THE UNIVERSITY OF TENNESSEE HEALTH SCIENCE CENTER

Menopause: Cases and Controversies

Pallavi Khanna MD, MSCP

38th Annual Contemporary Issues in Obstetrics and Gynecology, 2024

1

Disclosures

- Speaker – Astellas
- America's Board Review – Q bank contributor

2

Objectives

- **Determine** when to offer Menopausal Hormone Therapy (MHT).
- **Evaluate** the benefits versus risks of initiating MHT.
- **Select** the appropriate Menopausal Hormone Therapy.
- **Recommend** alternatives when Menopausal Hormone Therapy is not an option.

3

3 Cases

- 38 yo with premature menopause
- 48 yo in menopause transition with " symptoms of hormonal imbalance "
- 68 yo with hot flashes, vaginal dryness and pain with intercourse

4

38 yo with premature menopause

Primary Ovarian Insufficiency / Surgical

5

Diagnostic Work-up of POI

- **History and physical examination, detailed family history**
- **Estradiol, FSH, LH**
  - **If FSH elevated, repeat FSH and estradiol level at least 4 wk later**
- **Karyotype**
- **Anti-21hydroxylase antibodies**
- **Fragile X screen**
- **Thyroid-stimulating hormone (TSH), free thyroxine (T_4), anti-thyroid-peroxidase antibodies**
- **Glucose, metabolic profile, complete blood count**

Nelson LM. N Engl J Med. 2009;360(6):606-614.

6

Contraindications to HT

- Undiagnosed abnormal genital bleeding
- Known, suspected, or history of breast cancer, except in appropriately selected patients being treated for metastatic disease or with oncology involvement
- Suspected estrogen-dependent neoplasia
- Active or history of deep vein thrombosis, pulmonary embolism
- Active or recent (within the past year) arterial thromboembolic disease
- Liver dysfunction or disease
- Known or suspected pregnancy
- Known hypersensitivity to ET or EPT
- Porphyria cutanea tardis

7

Management of POI

- Standard of care is physiologic estrogen and progestin treatment
  - Estrogen: 100 µg transdermal estradiol patch, or 1.25 mg conjugated equine estrogens (CEE), or 2 mg of estradiol orally
  - If uterus is present, cyclical progestins should be added ≥12 d/mo
  - Combined hormone contraception or transdermal estradiol-progestin systems are alternatives
  - Recommended duration of therapy is at least until the natural age of menopause
- For those desiring pregnancy
  - Can still carry a pregnancy but will likely require an egg donor to become pregnant

European Society for Human Reproduction and Embryology (ESHRE) Guideline Group on POI; Webber L, et al. *Hum Reprod.* 2016;31(5):926-937.

8

Treatment options

- Estrogen containing contraception
- MHT : E+P – Oral/Transdermal Estradiol
  Micronized Progestin / LNG- IUS (Mirena)

Estrogen Dose in the Pill	Oral Estradiol Equivalent	Estradiol Patch Equivalent
Ethinyl estradiol 20 mcg	1.5-4 mg	75 mcg-200 mcg
Estradiol valerate 2 mg*	1.52 mg	75 mcg
17 beta-estradiol 1.5 mg	1.5 mg	75 mcg

*Most of the pills have 2 mg of estradiol valerate

Table 1. Bioequivalent Hormonal Dosages for Hormone Therapy for Primary Ovarian Insufficiency*

Estrogen	Progestogen	
	Continuous	Sequential
1–2 mg micronized 17β-estradiol (oral)	2.5–5 mg medroxyprogesterone acetate daily (oral)	10 mg medroxyprogesterone acetate daily (oral) for 12 days each month
100 micrograms 17β-estradiol (transdermal)	100 mg micronized progesterone daily (oral)	200 mg micronized progesterone daily (oral) for 12 days each month
0.625–1.25 mg conjugated equine estrogen (oral)		

*Select one of the estrogen options to be combined with one of the progestogen options.

9

Controversies

- When to discontinue?
- When to switch from contraception to menopausal HT?
- POI following cancer treatment
- Surgical premature menopause - when to initiate HT
- History of Endometriosis

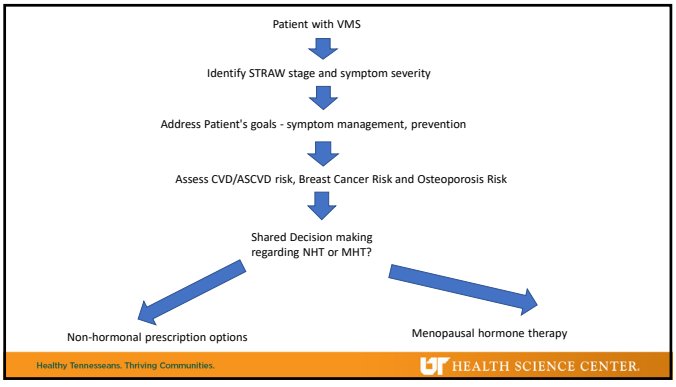
- Until average age of menopause (52)
- At average age of Menopause or when wishing to step down
- Shared decision making (+ oncologist)
- Within a week and at physiologic doses
- MHT dose E+P (if endo of bowel)

10

48 yo in menopause transition with bothersome hot flashes

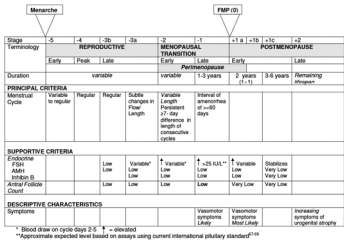
45-55 year olds

11



12

STRAW+10 Stages of Reproductive Aging Workshop



Stage	-5	-4	-3b	-3a	-2	-1	+1 a	+1b	+1c	+2
Terminology	REPRODUCTIVE				MENOPAUSAL TRANSITION		POSTMENOPAUSE			
	Early	Peak	Late		Early	Late	Early			Late
					Perimenopause					
Duration	variable				variable	1-3 years	2 years (1 ; 1)	3-6 years	Remaining lifespan	
PRINCIPAL CRITERIA										
Menstrual Cycle	Variable to regular	Regular	Regular	Subtle changes in Flow Length	Variable Length & Persistent ≥7- day difference in length of consecutive cycles	Interval of amenorrhea of ≥=60 days				
SUPPORTIVE CRITERIA										
Endocrine				Low	Variable*	↑ Variable*	↑ >25 IU/L*	↑ Variable	Stabilizes	
AMH				Low	Low	Low	Low	Low	Very Low	
Inhibin B				Low	Low	Low	Low	Low	Very Low	
Antral Follicle Count				Low	Low	Low	Low	Very Low	Very Low	
DESCRIPTIVE CHARACTERISTICS										
Symptoms						Vasomotor symptoms Likely	Vasomotor symptoms Most Likely		Increasing symptoms of urogenital atrophy	

* Blood draw on cycle days 2-5 ↑ = elevated
**Approximate expected level based on assays using current international pituitary standard[7,8,9]

Harlow SD, et al. *Menopause*. 2012;19(4):387-395.

HEALTH SCIENCE CENTER.

13

Symptom checklist (from Menopause Health Questionnaire)

Section 13. SYMPTOMS

Please indicate how bothered you are now and in the past few weeks by any of the following:

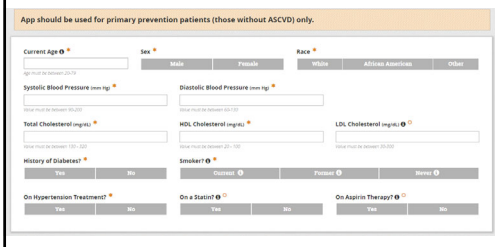
	Not at all	A little bit	Quite a bit	Extremely
I have hot flashes	❑	❑	❑	❑
I have night sweats	❑	❑	❑	❑
I have difficulty getting to sleep	❑	❑	❑	❑
I have difficulty staying asleep	❑	❑	❑	❑
I get heart palpitations or a sensation of butterflies in my chest or stomach	❑	❑	❑	❑
I feel like my skin is crawling or itching	❑	❑	❑	❑
I feel more tired than usual	❑	❑	❑	❑
I have difficulty concentrating	❑	❑	❑	❑
My memory is poor	❑	❑	❑	❑
I am more irritable than usual	❑	❑	❑	❑
I feel more anxious than usual	❑	❑	❑	❑
I have more depressed moods	❑	❑	❑	❑
I am having mood swings	❑	❑	❑	❑
I have crying spells	❑	❑	❑	❑
I have headaches	❑	❑	❑	❑
I need to urinate more often than usual	❑	❑	❑	❑
I leak urine	❑	❑	❑	❑
I have pain or burning when urinating	❑	❑	❑	❑
I have bladder infections	❑	❑	❑	❑
I have uncontrollable loss of stool or gas	❑	❑	❑	❑
My vagina is dry	❑	❑	❑	❑
I have vaginal itching	❑	❑	❑	❑
I have an abnormal vaginal discharge	❑	❑	❑	❑
I have vaginal infections	❑	❑	❑	❑
I have pain during intercourse	❑	❑	❑	❑
I have pain inside during intercourse	❑	❑	❑	❑
I have bleeding after intercourse	❑	❑	❑	❑
I lack desire or interest in sexual activity	❑	❑	❑	❑
I have difficulty achieving orgasm	❑	❑	❑	❑
My opportunity for sexual activity is limited	❑	❑	❑	❑
My stomach feels like it's bloated or I've gained weight	❑	❑	❑	❑
I have breast tenderness	❑	❑	❑	❑
I have joint pains	❑	❑	❑	❑

Healthy Tennesseans. Thriving Communities.

HEALTH SCIENCE CENTER.

14

ASCVD (CVD and stroke) Risk estimation



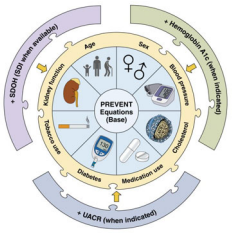
- Race as a biologic (not social) factor
- 40-79 year olds

Healthy Tennesseans. Thriving Communities.

HEALTH SCIENCE CENTER.

15

PREVENT™ (Predicting Risk of cardiovascular disease EVENTs) risk calculator



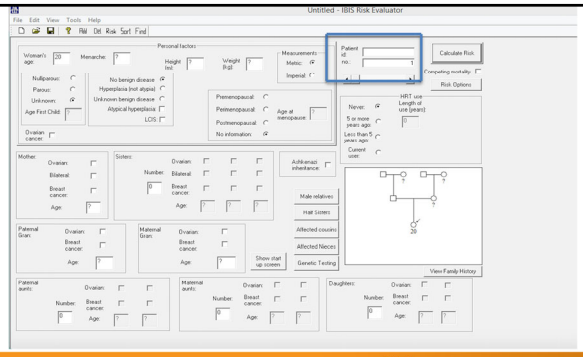
- https://professional.heart.org/en/guidelines-and-statements/prevent-calculator
- 30-79 years
- Kidney disease and metabolic disease, including obesity and diabetes, multiply the odds of developing cardiovascular disease.
- Eliminates race altogether and factor in social determinants of health to estimate cardiovascular disease risk.
- Cardiovascular-kidney-metabolic (CKM) health

16

Breast Cancer Risk Assessment

- https://ibis-risk-calculator.magview.com/
- Tyrer Cuzick Risk Assessment Calculator
- Includes Breast density on mammo

17



18

Your Breast Cancer Risk Assessment Score

The results below are based on the IBIS risk assessment model, also known as the Tyrer-Cuzick (v8) risk assessment model. These results show your lifetime risk for breast cancer compared to the U.S. population average.

Based on the information provided, your estimated lifetime risk for developing invasive breast cancer is **5.4%**. The U.S. population's average lifetime risk is **9.8%** for women of the same age.

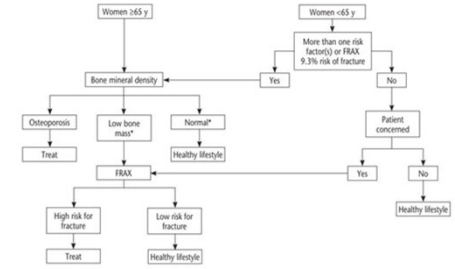
If your lifetime risk is 20% or greater: you are at high risk for developing breast cancer. Yearly MRI is recommended in addition to a mammogram. If MRI is not possible, a contrast-enhanced mammogram (CEM) or molecular breast imaging (MBI) is recommended. If these tests are not possible, an ultrasound should be considered.

If your lifetime risk is less than 20% and you have dense breasts: dense breasts make cancer more difficult to see on a mammogram. Consider yearly MRI in addition to your yearly mammogram as MRI finds more cancers than a mammogram alone in dense breasts. If MRI is not possible, consider a contrast-enhanced mammogram (CEM) or molecular breast imaging (MBI). If these tests are not possible, consider ultrasound.

If your lifetime risk is less than 20% and you do not have dense breasts, it is recommended that you follow protocol for women at average risk for breast cancer (and without dense breasts). A yearly mammogram beginning at age 40 is recommended for women at average risk.

19

Osteoporosis Screening - FRAX and DEXA



Fragility fracture is an indication for treatment despite lack of osteoporosis on DXA.

20

Prescription Therapies for VMS

- **FDA-approved prescription (HT and non HT) treatments**

-Hormone therapy - E + P, E only, E + SERM
-Paroxetine
-Fezolinetant

- **Off-label (non HT) prescription therapies**

-Selective serotonin reuptake inhibitors
-Serotonin-norepinephrine reuptake inhibitors
-Gabapentinoids
-Clonidine
-Oxybutynin

- Treatment based on the person's tolerance of symptoms, health history, risk factors, and personal preferences

21

UTHSC

Initiation : Estradiol Doses

- Depending on severity of symptoms: 0.025-0.05 mg E2 TD/0.3-0.625 mg CEE/0.5-1mg E2 oral and adjust as needed until stable symptoms

Estradiol-approximate equivalent doses				
	Ultra low	Low	Medium	High
Oral	0.5mg	1.0mg	2.0mg	3-4mg
Patch	Half 25	25	50	75-100
Gel-pump	½ pump	1 pump	2 pumps	3-4 pumps
Gel-Sachet	½ x 0.5mg sachet-0.25mg	0.5mg	1-1.5mg	2-3mg
Spray	1 spray	2 sprays	3 sprays	—

22

FDA Approved Systemic Estrogen Nonoral vs Oral




Healthy Tennesseans. Thriving Communities. HEALTH SCIENCE CENTER.

23

Transdermal estrogen products

Revised: February 2016

(Providers should check the full prescribing information for appropriate dosages for the indication and any updates or information that is not provided here, such as warnings and contraindications.)

Active ingredient(s)	Product Name	Dosage (mg E$_2$/day)
Patch, Film		
17β-estradiol*	Alora[†]	0.025, 0.05, 0.075, 0.1 twice/wk
	Climara	0.025, 0.0375,[‡] 0.05, 0.06,[‡] 0.075, 0.1 once/wk
	Estraderm[†]	0.05, 0.1 twice/wk
	Estradot[‡]	0.025, 0.0375, 0.05, 0.075, 0.1 twice/wk
	Minivelle[‡]	0.025, 0.0375, 0.05, 0.075, 0.1 twice/wk
	Oescim[‡]	0.025, 0.0375, 0.05, 0.075, 0.1 twice/wk
	Vivelle-Dot[‡]	0.025, 0.0375, 0.05, 0.075, 0.1 twice/wk
	Generic(s) available	
Transdermal gel		
17β-estradiol*	Divigel	0.25, 0.5, 1.0
	EstroGel	0.75 (US: single approved dose, Canada adjust to control symptoms)
	Elestrin[†]	0.52 (adjust based on clinical response)
Transdermal spray		
17β-estradiol*	Evamist[†]	1.53 (1 spray/d initially, adjust dosage by clinical response)

*Bioidentical: defined as compounds that have the same chemical and molecular structure as hormones that are produced in the body

Approved Prescription Products for Menopausal Symptoms in the United States and Canada

Oral estrogen products

Revised: February 2016

(Providers should check the full prescribing information for appropriate dosages for the indication and any updates or information that is not provided here, such as warnings and contraindications.)

Active Ingredient(s)	Product Name(s)	Dosages (mg/d)
17β-estradiol*	Estrace[†] Generic(s) available	0.5, 1.0, 2.0
Conjugated estrogens	Premarin	0.3, 0.45[‡], 0.625, 0.9[‡], 1.25
Synthetic conjugated estrogens, B	Enjuvia[‡]	0.3, 0.45, 0.625, 0.9, 1.25
Conjugated estrogens, CSD[‡] (synthetic)	C.E.S. pms-Conjugated estrogens, CSD	0.3, 0.625, 0.9, 1.25
Esterified estrogens	Menest[†]	0.3, 0.625, 1.25, 2.5 (administer cyclically)
	Estragyn[†]	0.3, 0.625
Estropipate	Generic(s) available[‡]	0.625 (0.75 estropipate), 1.25 (1.5), 2.5 (3.0)

*Bioidentical: defined as compounds that have the same chemical and molecular structure as hormones that are produced in the body
[†] Available in Canada but not the United States
[‡] Available in the United States but not Canada
Product names not marked are available in both the United States and Canada.

Healthy Tennesseans. Thriving Communities. HEALTH SCIENCE CENTER.

24

And don't forget the Progestin if uterus +

- Micronized Progesterone (Prometrium)
- Levonorgestrel Intrauterine System (Mirena IUS)
- Synthetic Progestins

25

HT Risks/Benefit counseling 45-55 yo

HT and CHD
- HT started within 10 y of menopause or in women aged <60 y lowers all-cause mortality and does not increase the risk of coronary events
- May reduce coronary events
-

HT and stroke
- Stroke risk not increased with HT in women aged <60 y or within 10 y of menopause
- Transdermal estrogen or lower doses of oral estrogen may have a lower stroke risk (observational evidence)

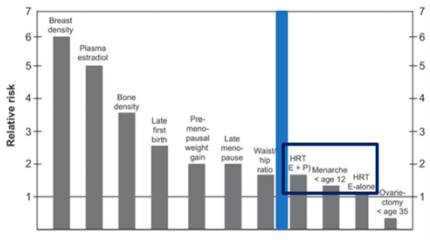
HT and VTE
- Increased VTE risk with oral HT
- The risk does not appear to be increased with transdermal estrogens and may be lower with lower dose of oral estrogens (observational evidence)
- Micronized Progestin (MP) less thrombogenic than synthetic progestogens
- No risk with vaginal ET
-

HT and Breast cancer
- Synthetic Progestogen use (dose and duration dependent) may be associated with continuous use over 5 years

Rossouw JE, et al. *JAMA*. 2002;288(3):321-333; Anderson GL, et al. *JAMA*. 2004;291(14):1701-1712; Canonico M , et al. Circulation. 2007;115(7):840-845; Canonico M, et al. *BMJ*. 2008;336(7655):1227-1231.

26

Endogenous Factors are a Greater Risk of Breast Cancer Than Menopausal Hormone Treatment[31]



27

UTHSC

Oral vs Transdermal Estradiol hormone therapy

• Plasma estrogen peaks & troughs	• Serum E2 levels relatively constant
• First pass through GI tract & liver (requires higher dose)	• Does not pass through liver – lower doses required
• Increased hepatic enzymes, inflammatory markers	• No change in inflammatory markers
• Increased triglycerides	• No change or decrease in triglycerides
• Increased blood pressure	• Decrease in blood pressure
• Decreased LDL cholesterol and increased HDL	• Decreases LDL but no change in HDL

28

Controversies

• MHT and hx of breast cancer?	• Shared decision making (+ oncologist)
• MHT and BRCA?	• Not a contraindication
• HT for non-FDA approved indications?	• Shared decision making
• HT for osteoporosis prevention	• Yes
• Compounded HT/ Pellets?	• PLEASE REFRAIN, educate and help transition to FDA approved options
• Menopause supplements?	• Not enough data/placebo effect
• MHT for cardio prevention?	• If used for FDA approved indications AND/OR in Menopause transition / within 10 years of Menopause

29

68 yo with hot flashes, vaginal dryness and pain with intercourse

LMP > 10 years ago, never-user of HT

30

Non-prescription and prescription therapies for VMS

- Nutrition
- Exercise
- Pharmacologic
- Non-pharmacologic

Freedman RR, et al. *Am J Obstet Gynecol.* 1992;167(2):436-439; Schmidt M, et al. *Gynecol Endocrinol.* 2016;32(6):427-430; Reid RL, et al. *Climacteric.* 2015;18(5):743-749; Mann E, et al. *BMC Cancer.* 2011;11:44; Ayers B, et al. *Menopause.* 2012;19(7):749-759; Elkins GR, et al. *Menopause.* 2013;20(3):291-298; Freedman RR, et al. *Am J Obstet Gynecol.* 1992;167(2):436-439; Walega DR, et al. *Menopause.* 2014;21(8):807-814; Reid RL, et al. *Climacteric.* 2015;18(5):743-749.

31

Timing of HT Initiation

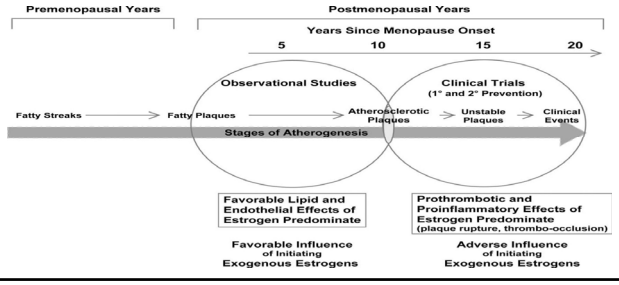
- **Timing hypothesis**
  - **There may be less risk associated with HT use and potential coronary heart disease (CHD) benefit if initiated closer to the time of menopause**
  - **In contrast, HT use initiated further from menopause may be harmful**
- **Evidence from the WHI**
  - **Absolute risk of CHD was lower in younger, recently postmenopausal women**
  - **Heart attack risk increased during the first year of EPT in older women**
  - **Use of HT within 10 y of the onset of menopause was associated with a lower CHD risk than if it was started ≥20 y from LMP**
  - **Women aged 50-59 y in the ET arm had a more favorable all-cause mortality and fewer MIs**
- **Early Estrogen Prevention Study and the Early Versus Late Intervention Trial With Estradiol also showed safety of HT use initiated early in menopause**

Rossouw JE, et al. *JAMA.* 2007;297(13):1465-1477. Manson JE, et al. *JAMA.* 2013;310(13)1353-1368. Manson JE, et al. *JAMA.* 2017;318(10):927-938. Harman SM, et al. *Ann Intern Med.* 2014;161(4):249-260. Hodis HN, et al. *N Engl J Med.* 2016;374(13):1221-1231.

32

UTHSC

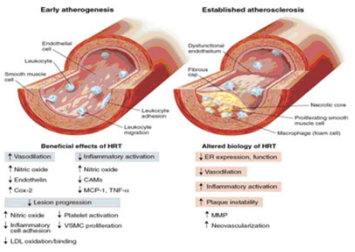
Timing of hormone therapy initiation in relation to stage of atherosclerosis: observational studies *vs.* clinical trials



33

UTHSC

The timing hypothesis: differential effects of HT on early and later stages of atherosclerotic disease



Mendelsohn ME and Karas RH. 10 JUNE 2005 VOL 308 SCIENCE

34

Non hormonal FDA approved for VMS

- 7.5mg Paroxetine
- 45mg Fezolinetant
- Nutrition
- Exercise

35

UTHSC

Off-Label Management of Symptoms:

SSRI/SNRI

- Venlafexine (*Effexor XR*) – 37.5 mg a day- titrate as needed; commonly 75 mg/day
- Desvenlafexine (*Pristiq*) – 50-100 mg/day

Escitalopram (*Lexapro*) – 10-20 mg/day

Gabapentin (*Neurontin*) – 300 mg hs/titrate 300 mg tid

36

Evaluation of GSM

Complete medical history
- **Symptom characterization, prior treatments**
- **Review of vaginal irritants**

Sexual history

Physical examination
- **Vaginal pH and wet prep as indicated**
- **Vulvar/Vaginal cultures as appropriate**
- **Biopsy white, pigmented, or thickened lesions**

➢ **Any vulvar lesion that does not respond to treatment should be biopsied**

The NAMS 2020 Genitourinary Syndrome of Menopause Position Statement Editorial Panel. *Menopause.* 2020;27(9):976-992.

37

Treatments for GSM: Nonhormone Therapies

Lubricants		Moisturizers
Water based	**Silicone based**	Replens
Astroglide Liquid	Astroglide X	Me Again
Astroglide Gel Liquid	ID Millennium	Feminease
Astroglide	K-Y Intrigue	K-Y SILK-Eluvena
Good Clean Love	Pink	Revaree
Just Like Me	Pjur Eros	Silken Secret
K-Y Jelly	Uberlube	Hyalo-gyn
Pre-Seed (pro-fertility)	Sliquid	
Slippery Stuff		
Liquid Silk	**Oil based**	
YES WB	Elégance Women's Lubricants	
SYLK	Olive oil	
Sliquid	YES OB	

The NAMS 2020 Genitourinary Syndrome of Menopause Position Statement Editorial Panel. *Menopause.* 2020;27(9):976-992.

38

Treatments for GSM: Hormone Treatments

- **For women with moderate to severe GSM and for those who do not respond to lubricants and moisturizers, several safe and effective hormone options are available**
  - **Low-dose vaginal ET**
  - **Vaginal DHEA**
  - **Ospemifene**
  - **Systemic ET (when VMS are also present)**

The NAMS 2020 Genitourinary Syndrome of Menopause Position Statement Editorial Panel. *Menopause.* 2020;27(9):976-992.

39

FDA-Approved Therapies for GSM in the United States and Canada

Type	Composition	Product name	Commonly used starting dose	Commonly used maintenance dose	Typical serum estradiol level (pg/mL)
Vaginal creams	17β-estradiol 0.01% (0.1 mg active ingredient/g)	Estrace vaginal cream-	0.5-1 g/d for 2 wk	0.5-1 g 1-3 times/wk	Variable
	Conjugated estrogens (0.625 mg active ingredient/g)	Premarin vaginal cream	0.5-1 g/d for 2 wk	0.5-1 g 1-3 times/wk	Variable
Vaginal inserts	17β-estradiol inserts	Imvexxy-	4 or 10 μg/d for 2 wk	1 insert twice/wk	3.6 (4 μg) 4.6 (10 μg)
	Estradiol hemihydrate tablets	Vagifem Yuvafem	10 μg/d for 2 wk	1 tablet twice/wk	5.5
	Prasterone (DHEA) inserts	Intrarosa	6.5 mg/d	1 insert/d	5
Vaginal ring	17β-estradiol	Estring	2 mg ring releases approx 7.5 μg/d	Replace ring every 90 days	8
Oral tablet	Ospemifene	Osphena-	60 mg/d	1 tablet by mouth/d	N/A

Products not marked are available in both the United States and Canada.
-Available in the United States but not Canada
-Available in Canada but not the United States

The NAMS 2020 Genitourinary Syndrome of Menopause Position Statement Editorial Panel. *Menopause*. 2020;27(9):976-992.

40

Controversies

- Hormone therapy for all..
- Testosterone in addition to E+P?
- Switching from compounded HT to FDA approved Rx
- Discontinuing HT
- MHT and dementia?

- No
- For postmenopausal with HSDD
- Yes

- Not routinely indicated
- May worsen if already at high risk (based on observational data)

41

THE UNIVERSITY OF TENNESSEE HEALTH SCIENCE CENTER.

42