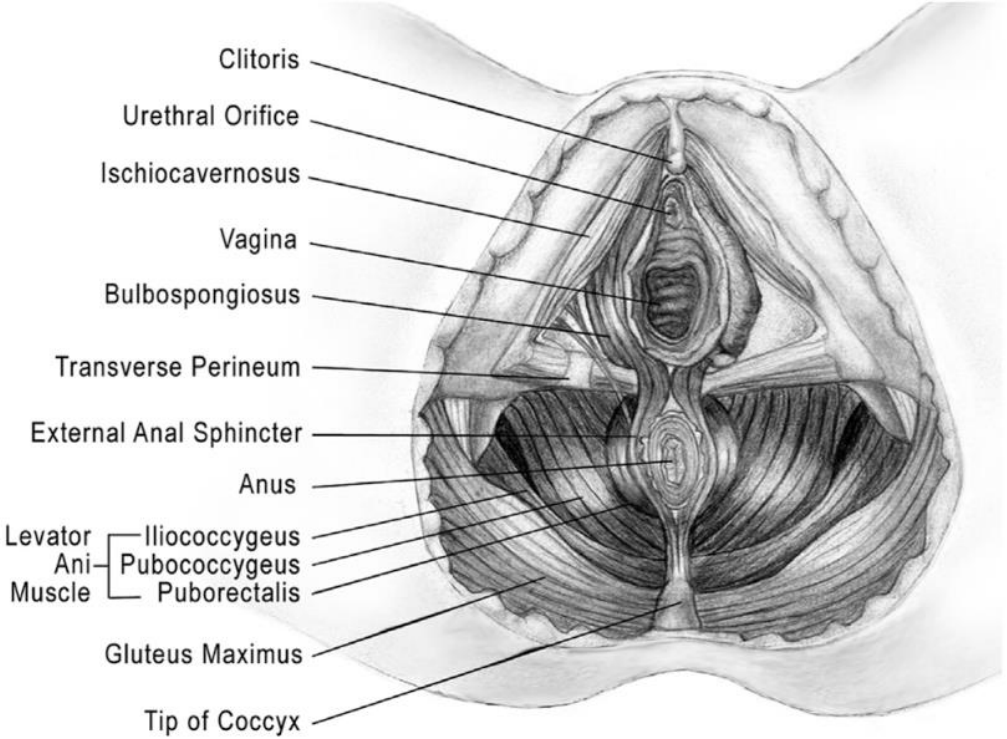
- If your patient is on systemic estrogen therapy PLEASE continue to strongly screen for GSM.

- Often systemic treatment doesn't get enough to the local tissue

- If the vestibule is still painful after GSM therapy thing you can also consider using compounded estradiol 0.01% and testosterone 0.1% in methylcellulose base

Pukall et al. *The Journal of Sexual Medicine.* 2016;13(3):291-304.
Burrows LJ, et al. *The Journal of Sexual Medicine* 2012;9(9):2213–2223.
Goldstein, S., et al. *The Journal of Sexual Medicine* 17.1 (2020): S8-S9.

Don’t forget about the pelvic floor!



Pelvic Floor Dysfunction

1. Pain in the posterior vestibule (5-7 o clock)
2. Get a pelvic floor physical therapist on speed dial
3. Dilator and manual therapy
4. Suppositories: diazepam, baclofen
5. Trigger point injections: anesthetic, steroid, botulinum toxin

But CANCER!!!!

Safety conversation.

Find out what they are most afraid of and drown them with data and reassurance

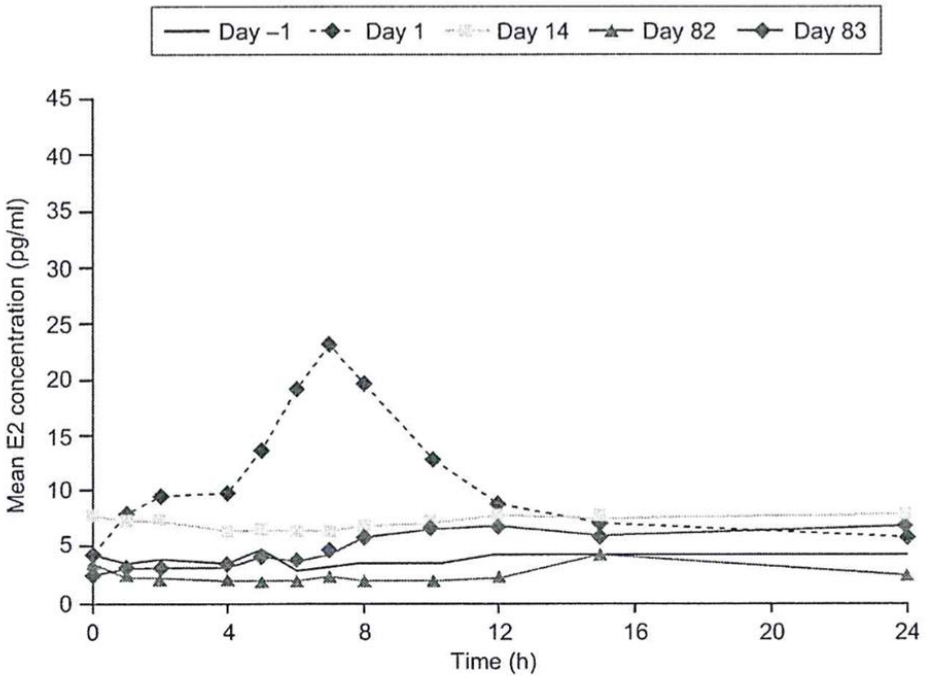


Figure 1 Absorption curve of estradiol (E2) as determined by GC-MS during 24 h after vaginal administration of 10 µg E2 tablet on days −1, 1, 14, 82, and 83 of treatment. Eugster-Hausmann M, *et al.*, *Climacteric* 2010;13:219–27. © 2010 International Menopause Society. Reproduced with permission of Informa Healthcare

Estradiol Preparations and Maximum Annual Delivered Dose

Product name	Route/Type of administration	Typical regimen	Nominal daily delivery rate or administered lowest approved dose (mg/day)	Typical serum level (pg/mL)	Maximum annual delivered dose (mg)[1]
Vaginal estradiol					
Vagifem	Vaginal tablet	1 Tablet daily × 14 then 2 × weekly	10 μg	4.6	1.14
Estring	Vaginal ring	1 Ring vaginally q 3 months	7.5 μg	8.0	2.74
Estrace	Vaginal cream	1 g cream vaginally q week[2]	variable[2]	NA	7.1
FemRing	Vaginal ring	1 Ring vaginally q 3 months	0.05 mg	40.6	18.25
Oral estradiol					
Estrace tablets and generics	Oral tablet	1 Tablet p.o. qd	0.5 mg	55.4	182.5
Transdermal estradiol					
Divigel[3]	Gel	0.25 mg packet qd	0.003	9.8	1.09
Estrogel	Gel	0.75 mg/pump qd	0.035	28.3	12.78
Evamist[3]	Spray	1.53 mg spray qd	0.021	19.6	7.67
Climara[4]	Patch	1 Patch weekly	0.025	22	9.13
Menostar	Patch	1 Patch weekly	0.014	13.7	5.11
Vivelle-Dot[5]	Patch	1 Patch twice weekly	0.0375	34	12.78

Serum estradiol concentrations obtained from respective prescribing information and/or published clinical trials, not comparative clinical studies. Studies may have used different analytical methods to measure serum concentrations. Relative differences in efficacy and safety, if any, may not correlate with the serum estradiol concentrations measured in these studies.

[1]Assumes perfect use (i.e., daily = 365 doses) and rounded to two decimal places.

[2]1 g cream equals 0.1 mg estradiol. Assumes 1 week of 0.2 mg/day; 1 week of 0.1 mg/day; then 0.1 mg weekly.

[3]Unadjusted for baseline. Mean serum estradiol concentration on day 14.

[4]Mean serum estradiol concentration on day 7.

[5]Unadjusted for baseline. Mean serum estradiol concentration over the applied period.

Divigel [prescribing information]. Upsher-Smith, Maple Grove, MN; June 2007.
Climara [prescribing information]. Bayer, Wayne, NJ; June 2007.
EstroGel [prescribing Information]. Ascend, Herndon, VA; January 2007.
Vivelle-Dot [prescribing information]. Novartis, East Hanover, NJ; August 2004.
Vagifem® Package Insert Version 6. Novo A/S, Bagsvaerd, Denmark; November 2009.
Estring® [Prescribing Information]. Pharmacia & Upjohn Company, Division of Pfizer, Inc, NY; August 2008.
Femring® [Prescribing Information]. Warner Chilcott (UK) Ltd, Larne, Northern Ireland, UK; April 2010.

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International Society for the Study of Women's Sexual Health, Inc.

Important Safety Information

Show Less

What is the most important information I should know about (an estrogen hormone)?

- **Using estrogen-alone may increase your chance of getting cancer of the uterus (womb). Report any unusual vaginal bleeding right away while you are using Vagifem®. Vaginal bleeding after menopause may be a warning sign of cancer of the uterus (womb). Your healthcare provider should check any unusual vaginal bleeding to find the cause.**
- **Do not use estrogen with or without progestins to prevent heart disease, heart attacks, strokes, or dementia (decline of brain function).**
- **Using estrogen-alone may increase your chances of getting strokes or blood clots. Using estrogens with progestins may increase your chances of getting heart attacks, strokes, breast cancer, or blood clots.**
- **Using estrogens with or without progestins may increase your chance of getting dementia, based on a study of women age 65 years or older.**
- **You and your healthcare provider should talk regularly about whether you still need treatment wit .**

Boxed Warning

WARNING: ENDOMETRIAL CANCER, CARDIOVASCULAR DISORDERS, BREAST CANCER and PROBABLE DEMENTIA

Estrogen-Alone Therapy

Endometrial Cancer

There is an increased risk of endometrial cancer in a woman with a uterus who uses unopposed estrogens. Adding a progestin to estrogen therapy has been shown to reduce the risk of endometrial hyperplasia, which may be a precursor to endometrial cancer. Adequate diagnostic measures, including directed or random endometrial sampling when indicated, should be undertaken to rule out malignancy in postmenopausal women with undiagnosed persistent or recurring abnormal genital bleeding [see **WARNINGS, Malignant Neoplasms, Endometrial Cancer**].

Cardiovascular Disorders and Probable Dementia

Estrogen-alone therapy should not be used for the prevention of cardiovascular disease or dementia [see **CLINICAL STUDIES** and **WARNINGS, Cardiovascular Disorders**, and **Probable Dementia**].

The Women's Health Initiative (WHI) estrogen-alone substudy reported increased risks of stroke and deep vein thrombosis (DVT) in postmenopausal women (50 to 79 years of age) during 7.1 years of treatment with daily oral conjugated estrogens (CE) [0.625 mg]-alone, relative to placebo [see **CLINICAL STUDIES** and **WARNINGS, Cardiovascular Disorders**].

The WHI Memory Study (WHIMS) estrogen-alone ancillary study of WHI re
increased risk of developing probable dementia in postmenopausal women 65
older during 5.2 years of treatment with daily CE (0.625 mg) -alone, relative t
unknown whether this finding applies to younger postmenopausal women [se
STUDIES and **WARNINGS, Probable Dementia** and **PRECAUTIONS, G**

In the absence of comparable data, these risks should be assumed to be simila
doses of CE and other dosage forms of estrogens.

Estrogens with or without progestins should be prescribed at the lowest effect
the shortest duration consistent with treatment goals and risks for the individu

Estrogen Plus Progestin Therapy

Cardiovascular Disorders and Probable Dementia

Estrogen plus progestin therapy should not be used for the prevention of cardi
disease or dementia [see **CLINICAL STUDIES** and **WARNINGS, Cardiov
Disorders**, and **Probable Dementia**].

The WHI estrogen plus progestin substudy reported increased risks of DVT, pulmonary embolism (PE), stroke and myocardial infarction (MI) in postmenopausal women (50 to 79 years of age) during 5.6 years of treatment with daily oral CE (0.625 mg) combined with medroxyprogesterone acetate (MPA) [2.5 mg], relative to placebo [see **CLINICAL STUDIES** and **WARNINGS, Cardiovascular Disorders**].

The WHIMS estrogen plus progestin ancillary study of the WHI reported an increased risk of developing probable dementia in postmenopausal women 65 years of age or older during 4 years of treatment with daily CE (0.625 mg) combined with MPA (2.5 mg), relative to placebo. It is unknown whether this finding applies to younger postmenopausal women [see **CLINICAL STUDIES** and **WARNINGS, Probable Dementia** and **PRECAUTIONS, Geriatric Use**].

Breast Cancer

The WHI estrogen plus progestin substudy also demonstrated an increased risk of invasive breast cancer [see **CLINICAL STUDIES** and **WARNINGS, Malignant Neoplasms, Breast Cancer**].

In the absence of comparable data, these risks should be assumed to be similar for other doses of CE and MPA, and other combinations and dosage forms of estrogens and progestins.

Estrogens with or without progestins should be prescribed at the lowest effective doses and for the shortest duration consistent with treatment goals and risks for the individual woman.

Menopause: The Journal of The North American Menopause Society
Vol. 21, No. 9, pp. 911-916
DOI: 10.1097/gme.0000000000000316

EDITORIAL

Why the product labeling for low-dose vaginal estrogen should be changed

Breast cancer, endometrial cancer, and cardiovascular events in participants who used vaginal estrogen in the Women's Health Initiative Observational Study.

Crandall CJ[1], Hovey KM[2], Andrews CA[3], Chlebowski RT[4], Stefanick ML[5], Lane DS[6], Shifren J[7], Chen C[8], Kaunitz AM[9], Cauley JA[10], Manson JE[11]

Author information

Menopause (New York, N.Y.), 31 Dec 2017, 25(1):11-20
DOI: 10.1097/gme.0000000000000956 PMID: 28816933 PMCID: PMC5734988

CONCLUSIONS: The risks of cardiovascular disease and cancer were not elevated among postmenopausal women using vaginal estrogens, providing reassurance about the safety of treatment.

JAMA | Original Investigation

Association of Menopausal Hormone Therapy With Breast Cancer Incidence and Mortality During Long-term Follow-up of the Women's Health Initiative Randomized Clinical Trials

Rowan T. Chlebowski, MD, PhD; Garnet L. Anderson, PhD; Aaron K. Aragaki, MS; JoAnn E. Manson, MD, DrPH; Marcia L. Stefanick, PhD; Kathy Pan, MD; Wendy Barrington, PhD; Lewis H. Kuller, MD; Michael S. Simon, MD; Dorothy Lane, MD; Karen C. Johnson, MD; Thomas E. Rohan, MBBS; Margery L. S. Gass, MD; Jane A. Cauley, PhD; Electra D. Paskett, PhD; Maryam Sattari, MD; Ross L. Prentice, PhD

CONCLUSIONS AND RELEVANCE In this long-term follow-up study of 2 randomized trials, prior randomized use of CEE alone, compared with placebo, among women who had a previous hysterectomy, was significantly associated with lower breast cancer incidence and lower breast cancer mortality, whereas prior randomized use of CEE plus MPA, compared with placebo, among women who had an intact uterus, was significantly associated with a higher breast cancer incidence but no significant difference in breast cancer mortality.

JAMA. 2020;324(4):369-380. doi:10.1001/jama.2020.9482

JAMA Network | Open

Original Investigation | Obstetrics and Gynecology

Association of Vaginal Estradiol Tablet With Serum Estrogen Levels in Women Who Are Postmenopausal

Secondary Analysis of a Randomized Clinical Trial

Caroline M. Mitchell, MD, MPH; Joseph C. Larson, MS; Carolyn J. Crandall, MD; Shalender Bhasin, MBBS; Andrea Z. LaCroix, PhD; Kristine E. Ensrud, MD; Katherine A. Guthrie, PhD; Susan D. Reed, MD, MPH

RESULTS A total of 174 women, mean (SD) age 61 (4) years, were included. Those in the estrogen group (n = 88) were more likely to have higher geometric mean (SD) week 12 serum estradiol concentrations (4.3 [2.2 pg/mL]) than those in the placebo group (n = 86) (3.5 [2.1] pg/mL) (*P* = .01). Adjusted for pretreatment hormone concentrations, age, clinical site, and body mass index, assignment to the estrogen vs placebo treatment group was significantly associated with higher week 12 estradiol concentrations (23.8% difference; 95% CI, 6.9%-43.3%). Most (121 of 174 [69.5%]) participants had enrollment serum estradiol concentrations higher than 2.7 pg/mL. Of women starting treatment at estradiol levels lower than or equal to 2.7 pg/mL, 38.1% (8 of 21) in the estrogen group and 34.4% (11 of 32) in the placebo group had estradiol concentrations higher than 2.7 pg/mL after 12 weeks of study participation (*P* = .78). Treatment assignment was not associated with week 12 estrone or SHBG concentrations.

Breast Cancer Risk Associations

Factor	Relative Risk
Body mass index ≥30 kg/m^2	1.5
≥7 Alcoholic drinks per week	1.9
Current smoker	2.2
Current smoker + ≥7 alcoholic drinks per week	7.0
Diabetes	2.3
Diabetes before age 54 years	6.2
Calcium Channel Blockers[1] (Ductal breast cancer)	2.4 (1.2–4.9)
Calcium Channel Blockers[1] (Lobular breast cancer)	2.6 (1.3–5.3)

WHI CEE+MPA **1.26**

[1]Li CI, et al. *JAMA Internal Medicine* 2013;173:1629-1637.

Menopause: The Journal of The North American Menopause Society
Vol. 26, No. 6, pp. 603-610
DOI: 10.1097/GME.0000000000001284

Vaginal estrogen use and chronic disease risk in the Nurses' Health Study

Shilpa N. Bhupathiraju, PhD,[1,2] *Francine Grodstein, ScD,*[1,3] *Meir J. Stampfer, MD, DrPH,*[1,2,3,4] *Walter C. Willett, MD, DrPH,*[1,2,3] *Carolyn J. Crandall, MD, MS,*[5] *Jan L. Shifren, MD,*[6] *and JoAnn E. Manson, MD, DrPH*[1,3,4]

Abstract

Objective: To examine the associations between vaginal estrogen use and multiple health outcomes including cardiovascular disease (total myocardial infarction, stroke, and pulmonary embolism/deep vein thrombosis), cancer (total invasive, breast, endometrial, ovarian, and colorectal cancer), and hip fracture.

Methods: We included postmenopausal women from the Nurses' Health Study (1982-2012) who were not current users of systemic hormone therapy at the start of the study or during follow-up. Vaginal estrogen use was self-reported on the biennial questionnaires. Information on incident health outcomes were self-reported and confirmed by medical records. We used Cox proportional hazards regression to model the multivariable adjusted hazard ratios and the 95% confidence intervals for vaginal estrogen use and multiple health outcomes.

Results: Over 18 years of follow-up, after adjusting for covariates, risks for cardiovascular disease, cancer, and hip fracture were not different between users and nonusers of vaginal estrogen. No statistically significant increase in risk of any health outcome was observed with vaginal estrogen use. In sensitivity analyses, when we examined associations by hysterectomy status, the stratified results were generally similar to those for the total cohort.

Conclusions: Vaginal estrogen use was not associated with a higher risk of cardiovascular disease or cancer. Our findings lend support to the safety of vaginal estrogen use, a highly effective treatment for genitourinary syndrome of menopause.

Key Words: Cancer – Cardiovascular disease – Chronic disease – Hormone therapy – Vaginal estradiol – Vaginal estrogen.

› Int J Gynecol Cancer. 2020 Apr;30(4):515-524. doi: 10.1136/ijgc-2019-001034.
Epub 2020 Feb 18.

Vaginal estrogen use for genitourinary symptoms in women with a history of uterine, cervical, or ovarian carcinoma

Laura M Chambers [1], Alyssa Herrmann [2], Chad M Michener [3], Cecile A Ferrando [4], Stephanie Ricci [5]

Affiliations + expand

PMID: 32075898 DOI: 10.1136/ijgc-2019-001034

Results: Of 244 women who received vaginal estrogen, 52% (n=127) had a history of endometrial, 25.4% (n=62) cervical, 18.9% (n=46) ovarian cancer, and 3.7% (n=9) low malignant potential tumors. The mean age and body mass index were 55.5±12.5 years and 29.2±8.6 mg/kg^2, respectively. With a median follow-up of 80.2 months, the incidence of recurrence for endometrial, ovarian, and cervical cancer was 7.1% (n=9), 18.2% (n=10), and 9.7% (n=6), respectively. In patients with endometrial cancer who recurred, the incidence was 2.4% (n=3) for stage I/II and 4.7% (n=6) for stage III/IV disease. Similarly, recurrence rates for ovarian cancer were 4.3% (n=2) for stage I/II and 17.4% (n=8) for stage III/IV disease. All cervical cancer recurrences were in patients with stage I/II disease. Adverse outcomes including breast cancer (1.6%, n=4), secondary malignancy (2.5%, n=6), and venous thromboembolism (2.5%, n=6) were rare.

Conclusion: In women with a history of endometrial, ovarian, or cervical cancer prescribed vaginal estrogen use for genitourinary syndrome of menopause, adverse outcomes, including recurrence and thromboembolic events, are infrequent. Vaginal estrogen may be considered safe in gynecologic cancer survivors.

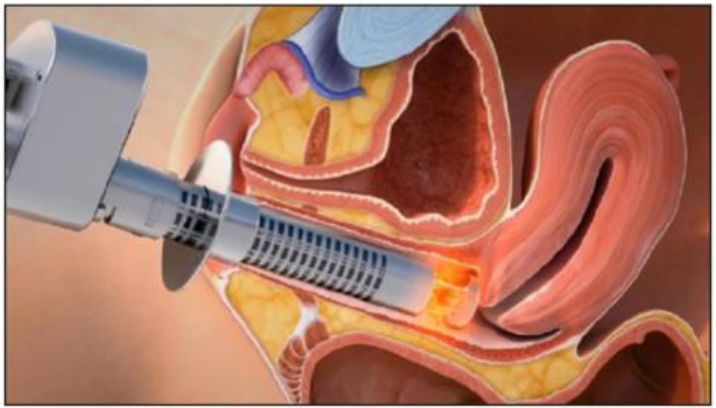
Laser based therapy

is there consensus yet?

….of course not

CO_2 fractionated laser

FIGURE 3 Fractional CO_2 laser treatment



The probe is slowly inserted to the top of the vaginal canal and then gradually withdrawn, treating the vaginal epithelium at increments of almost 1 cm.

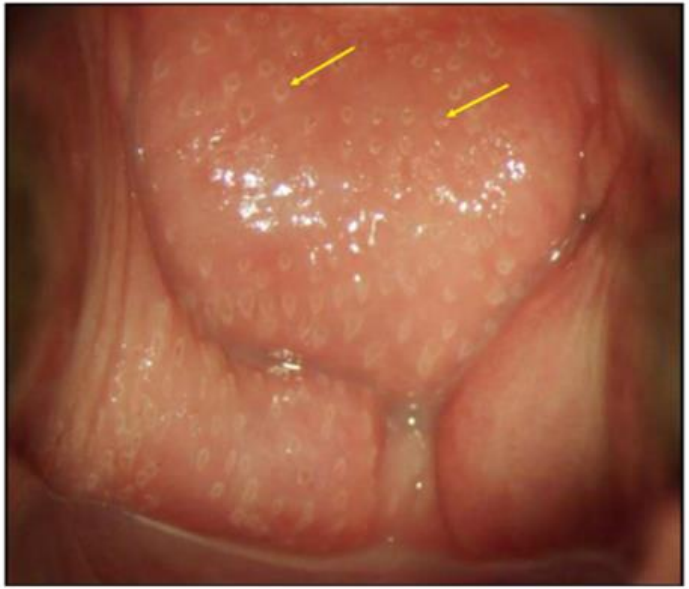
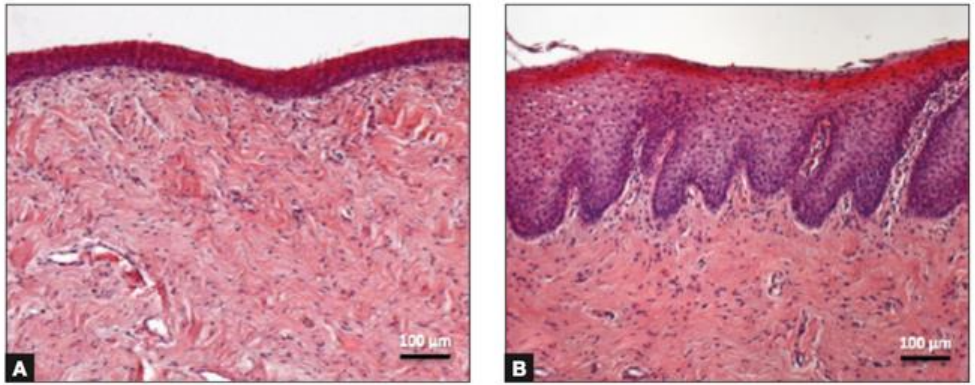


Fig. 1. Colposcopic view of vaginal walls immediately after a session of fractional CO_2 laser therapy. Arrows indicate macroscopic ablation zones.

Karram et al, OBG Manag. 2015; 27 (8): e1–e6.

CO_2 fractionated laser

FIGURE 2 Atrophic vaginitis

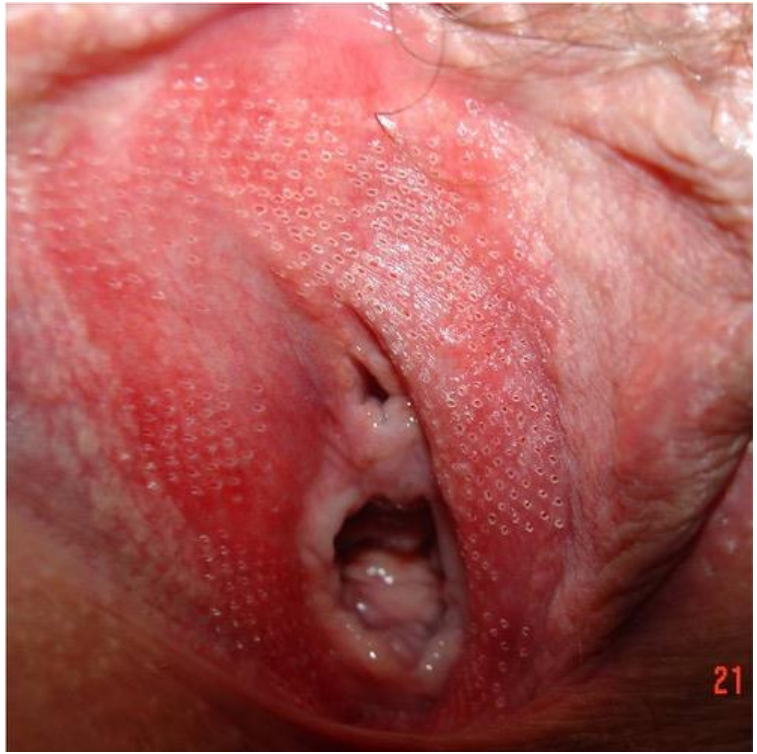


This histologic preparation of vaginal mucosa sections shows untreated atrophic vaginitis (A) and the same mucosa 1 month after treatment with fractional CO_2 laser therapy (B). *Reprinted with permission from DEKA M.E.L.A. Srl (Calenzano, Italy) and Professor A. Calligaro, University of Pavia, Italy.*

- 1 month after laser: thicker epithelium with wide columns of large epithelial cells rich in glycogen.
- reorganization of connective tissue, both in the lamina propria and the core of the papillae

Karram et al, OBG Manag. 2015; 27 (8): e1–e6.

Vestibular treatment



A randomized clinical trial comparing vaginal laser therapy to vaginal estrogen therapy in women with genitourinary syndrome of menopause: The VeLVET Trial

Paraiso, Marie Fidela R. MD[1]; Ferrando, Cecile A. MD, MPH[1]; Sokol, Eric R. MD[2]; Rardin, Charles R. MD[3]; Matthews, Catherine A. MD[4]; Karram, Mickey M. MD[5]; Iglesia, Cheryl B. MD[6]

Author Information

Menopause: January 2020 - Volume 27 - Issue 1 - p 50-56
doi: 10.1097/GME.0000000000001416

Conclusions:

At 6 months, fractionated CO_2 vaginal laser and vaginal estrogen treatment resulted in similar improvement in genitourinary syndrome of menopause symptoms as well as urinary and sexual function. Overall, 70% to 80% of participants were satisfied or very satisfied with either treatment and there were no serious adverse events.

Original Investigation

October 12, 2021

Effect of Fractional Carbon Dioxide Laser vs Sham Treatment on Symptom Severity in Women With Postmenopausal Vaginal Symptoms

A Randomized Clinical Trial

Fiona G. Li, MD[1]; Sarah Maheux-Lacroix, PhD[1]; Rebecca Deans, PhD[1]; et al

- There were no differences between the groups in any metric evaluated.
- No change in pain, sexual activity, quality of sex, or quality of life.
- Also, no differences in the biopsy specimens, 9% of people who had laser therapy and 12.5% who had the sham treatment had an improvement in how the tissues looked under the microscope.

My promise to you

- Invest YOUR time educating patients about importance and safety of GSM treatment.
- Find the right product that is affordable and they will keep refilling.
- Your after hours and weekend on call phone calls will dramatically decrease as will your “urgent” urine culture requests
- Within 2 months your patients will be believers and they and their partners will call you a super-hero

Education is ESSENTIAL for adherence

GSM treatment
should be life long treatment

This is not *just* about sex.

AUA 2023

CHICAGO

APR 28-MAY 1

Case studies in GSM

Faculty and you!

Case # 1 – Mrs. J

- 63 y/o female presents with vaginal burning, chronic dysuria
- PMH significant for prior hysterectomy for prolapse, breast cancer
- Finished a selective estrogen receptor modulator treatment 1 year ago

Case # 1 – Mrs. J

- Poll everywhere question

Case # 1 – Mrs. J

- What if she was on tamoxifen currently?
- What if she is on an aromatase inhibitors?

JOURNAL ARTICLE EDITOR'S CHOICE

Systemic or Vaginal Hormone Therapy After Early Breast Cancer: A Danish Observational Cohort Study

Søren Cold, MD ✉, Frederik Cold, MD, Maj-Britt Jensen, MSc, Deirdre Cronin-Fenton, PhD, Peer Christiansen, MD, Bent Ejlertsen, MD

JNCI: Journal of the National Cancer Institute, Volume 114, Issue 10, October 2022, Pages 1347–1354, https://doi.org/10.1093/jnci/djac112
Published: 20 July 2022 **Article history** ▾

Results

Among 8461 women who had not received VET or MHT before BC diagnosis, 1957 and 133 used VET and MHT, respectively, after diagnosis. Median follow-up was 9.8 years for recurrence and 15.2 years for mortality. The adjusted relative risk of recurrence was 1.08 (95% confidence interval [CI] = 0.89 to 1.32) for VET (1.39 [95% CI = 1.04 to 1.85 in the subgroup receiving adjuvant aromatase inhibitors]) and 1.05 (95% CI = 0.62 to 1.78) for MHT. The adjusted hazard ratios for overall mortality were 0.78 (95% CI = 0.71 to 0.87) and 0.94 (95% CI = 0.70 to 1.26) for VET and MHT, respectively.

Conclusions

In postmenopausal women treated for early-stage estrogen receptor–positive BC, neither VET nor MHT was associated with increased risk of recurrence or mortality. A subgroup analysis revealed an increased risk of recurrence, but not mortality, in patients receiving VET with adjuvant aromatase inhibitors.

Case # 2 – Mrs. S

- 77 y/o presented with recurrent urinary tract infections, urgency incontinence
- Prescribed transvaginal estrogen
- Presents today to discuss the information she has read on the label

Case # 2 – Mrs. S

WARNING: ENDOMETRIAL CANCER, CARDIOVASCULAR DISORDERS, BREAST CANCER and PROBABLE DEMENTIA

Estrogen-Alone Therapy

Endometrial Cancer

There is an increased risk of endometrial cancer in a woman with a uterus who uses unopposed estrogens. Adding a progestin to estrogen therapy has been shown to reduce the risk of endometrial hyperplasia, which may be a precursor to endometrial cancer. Adequate diagnostic measures, including directed or random endometrial sampling when indicated, should be undertaken to rule out malignancy in postmenopausal women with undiagnosed persistent or recurring abnormal genital bleeding [see **WARNINGS, Malignant Neoplasms, Endometrial Cancer**].

Cardiovascular Disorders and Probable Dementia

Estrogen-alone therapy should not be used for the prevention of cardiovascular disease or dementia [see **CLINICAL STUDIES** and **WARNINGS, Cardiovascular Disorders**, and

Case # 2 – Mrs. S

- Poll everywhere question

Case # 3 – Ms. R

- 52 y/o perimenopausal woman with pelvic pain, dyspareunia
- Prior pelvic floor physical therapy seemed to worsen condition
- Desperate for other options

Case # 3 – Ms. R

- Poll everywhere question

Case # 4 – Mrs. W

- 66 y/o sexually active woman initially presented with vaginal pain, dyspareunia, urinary urgency, dysuria
- Initiated on transvaginal estrogen, beta-3 adrenergic receptor agonist
- Urinary symptoms dramatically improved
- No change in vaginal, vestibular, or sexual symptoms
- How do you counsel her now?

Case # 4 – Mrs. W

- Poll everywhere question

Conclusions

- XXXX
- XXXX
- XXXX

Thank you