Menopause Management

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Preface

- No financial disclosures

Menopause Demographics

- The menopause transition is a natural event; postmenopause is defined by the final menstrual period (FMP) and confirmed after 1 year of no menstrual bleeding
- Represents the permanent cessation of menses resulting from loss of ovarian follicular function, usually because of aging
- Median age in US women, 52.54 years

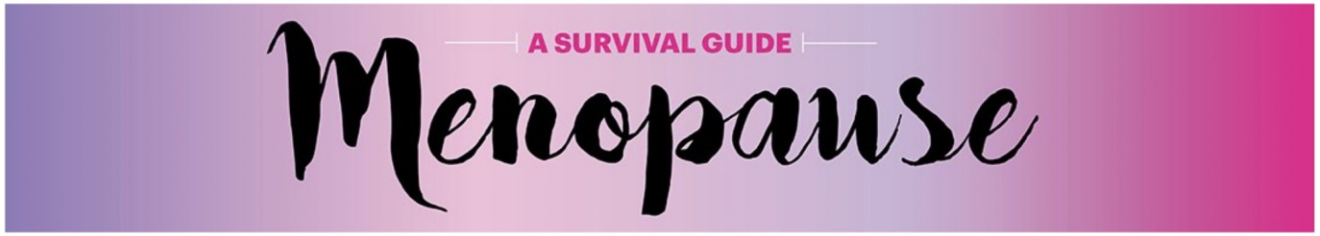
Arias E, et al. *United States Life Tables, 2013.* National Vital Statistics Reports. April 11, 2017;
Gold EB, et al. *Am J Epidemiol*. 2013;178(1):70-83.

Menopause Matters

- U.S. populations are projected to age over the coming decades with the number of women aged 50+ expected to grow significantly
  - 2020: 64 million
  - 2060: 90 million
- Overall life expectancy of US females is 81.2 years
  - Women may spend 40% of their lives postmenopausal
- 2013 survey of OB/GYN residents found <20% received formal training in menopause and 80% felt “barely comfortable” discussing or treating menopause

US Census Bureau, Population Division. *2014 National Population Projections Tables*. Table 9. Projections of the population by sex and age for the United States: 2015 to 2060 (NP2014-T9). Revised May 9, 2017. www.census.gov/data/tables/2014/demo/popproj/2014- summary-tables.html. Accessed March 1, 2019.
Arias E, Heron M, Xu J; Division of Vital Statistics. *United States Life Tables, 2013*. National Vital Statistics Reports. Vol 66, No 3. Hyattsville, MD: National Center for Health Statistics. April 11, 2017. www.cdc.gov/ nchs/data/nvsr/nvsr66/nvsr66_03.pdf. Accessed March 1, 2019.
Christianson MS, Ducie JA, Altman K, Khafagy AM, Shen W. Menopause education: needs assessment of American obstetrics and gynecology residents. Menopause. 2013 Nov;20(11):1120-5.

So where are patients getting answers?



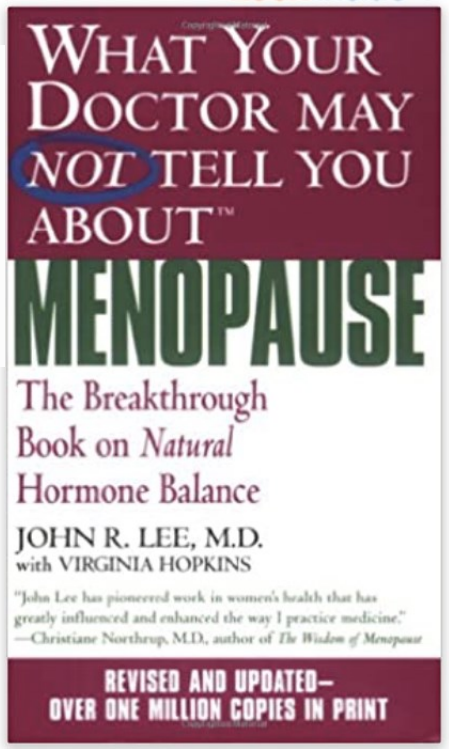
What Doctors Don't Know About Menopause

Three out of four women who seek help for symptoms don't receive it

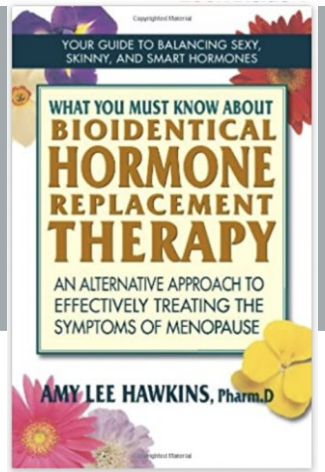
by Jennifer Wolff, **AARP The Magazine**, August/September 2018

Struggling with Hormone Imbalance? Conventional Doctors May Not Be Your Strongest Ally!

"Doctors Are Failing Women": A New Approach to Menopause Care



Menopause is a $600 billion opportunity, report finds



What to do when your Doctor wont check your Hormones

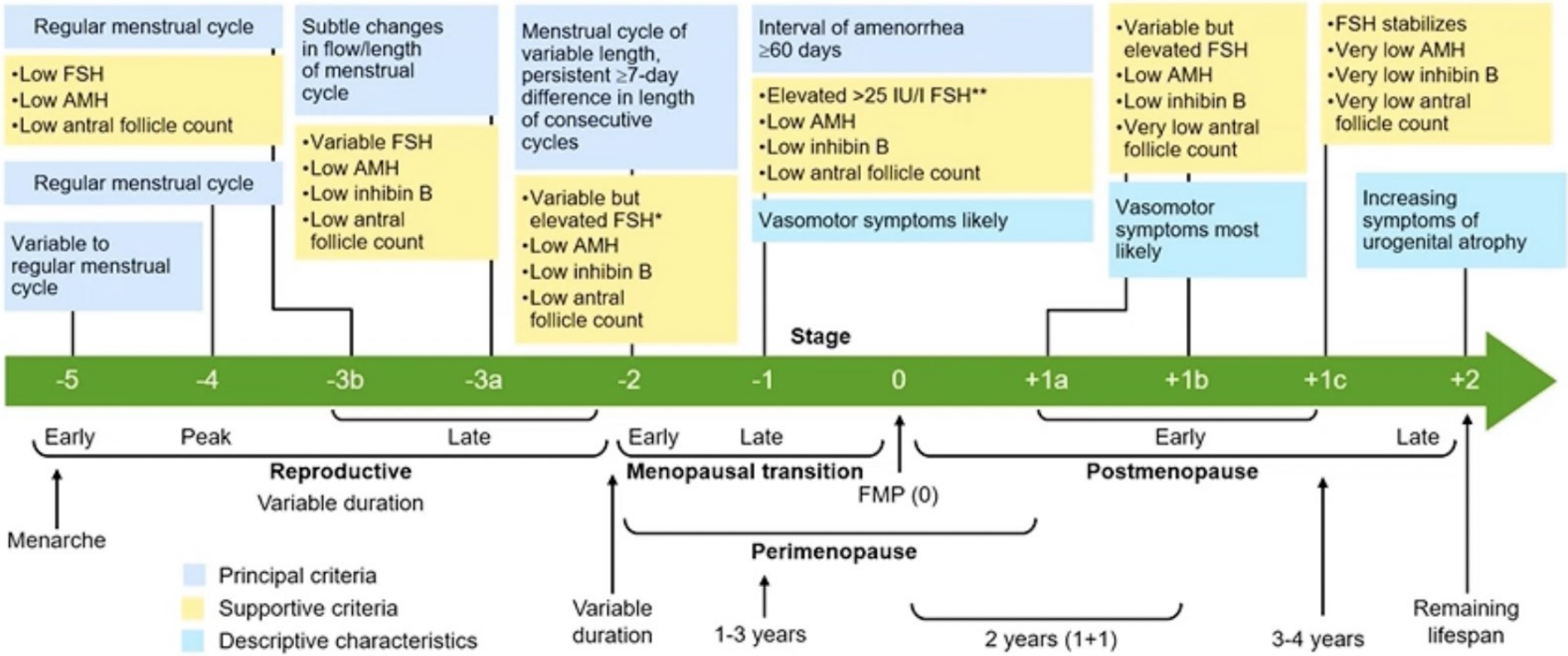
Objectives

- Terminology & Staging
- Physiology
- Signs and Symptoms
- Management considerations for common concerns
  - Vasomotor symptoms
    - Menopausal hormone therapy (MHT) and nonhormonal options
  - Genitourinary syndrome of menopause (GSM)
- Clinical Decision Making
- Patient Education Resources

Terminology

- *Early menopause:* FMP before age 45 years
- *Late menopause:* FMP after age 54 years
- *Natural menopause*: Permanent cessation of menses because of loss of follicular activity
- *Induced menopause*: Surgical or iatrogenic loss of ovarian function
- *Perimenopause*: Stage in menopause transition characterized by irregular menstrual cycles (early perimenopause) or 2-12 months of amenorrhea (late perimenopause)
- *Postmenopause*: Defined as 12 months of amenorrhea
- *Premature menopause:* FMP before age 40 years
- *Premenopause*: Reproductive stage between menarche and onset of perimenopause
- *Primary ovarian insufficiency*: Menopause occurring at age <40 years

The Stages of Reproductive Age Workshop (STRAW) +10 Staging System for Reproductive Age in Women



STRAW defined 7 stages ranging from the onset of menstrual cycles at menarche and the reproductive age to the perimenopausal and postmenopausal phases. Principal (menstrual cycle), supportive (biochemical and imaging), and descriptive (symptoms) criteria are used to characterize the phases. AMH indicates anti-Müllerian hormone; FMP, final menstrual period; and FSH, follicle-stimulating hormone. *Blood drawn on cycle days 2 to 5. **Approximate expected level based on assays using current international pituitary standard.

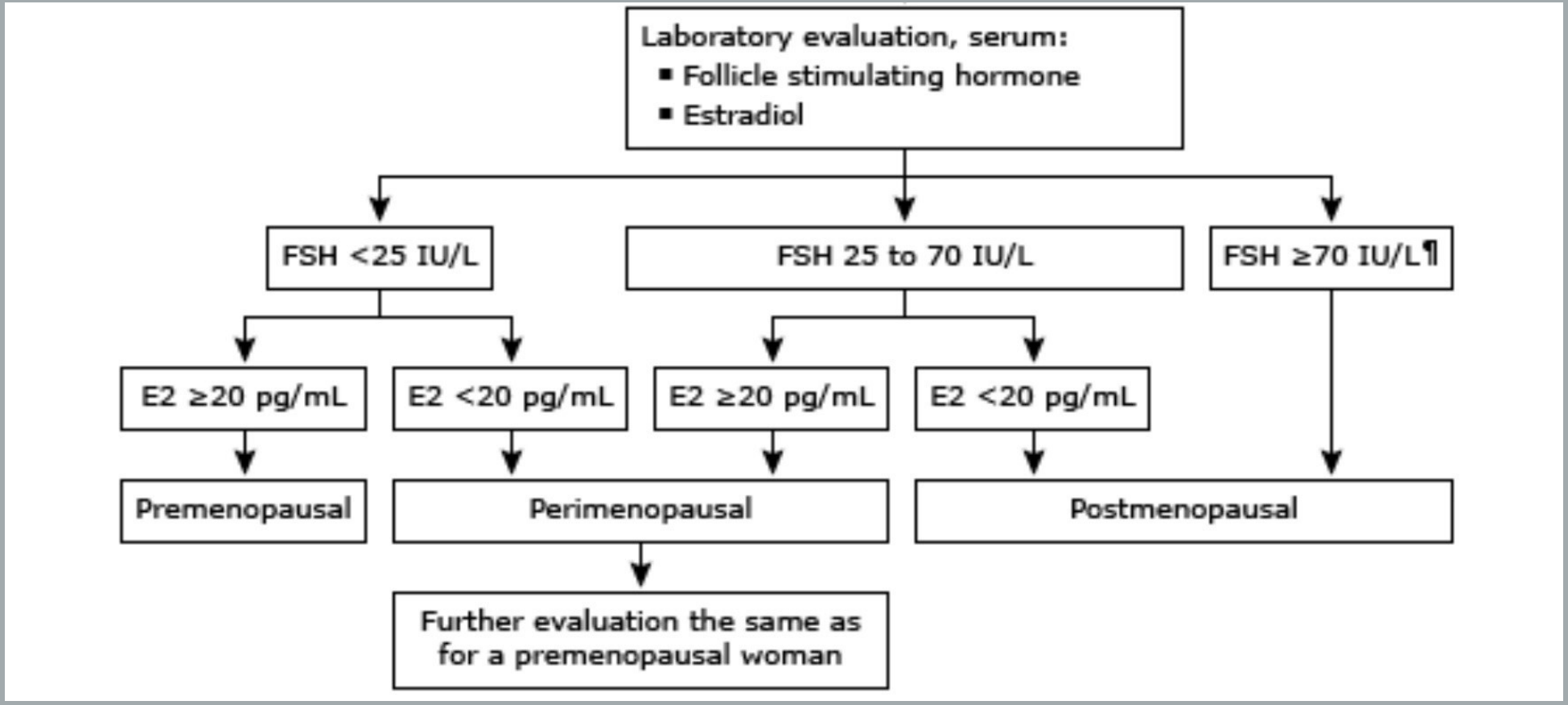
Harlow SD, et al. Menopause. 2012;19(4):387-395.

Special Clinical Situations

- Menstrual cycle is the principal criteria in STRAW
- Criteria cannot be applied if there is history of primary ovarian insufficiency (POI), irregular menstrual cycles, hysterectomy, or endometrial ablation
- Endocrine markers can be used to assess reproductive aging in those clinical situations
  - FSH
  - AFC
  - AMH
  - Inhibin B
  - Estradiol

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

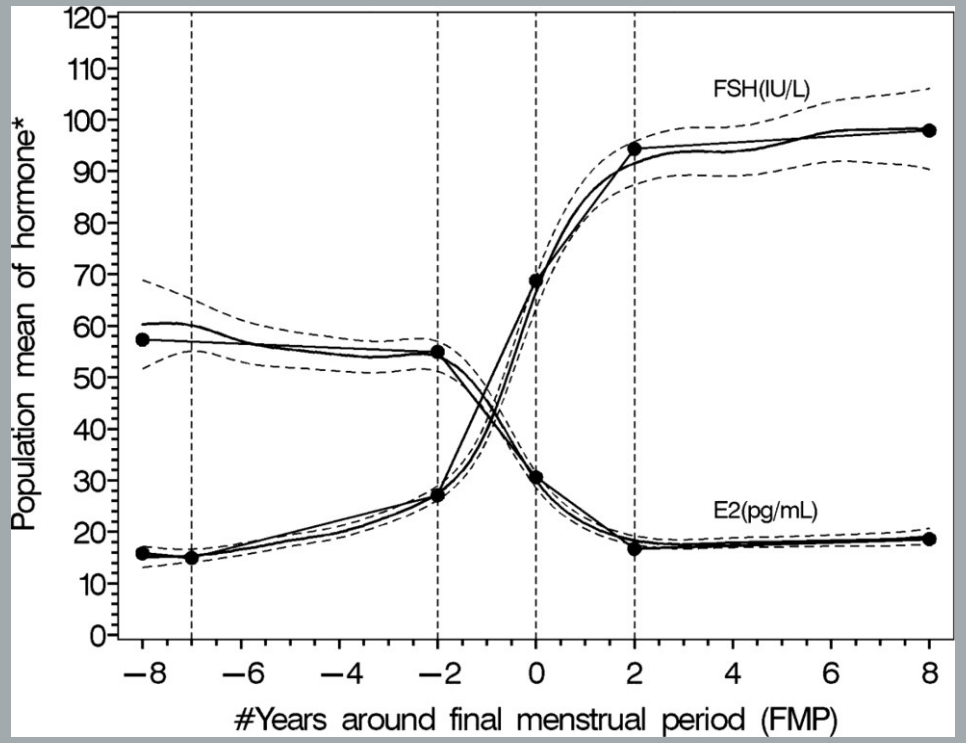
Menopausal Status Algorithm



Goldstein, S. R., Bakkum-Gamez, J. N. 2022). Abnormal uterine bleeding and uterine pathology in patients on tamoxifen therapy. In A. Chakrabarti (Ed), *UpToDate*. Available from https://www.uptodate.com/contents/abnormal-uterine-bleeding-and-uterine-pathology-in-patients-on-tamoxifen-therapy

Physiology of the Menopause Transition

- Changes in estradiol and FSH during the menopause transition (SWAN)



***The y axis is unitless. The units of hormone are marked in the corresponding curves.**

Burger HC, et al. *J Clin Endocrinol Metab*. 1999;84(11):4025-4030;
Harlow SD, et al. *Menopause*. 2012;19(4):387-395.
Figure reproduced with permission from Randolph JF Jr, et al. *J Clin Endocrinol Metab*. 2011;96(3):746-754.

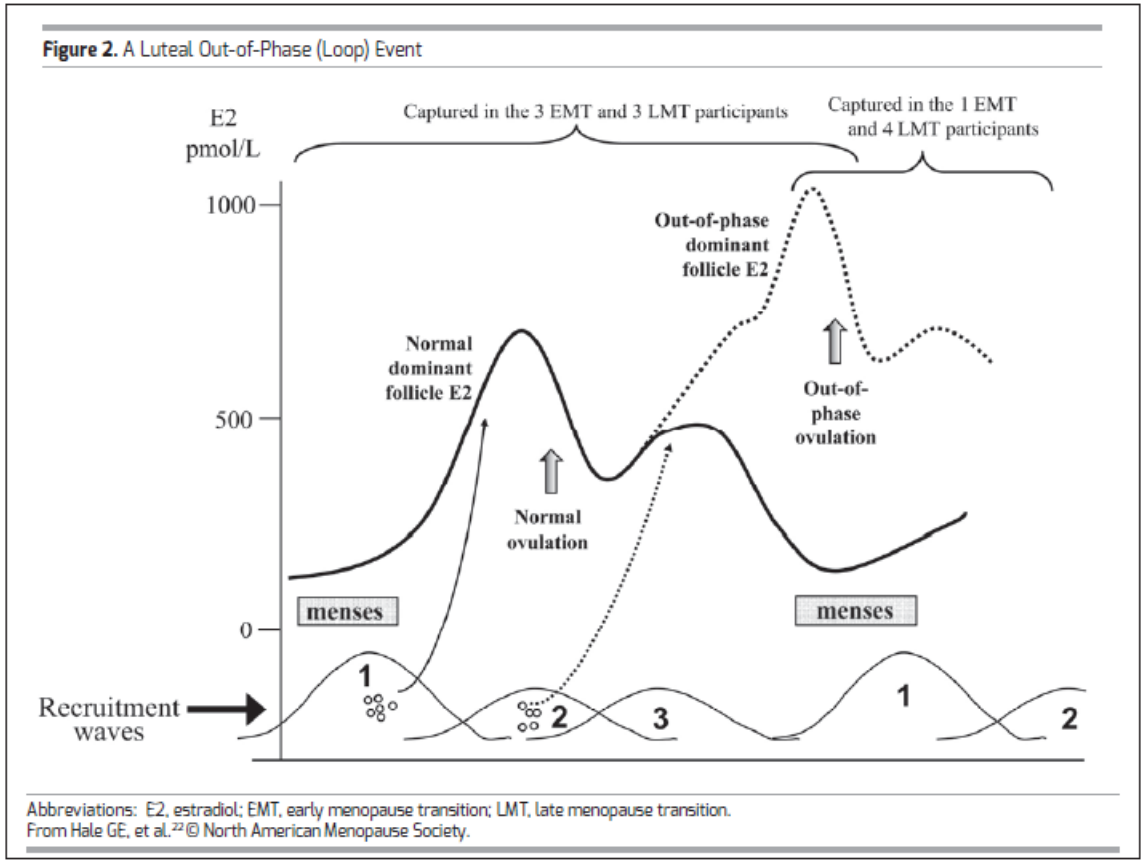
The Early Menopause Transition

- Decreasing ovarian reserve and reduced cohort of follicles; inhibin B and AMH drop
- Loss of inhibin restraint of FSH leads to
  - Monotropic rise in FSH
  - Faster growth of remaining follicles (short follicular phase)
  - Increase in atresia
  - Occasional LOOP cycles
- Common symptoms
  - Cycle irregularity by ≥7 days
  - Skipped menstrual cycles (because of ovulatory failure)
  - Pronounced premenstrual syndrome symptoms (because of longer luteal phase)

Harlow SD, et al. *Menopause*. 2012;19(4):387-395; Burger HG, et al. *Recent Prog Horm Res*. 2002;57: 257-275.

Perimenopause Elevations in Estrogen: The LOOP Phenomenon

- **LOOP: Luteal-Out-Of-Phase event**
  - Luteal phase FSH elevation recruits follicles for the subsequent cycle before the current cycle is over (second follicle during luteal phase of ongoing cycle)
  - Excess luteal estradiol production as new follicles start growing
  - Very short follicular phase
- LOOP cycles may explain common early perimenopause symptoms:
  - Mastalgia
  - Worsening migraine
  - Growing fibroids
  - Risk of endometrial hyperplasia



Hale GE, et al. *Menopause*. 2009;16(1):50-59; Hale GE, et al. *J Steroid Biochem Mol Biol*. 2014;142:121-131.

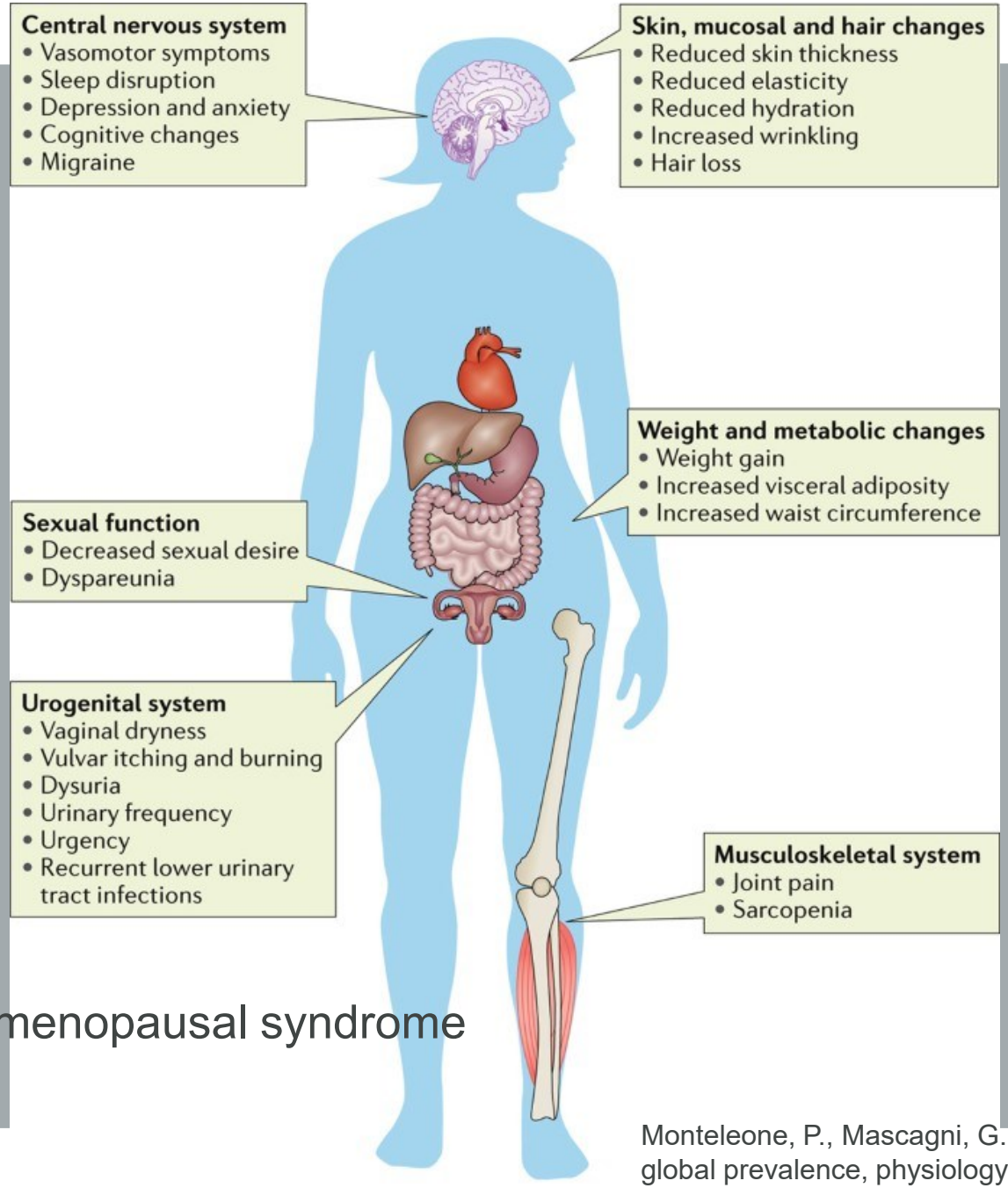
The Late Menopause Transition

- Number of remaining oocytes drops below a critical level, with sporadic follicular development
- Ovulation is more sporadic
- Rare follicular development results in poor rate of ovulation with low progesterone levels
- Eventually follicular development stops, resulting in estradiol deficiency
- Common symptoms
  - Amenorrhea >60 days
  - Estrogen deficiency symptoms such hot flashes and vaginal dryness

Santoro N, et al. *J Clin Endocrinol Metab*. 2008;93(5):1711-1721.

MENOPAUSE SIGNS AND SYMPTOMS

There is no one universal menopausal syndrome



Monteleone, P., Mascagni, G., Giannini, A. *et al.* Symptoms of menopause — global prevalence, physiology and implications. *Nat Rev Endocrinol* **14,** 199–215 (2018). https://doi.org/10.1038/nrendo.2017.180

Nature Reviews | Endocrinology

VASOMOTOR SYMPTOMS

Vasomotor Symptoms (VMS)

- Frequently termed *hot flashes (or flushes)* when occur during the day and *night sweats* when occur at night
- Characterized by sudden intense sensation of heat in the upper body, particularly the face, neck, and chest, that last 1-5 minutes
- Can be accompanied by perspiration, chills, anxiety, and occasionally, heart palpitations
- Number of episodes per day varies
- *VMS last for median of 7-10 years*

Kronenberg F. *Ann N Y Acad Sci*. 1990;592:52-86; Avis NE, et al. *JAMA Intern Med*. 2015;175(4):531-539; Freeman EW, et al. *Obstet Gynecol*. 2011;117(5):1094-1104.

Intensity of VMS

- Mild: sensation of heat without sweating
- Moderate: sensation of heat with sweating, able to continue activity
- Severe: sensation of heat with sweating, causing cessation of activity
- *Most intense and frequent in perimenopause and for first 1-2 years after the last menstrual period*

Gold EB, et al. *Am J Epidemiol*. 2000;152(5):463-473.

Prevalence of VMS

- Most commonly reported symptom of the menopause transition; affects 60%-80% of women at some point during menopause transition
- Varies by menopause phase
  - 21% reported VMS in premenopause
  - 41% reported VMS in perimenopause
  - 42% reported VMS in postmenopause
- Varies by racial/ethnic group
  - Black women > Hispanic women > White women > Chinese women > Japanese women

Gold EB, et al. *Am J Public Health*. 2005;96(7):1226-1235; Gold EB, et al. *Am J Epidemiol*. 2000;152(5):463-473; Thurston RC, et al. *Obstet Gynecol Clin North Am*. 2011;38(3):489-501; Freeman EW, et al. *Climacteric*. 2007;10(3):197-214.

Risk Factors for VMS

- Low socioeconomic position
- Low educational attainment
- Obesity (only in perimenopause)
- Tobacco/Nicotine use
- Hysterectomy/Oophorectomy

Gold EB, et al. *Am J Epidemiol*. 2000;152(5):463-473; Thurston RC, et al. *Obstet Gynecol Clin North Am*. 2011;38(3):489-501; Shobeirl F, et al. *J Menopausal Med*. 2016;22(1):78-85; Wilson LF, et al. *Maturitas*. 2016;91:1-7; Herber-Gast GC, et al. *Am J Clin Nutr*. 2013;97(5):1092-1099.

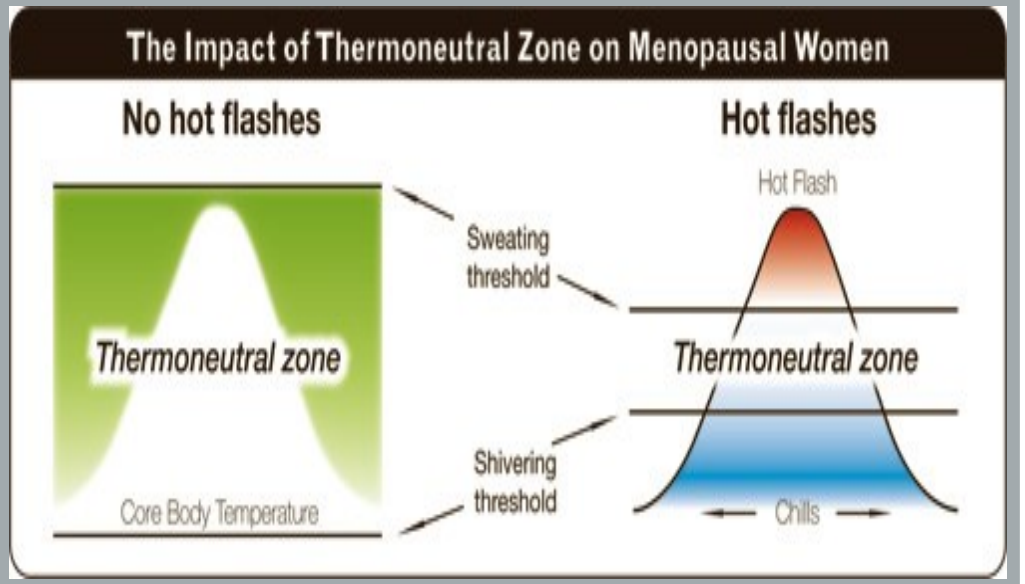
Health-Related Outcomes of VMS

- VMS are associated with
  - Sleep disturbance
  - Depressive symptoms
  - Cognitive function
- Evidence of link between VMS and CVD and poor bone health

Thurston RC, et al. *Obstet Gynecol Clin North Am*. 2011;38(3):489-501; Kravitz HM, et al. *Sleep*. 2008;31(7):979-990; Thurston RC, et al. *Circulation*. 2008;118(12):1234-1240; Gast GC, et al. *Menopause*. 2009;16(2):231-238; Crandall CJ, et al. *J Clin Endocrinol Metab*. 2015;100(2):524-534.

Physiology of VMS

- Not completely understood
- Likely involves complex interplay between central nervous system and peripheral physiologic processes
- Thermoregulatory center is altered after menopause by an increase in kisspeptin-neurokinin B-dynorphin (KNDy) neurons; activation of the neurokinin-3 receptor (NK3R) causes hot flashes; blockade of the NK3R reduces/eliminates them
- May also be affected by serotonin, epinephrine, and norepinephrine, as well as sympathetic and parasympathetic nerve activity



Skorupskaite K, et al. *Hum Reprod Update*. 2014;20(4):485-500; Prague JK, et al. *Lancet.* 2017;389(10081):1809-1820.

Nonprescription Therapies for VMS

- Cognitive-behavior therapy, clinical hypnosis, and stellate ganglion block have shown some efficacy in RCTs to be effective in reducing VMS
- S-equol derivatives of soy isoflavones may have some benefit, but evidence supporting use is mixed
- Behavior modifications to minimize symptoms (dressing in layers, avoiding triggers, cool ambient temperatures)

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.

WAVS (Women's Study for Alleviation of VMS)

- Postmenopausal women (n = 38) reporting two or more hot flashes/day were randomly assigned to a low-fat, vegan diet, including ½ cup (86 g) of cooked soybeans daily, or to no diet changes for 12 weeks.
- Total hot flashes decreased 79% in the intervention group and 49% in the control group.
- Moderate-to-severe hot flashes decreased 84% in the intervention group and 42% in the control group.
- From 0 to 12 weeks, 59% (10/17) of intervention-group participants reported becoming free of moderate and severe hot flashes. There was no change in this variable in the control group.

Barnard ND, Kahleova H, Holtz DN, Del Aguila F, Neola M, Crosby LM, Holubkov R. The Women's Study for the Alleviation of Vasomotor Symptoms (WAVS): a randomized, controlled trial of a plant-based diet and whole soybeans for postmenopausal women. Menopause. 2021 Jul 12;28(10):1150-1156.

Prescription Therapies for VMS

- Treatment based on the person's tolerance of symptoms, health history, risk factors, and personal preferences
- FDA-approved prescription treatments
  - Hormone therapy (gold standard/most effective, 75% ↓ VMS frequency)
  - Paroxetine
- Off-label prescription therapies
  - Selective serotonin reuptake inhibitors (SSRIs)
  - Serotonin-norepinephrine reuptake inhibitors (SNRIs)
  - Gabapentinoids
  - Clonidine
  - Oxybutynin

Carroll DG, et al. *Int J Womens Health*. 2015;7:615-624; Reddy SY, et al. *Obstet Gynecol*. 2006;108: 41-48; Rada G, et al. *Cochrane Database Syst Rev*. 2010;CD004923; Simon JA, et al. *Menopause*. 2016;23(11):1214-1

FDA Approved Indications for Hormone Therapy

1. First-line therapy for relief of vasomotor symptoms in appropriate candidates
2. To prevent bone loss and reduce fractures in postmenopausal women at elevated risk of osteoporosis or fractures
3. For women with hypogonadism, primary ovarian insufficiency, or premature surgical menopause without contraindication, hormone therapy is recommended for health benefits until the average age of menopause
4. Low-dose vaginal estrogen therapy is recommended first line for isolated genitourinary syndrome of menopause to treat symptoms of vulvovaginal atrophy

The 2017 hormone therapy position statement of The North American Menopause Society. *Menopause*. 2017;24(7):728-75

ET and EPT Hormone Therapy

- Categories of Menopausal Hormone Therapy
  - **Estrogen therapy (ET)**
    - Unopposed estrogen for postmenopausal women who have undergone hysterectomy or in low doses for women with vaginal symptoms regardless of presence of uterus
  - **Estrogen-progestogen therapy (EPT)**
    - For postmenopausal women with a uterus
    - Progestogen reduces the risk of endometrial adenocarcinoma because of unopposed estrogen
  - **Estrogen agonist/antagonist therapy**
    - For postmenopausal women with a uterus who prefer a progestogen-free option
    - Estrogen antagonist/agonist has a similar effect to progestogen on the uterine lining

Types of Estrogen Therapy

- **Conjugated equine estrogens (CEE)**
  - On the US market >65 years
  - The most used in RCTs
  - More is known about efficacy and safety than any other estrogen product
  - Approved for prevention of osteoporosis
- **Synthetic conjugated estrogens (CE)**
  - US government does not view as a generic equivalent to CEE; approved generic equivalent in Canada
  - Not approved for prevention of osteoporosis
- **Estradiol**
  - Most widely used estrogen in Europe
  - Only estrogen available in a government-approved, bioidentical formulation
  - Approved for prevention of osteoporosis

Types of Estrogen Therapy (cont)

- **Esterified estrogens**
  - Oral products of synthetic estrogen mixtures containing 75%-85% sodium estrone sulfate
  - Not indicated for osteoporosis
- **Estropipate**
  - Oral form of estrone sulfate that has been solubilized and stabilized by piperazine
  - Approved for prevention of osteoporosis
- **Ethinyl estradiol**
  - Widely used in combination contraceptives

Routes of ET Administration

- **Oral**
  - Most widely used form in North America
  - Because of first-pass uptake and metabolism in the gastrointestinal tract and the liver
    - Increase high-density lipoprotein cholesterol (HDL-C)
    - Associated with 25% increase in triglycerides
    - Increase in hepatic globulins, coagulation factors, and some inflammatory markers
    - Decrease in E-selectin, which may affect coronary artery disease

Shifren JL, et al. *J Clin Endocrinol Metab*. 2008;93(5):1702-1710; Goodman MP. *J Womens Health (Larchmt)*. 2012;21(2):161-169; Canonico M, et al. *Stroke*. 2016;47(7):1734-174; Laliberte F, et al. *Menopause*. 2011;18(10):1052-1059; Renoux C, et al. *BMJ*. 2010;340:c2519; Santen RJ. *Climacteric*. 2015;18:121-134; Suckling J, et al. *Cochrane Database Syst Rev*. 2006;CD001500.

Routes of ET Administration (cont)

- **Vaginal**
  - Cream, tablet, insert, and rings (low dose for local therapy and two higher doses for systemic therapy) available
  - Small amounts of estrogen administered locally are effective for treating vaginal atrophy
  - *Endometrial protection is not needed with local doses of estrogen*
  - Women with a uterus using one of the systemic rings need endometrial protection

Shifren JL, et al. *J Clin Endocrinol Metab*. 2008;93(5):1702-1710; Goodman MP. *J Womens Health (Larchmt)*. 2012;21(2):161-169; Canonico M, et al. *Stroke*. 2016;47(7):1734-174; Laliberte F, et al. *Menopause*. 2011;18(10):1052-1059; Renoux C, et al. *BMJ*. 2010;340:c2519; Santen RJ. *Climacteric*. 2015;18:121-134; Suckling J, et al. *Cochrane Database Syst Rev*. 2006;CD001500.

Routes of ET Administration (cont)

- **Transdermal/Topical**
  - Patch, gel, spray, and emulsion forms available
  - Not subjected to first-pass hepatic metabolism
  - Associated with more stable serum levels
  - Minimal effect on sex hormone-binding globulin; therefore, less of a negative effect on sexual functioning
  - Risk of skin-to-skin transfer of small amounts
  - *Some studies have shown increase in VTE and stroke with oral ET but not with transdermal*
  - Stroke and VTE events were comparable across oral, transdermal, and placebo groups in the Kronos Early Estrogen Prevention Study (KEEPS)

Shifren JL, et al. *J Clin Endocrinol Metab*. 2008;93(5):1702-1710; Goodman MP. *J Womens Health (Larchmt)*. 2012;21(2):161-169; Canonico M, et al. *Stroke*. 2016;47(7):1734-174; Laliberte F, et al. *Menopause*. 2011;18(10):1052-1059; Renoux C, et al. *BMJ*. 2010;340:c2519; Santen RJ. *Climacteric*. 2015;18:121-134; Suckling J, et al. *Cochrane Database Syst Rev*. 2006;CD001500.

Types of Progestogen Therapy

- **Micronized progesterone (MP)**
  - Compound identical to endogenous progesterone
  - Prometrium is the only FDA-approved bioidentical progestogen
  - Contraindicated in women with peanut allergy
  - Bedtime dosing advised because of sedating effects
- **Progestin**
  - *Synthetic* products with progesterone-like activity
  - Classified into two groups based on structure
  - Chemical structure similar to progesterone
    - Medroxyprogesterone acetate (MPA) is the most commonly used and studied in the United States for endometrial protection
  - Chemical structure similar to testosterone
    - More potent than those structurally similar to MP or progesterone

Schussler P, et al. *Psychoneuroendorinology*. 2008;33(8):1124-1131. Montplaisir J, et al. *Menopause*. 2001;8(1):10-16.

Methods of EPT Administration

Table 11. Estrogen-Progestogen Therapy Regimens, Terminology

Regimen	Estrogen	Progestogen
Continuous-cyclic (sequential)	Daily	12-14 d/mo
Continuous-cyclic (sequential) long cycle	Daily	14 d q 2-6 mo
Continuous-combined	Daily	Daily
Intermittent-combined (pulsed-progestogen; continuous pulsed)	Daily	Repeated cycles, 3 d on, 3 d off

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ET Combined With an Estrogen Agonist/Antagonist

- Tissue-selective estrogen complex (TSEC)
- Daily estrogen combined with a daily selective estrogen-receptor modulator (SERM)
- **Bazedoxifene**
  - Third-generation SERM
  - Estrogen agonist on bone
  - Estrogen antagonist on breast and endometrial tissue
  - Approved in Europe and Japan for treatment of osteoporosis
  - Bazedoxifene and CEE combination is available in the United States for treatment of VMS and prevention of osteoporosis
- Amenorrhea rates similar to placebo
- Safety profile comparable to placebo

Archer DF, et al. *Fertil Steril*. 2009;92(3):1039-1044. Pinkerton JV, et al. *Obstet Gynecol*. 2013;121(5):959-968. Pinkerton JV, et al. *J Clin Endocrinol Metab*. 2014;99(2):E189-E198. Pickar JH, et al. *Menopause*. 2018;25(9):1033-1045.

Alternative Progestogen Options

- Progestin-containing IUD and progesterone vaginal gel
- Potentially may provide endometrial cancer protection
- Long-term efficacy data is needed
  - Not FDA-approved for endometrial protection with ET

Warren MP, et al. *Am J Obstet Gynecol*. 1999;180(1 pt 1):42-48. Luo L, et al. *Cochrane Database Syst Rev*. 2018;12:CD009458.

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

Potential Adverse Events of HT

- Uterine bleeding (starting or returning)
- Breast tenderness (sometimes enlargement)
- Nausea
- Abdominal bloating
- Fluid retention in extremities
- Changes to the shape of the cornea (sometimes leading to contact lens intolerance)
- Headache (sometimes migraine)
- Dizziness
- Mood changes with EPT, particularly with progestin
- Angioedema
- Gallstones, pancreatitis

Timing of HT Initiation

- **Timing hypothesis**
  - 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.

Transitioning From Hormone Contraception to HT

- Individualization is required
- May continue contraception until typical age of menopause (52 years) or mid-50s, when women will likely reach menopause (90% by 55 years)
- Can transition from OCs to HT if still symptomatic
- As low-dose OCs have higher hormone levels than HT, hot flashes may reappear transiently

Curtis KM, et al. *MMWR Recomm Rep*. 2016;65(4):1-66; Kaunitz AM. *N Engl J Med*. 2008;358(12): 1262-1

Determining CVD Risk

- **EPIC .ASCVD**
  - Consider checking lipids on all patients before starting MHT (especially with oral estrogen)
- **Low (<5%)** 10-year CVD risk and less than 10 years since menopause: patient appears to be a *candidate for either oral or transdermal therapy*
- **Moderate (5-10%)** 10-year CVD risk and less than 10 years since menopause: patient should *avoid oral estrogen, but transdermal estrogen may be an option* because it has a less adverse effect on clotting factors, triglyceride levels, and inflammation factors than oral estrogen
  - Women with obesity, diabetes, or metabolic syndrome, if otherwise considered candidates for HT, may do better with transdermal than oral estrogen
- **High (>10%)** 10-year CVD risk: patient should *avoid initiation of systemic hormone therapy*
  - Women >10 years past menopause also are not good candidates for starting (first use of) systemic HT

https://www.menopause.org/docs/default-source/2014/menopro-app-algorithm-2014.pdf

Monitoring HT

- Annual return visits
  - More frequent visits for new starts or those with AEs
- Annual mammogram
- Endometrial sampling is not required unless postmenopausal bleeding develops
- Clinical goal
  - ***Use the appropriate HT dose, duration, regimen, and route of administration***
  - Periodic reevaluation

Stopping Systemic HT

- Decision should be individualized on the basis of severity of symptoms and risk-benefit ratio considerations
- *No general rule for stopping at age 65*
- Can consider continuation beyond age 65 years for persistent VMS, QOL issues, or prevention of osteoporosis after appropriate evaluation and counseling of benefits and risks
  - Annual reevaluation, including reviewing comorbidities and periodic trials of lowering or discontinuing HT or changing to potentially safer low-dose transdermal routes, should be considered
- Approximately 50% of women will experience recurrence of symptoms with discontinuation, independent of age and duration of use
- Low-dose, local ET may be continued as long as vaginal symptoms are present

The 2017 hormone therapy position statement of The North American Menopause Society. *Menopause*. 2017;24(7):728-753.
Ockene JK, et al. *JAMA*. 2005;294(2):183-193.

Bioidentical Hormone Therapy

- Hormones that are chemically identical to the hormones produced by the ovaries during the reproductive years
- The term also is used for *custom-compounded* HT by compounding pharmacies
  - These products are not FDA approved
- *Bioidentical hormone therapy* is a marketing term not recognized by FDA
- **Several FDA-approved bioidentical hormone preparations on the market (eg, estradiol pills, patches, gels, sprays, vaginal ring) and oral micronized progesterone**

Bio-identicals: Sorting Myths From Facts [FDA Consumer Update]. January 9, 2008. Simon JA, et al. Proceedings from the Postgraduate Course presented prior to the 17th Annual Meeting of The North American Menopause Society. Nashville, TN: October 11, 2006.

Pros and Cons of Custom-Compounded HT Formulations

- Pros
  - Allows individualized dosing and combinations of therapy
  - Allows for different modes of administration: subdermal implants, subliquinal tablets, rectal suppositories, nasal sprays
  - Products can be prepared without binders, fillers, dyes, preservatives, or adhesives

Rosenthal MS. *Menopause*. 2008;15(5):1014-1022. Cirigliano M. *J Womens Health (Larchmt)*. 2007;16(5):600-631. Bhavnani BR, et al. *J Clin Endocrinol Metab*. 2012;72(16):2043-2050. US Food and Drug Administration. FDA Takes Action Against Compounded Menopause Hormone Therapy Drugs. January 10, 2008. Gaudard AM, et al. *Cochrane Database Syst Rev*.

Pros and Cons of Custom-Compounded HT Formulations (cont)

- Cons
  - Do not have to undergo FDA approval
  - Not FDA regulated
    - Do not require proof of claim and are not held to same standard of manufacture
  - Often not covered by third-party payers
  - Not found to be safer than FDA-approved formulations in clinical trials
    - May even have harms associated with unknown pharmacokinetics
  - Lack of evidence of efficacy superior to FDA-approved products
  - Concerns about purity and potency
  - Lack of monitoring of AEs

Rosenthal MS. *Menopause*. 2008;15(5):1014-1022. Cirigliano M. *J Womens Health (Larchmt)*. 2007;16(5):600-631. Bhavnani BR, et al. *J Clin Endocrinol Metab*. 2012;72(16):2043-2050. US Food and Drug Administration. FDA Takes Action Against Compounded Menopause Hormone Therapy Drugs. January 10, 2008. Gaudard AM, et al. *Cochrane Database Syst Rev*. 2016;(8):CD010407.

Bioidenticals: 2020 NASEM Recommendations

- In July 2020 the National Academy of Sciences, Engineering, and Medicine (NASEM) issued a report that assessed the clinical utility of compounded bioidentical hormone therapy (cBHT). Recommendations included:
  - **Restricting the use of cBHT to certain situations, such as to people with allergies, unavailable doses in FDA-approved products, or testosterone for women with sexual dysfunction**
  - Improved education for prescribers and pharmacists who market, prescribe, compound, and dispense cBHT preparations
  - Expanding and improving oversight and review of compounding pharmacies
  - Collecting and disclosing information on conflicts of interest
  - The evidence base on the safety, effectiveness, and use of cBHT preparations should be strengthened and expanded
  - Patient preference is not reason alone to use these products

National Academies of Sciences, Engineering, and Medicine. *The Clinical Utility of Compounded Bioidentical Hormone Therapy: A Review of Safety, Effectiveness, and Use*. Washington, DC: The National Academies Press; 2020.

The Experts Agree About Hormone Therapy

- **Benefits are likely to outweigh risks for symptomatic women who initiate hormone therapy aged younger than 60 years or within 10 years of menopause onset (Level I)**
- **For women who initiate hormone therapy more than 10 or 20 years from menopause onset or aged 60 years and older, the benefit-risk ratio appears less favorable than for younger women**
  - Greater absolute risks: coronary heart disease, stroke, venous thromboembolism, and dementia

The 2017 hormone therapy position statement of The North American Menopause Society. *Menopause*. 2017;24(7):728-

Initiation Estrogen Doses

- Depending on severity of symptoms:
  - 0.025-0.05 mg TDE2
  - 0.3-0.625 mg CEE
  - 0.5-1 mg E2 oral
- Premature and early menopause:
  - 0.1 mg TDE2
  - 1.25 mg CEE
  - 2 mg (1 mg 2x/day) oral E2 (half life 16 hours)
  - COC or hormonal contraception doses
- See patient back in 1-3 months and adjust dose as needed until stable symptoms

MHT Reference Tables

Table 6. Oral Estrogen Therapy Products for Postmenopause Use in the United States and Canada

Composition	Product name	Dosages, mg/d
Conjugated estrogen	Premarin	0.3, 0.45,[a] 0.625, 0.9,[a] 1.25
Synthetic conjugated estrogen[a]	Cenestin[a]	0.3. 0.45, 0.625, 0.9, 1.25
	Congest[b]	0.3, 0.625, 0.9, 1.25, 2.5
	C.E.S.[b]	0.3, 0.625, 0.9, 1.25
	PMS-Conjugated[b]	0.3, 0.625, 0.9, 1.25
Synthetic conjugated estrogen[b]	Enjuvia[a]	0.3, 0.45, 0.625, 0.9, 1.25
Esterified estrogen	Menest[a]	0.3, 0.625, 1.25, 2.5
17β-estradiol	Estrace, various generics Gynodiol, Innofem	0.5, 1.0, 2.0
Estradiol acetate	Femtrace[a]	0.45, 0.9, 1.8
Estropipate	Ortho-Est[a]	0.625 (0.75 estropipate), 1.25 (1.5), 2.5 (3.0), 5.0 (6.0)
	Ogen	0.625 (0.75), 1.25 (1.5), 2.5 (3.0)
	Various generics	0.625 (0.75), 1.5 (3.0), 5.0 (6.0)

Estradiol-containing products are considered bioidentical.
Products not noted are available in the United States and in Canada.
[a]Available in the United States but not Canada.
[b]Available in Canada but not the United States.

Table 7. Transdermal Estrogen Therapy Products for Postmenopause Use in the United States and Canada

Composition	Product name	Dosage, mg
17β-estradiol matrix patch	Alora[a]	0.025, 0.05, 0.075, 0.1 twice/wk
	Climar[a]	0.025, 0.0375,[a] 0.05, 0.075, 0.1 once/wk
	Esclim[a]	0.025, 0.0375, 0.05, 0.075, 0.1 twice/wk
	Estradot[b]	0.025, 0.0375, 0.05, 0.075, 0.1 twice/wk
	Fempatch	0.025 once/wk
	Menostar[a]	0.014 once/wk
	Minivelle	0.025, 0.0375, 0.05, 0.075, 0.1 twice/wk
	Oesclim[b]	0.05, 0.1 twice/wk
	Vivelle[a]	0.025, 0.0375, 0.05, 0.075, 0.1 twice/wk
	Vivelle-Dot[a]	0.025, 0.0375, 0.05, 0.075, 0.1 twice/wk
	Various generics	0.1, 0.05 once or twice/wk
17β-estradiol reservoir patch	Estraderm	0.025,[b] 0.05,[a] 0.1 twice/wk
17β-estradiol transdermal gel	EstroGel,[a] Estrogel[b]	0.035/d
	Elestrin[a]	0.0125/d
	Divigel[a]	0.25, 0.5, and 1.0 g/d
17β-estradiol topical emulsion	Estrasorb[a]	0.05/d (2 packets)
17β-estradiol topical emulsion (estradiol hemihydrate 2.5 mg/g)		
17β-estradiol transdermal spray	Evamist[a]	0.021/90 μL/d (increase to 1.5/90 μL/d if needed)

Estradiol-containing products are considered bioidentical.
Products not noted are available in the United States and in Canada.
[a]Available in the United States but not Canada.
[b]Available in Canada but not the United States.

Vaginal rings		
17β-estradiol	Estring	Device containing 2 mg releases 7.5 μg/d for 90 d (for GSM).
Estradiol acetate	Femring[b]	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 GSM and VMS. (Progestogen recommended.)

Table 10. Combination Estrogen-Progestogen Therapy Products for Postmenopause Use in the United States and Canada

Composition	Product name	Dosage, mg/d
Oral continuous-cyclic regimen		
CE (E) + MPA (P)	Premphase[a]	0.625 mg E + 5.0 mg P (2 tablets: E and E + P) (E alone for days 1-14, followed by E + P on days 15-28)
Oral continuous-combined regimen		
17 β-estradiol (E) + progesterone	Bijuva	1 mg E + 100 mg P
CE (E) + MPA (P)	Prempro[a]	0.625 mg E + 2.5 or 5.0 mg P (1 tablet); 0.3 or 0.45 mg E + 1.5 mg P (1 tablet)
Ethinyl estradiol (E) + NETA (P)	Femhrt,[a] femHRT[b]	2.5 µg E + 0.5 mg P (1 tablet); 5 µg E + 1 mg P (1 tablet)
17β-estradiol (E) + NETA (P)	Activella[a]	0.5 mg E + 0.1 mg P (1 tablet); 1 mg E + 0.5 mg P (1 tablet)
	Activelle LD[b]	0.5 mg E + 0.1 mg P (1 tablet)
	Activelle[b]	1 mg E + 0.5 mg P (1 tablet)
17β-estradiol (E) + drospirenone (P)	Angeliq	0.5 mg E + 0.25 mg P (1 tablet)[a]; 1 mg E + 0.5 mg P (1 tablet)[b]
Oral intermittent-combined regimen		
17β-estradiol (E) + norgestimate (P)	Prefest[a]	1 mg E + 0.09 mg P (2 tablets: E and E + P) (E alone for 3 d, followed by E+P for 3 d, repeated continuously)
Transdermal continuous-combined regimen		
17β-estradiol (E) + NETA (P)	CombiPatch,[a] Estalis[b]	0.05 mg E + 0.14 mg P (9 cm2 patch, twice/wk); 0.05 mg E + 0.25 mg P (16 cm^2 patch, twice/wk)
17β-estradiol (E) + LNG (P)	Climara Pro	0.045 mg E + 0.015 mg P (22 cm^2 patch, once/wk)

Products not noted are available in the United States and in Canada.
Abbreviations: CE, conjugated estrogens; LNG, levonorgestrel; MPA, medroxyprogesterone acetate; NETA, norethindrone acetate.
[a]Available in the United States but not Canada.
[b]Available in Canada but not the United States.

Table 9. Progestogens Available in the United States and Canada

Composition	Product name	Dosage/d
Oral tablet: progestin		
MPA	Provera, various generics	2.5 mg, 5 mg, 10 mg
Norethindrone	Micronor,[a] Nor-QD,[a,b] various generics	0.35 mg
NETA	Aygestin,[a,b] various generics	5 mg
Megestrol acetate	Megace,[a] various generics	20 mg,[b] 40 mg, 40-mg suspension
Oral capsule: progesterone		
Micronized progesterone (in peanut oil)	Prometrium, generic	100 mg, 200 mg[b]
Intrauterine system: progestin		
Levonorgestrel	Mirena[a]	20 µg/d approx release rate (52 mg has 5-y use)
	Skyla	6 µg /d release rate (13.5 mg has 3-y use)
		Liletta: 19.5 µg /d release rate; 17 µg /d at 1 y (52 mg has 5-y use)
		Kyleena: 17.5 µg/d release rate (19.5 µg has 5-y use)
Vaginal gel		
Progesterone	Crinone[a] 4%,[b] 8%	45- or 90-mg applicator
Vaginal tablet		
Progesterone	Endometrin[a]	100 mg

Progesterone-containing products are considered bioidentical.
Abbreviations: MPA, medroxyprogesterone acetate; NETA, norethindrone acetate.
[a]Not approved by FDA for hormone therapy.
[b]Available in the United States but not Canada.

Table 12. Minimum Progestogen Dosing Requirements for Endometrial Protection With Standard Estrogen Dosing

	Continuous-cyclic EPT (daily, 12-14 d/mo)	Continuous-combined EPT (daily)
Oral tablets		
Medroxyprogesterone acetate	5 mg	2.5 mg
Norethindrone	0.35 mg-0.7 mg	0.35 mg
Norethindrone acetate	2.5 mg	0.5 mg-1 mg
Micronized progesterone	200 mg	100 mg
Intrauterine system		
Levonorgestrel[a]	—	20 µg/d or 6 µg /d
Vaginal		
Progesterone gel[a]	45 mg	45 mg

Progesterone-containing products are considered bioidentical.
Standard estrogen dosing is 0.625 mg conjugated estrogens, 1 mg oral estradiol, 0.05 mg patch, or the equivalent.
Abbreviations: EPT, estrogen-progestogen therapy; ET, estrogen therapy.
[a]Not FDA approved for endometrial protection with ET.

Non-hormonal Prescription Therapies

- Herbal alternatives are comparable to placebo for treatment of VMS (30% ↓)
- Gabapentin (~45-71% ↓ VMS)
  - Start with 300 mg at night, up titrate to recommended dose of 300 mg TID
  - Drowsiness should improve after 2 to 3 weeks
- Paroxetine 7.5 mg/d (~60% ↓ VMS) *Only FDA-approved nonhormone option for VMS tx
- Venlafaxine 75 mg/d (~61% ↓ VMS)
- Fluoxetine 20 mg/d (~50% ↓ VMS)
- ER oxybutynin 15 mg/d (~73% ↓ VMS)
- Clonidine 0.1 mg/d (~46% ↓ VMS)
  - Not as effective as other options and associated with AEs

Sideras K, Loprinzi CL. Nonhormonal management of hot flashes for women on risk reduction therapy. *J Natl Compr Canc N* 2010;8(10):1171-1179.

GENITOURINARY SYNDROME OF MENOPAUSE

Genitourinary Syndrome of Menopause

- A collection of signs and symptoms associated with estrogen deficiency that can involve changes to the labia, introitus, vagina, clitoris, bladder, and urethra that must be bothersome to the woman and are not caused by another diagnosis
- Vulvovaginal atrophy (VVA) is a component of genitourinary syndrome of menopause (GSM)
- *A chronic and progressive condition*
- Symptoms are unlikely to improve without treatment

Portman DJ, et al. *Menopause*. 2014;21(10):1063-1068; Mac Bride MB, et al . *Mayo Clin Proc.* 2010;85(1):87-94; The NAMS 2020 Genitourinary Syndrome of Menopause Position Statement Editorial Panel. *Menopause.* 2020;27(9):976-992.

Signs and Symptoms of GSM

- Loss of elasticity
- Shortening of the vaginal vault
- Narrowing of the introitus
- Loss of vaginal rugae
- Diminished blood flow
- Thinning of vaginal tissue

- Mucosal abnormalities
  - Petechiae, pallor, microfissures
  - Dryness
  - Irritation
  - Burning
  - Soreness
  - Tightness
  - Frequent/Recurrent UTIs
  - Lack of moisture with sexual activity
  - Dyspareunia

Portman DJ, et al. *Menopause*. 2014;21(10):1063-1068; The NAMS 2020 Genitourinary Syndrome of Menopause Position Statement Editorial Panel. *Menopause.* 2020;27(9):976-992.

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. *Menopaus* 2020;27(9):976-992.

Prevalence of GSM

- More than 50 million US women aged older than 52 years
- 20%-84% of menopausal women are affected by VVA
- Approximately half of sexually active menopausal women experience bothersome symptoms of GSM/VVA
- Menopausal women with sexual dysfunction are four times more likely to have VVA symptoms
- Most bothersome symptoms are vaginal dryness and dyspareunia
- Negatively affects sexual intimacy and quality of life

Gold EB, et al. *Am J Epidemiol.* 2000;152(5):463-473; Santoro N, et al. *J Sex Med*. 2009;6(8):2133-2142; Palma F, et al. *Maturitas*. 2016;83:40-44; Simon JA, et al. *Menopause*. 2013;20(10):1043-1048; Levine KB, et al. *Menopause*. 2008;15(4):661-666; The NAMS 2020 Genitourinary Syndrome of Menopause Position Statement Editorial Panel.

Treatments for GSM: Nonhormone Therapies

- Vulvovaginal moisturizers
- Vulvovaginal lubricants
- Pelvic floor physical therapy (PFPT)
- Vaginal dilators
- Regular vulvovaginal stimulation
- Penetrative sexual activity
- Topical lidocaine
- Fractional laser

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

Treatments for GSM: Lubricants and Moisturizers

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

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Treatments for GSM: Vaginal and Pelvic Floor Activity

- Regular stimulation of the vulva and vagina promote blood flow to the genital area and natural secretions may help maintain vaginal health
- Penetrative sexual activity, with or without a partner, may help to maintain vaginal width, length, and tone
- Severe GSM may require PFPT and vaginal dilators to treat provoked pelvic floor hypertonus in combination with pharmacologic interventions to treat atrophic epithelial changes for optimal outcomes

Yang EJ, et al. *Gynecol Oncol*. 2012;125(3):705-711; The NAMS 2020 Genitourinary Syndrome of Menopause Position Statement Editorial Panel. *Menopause.* 2020;27(9):976-992.

Treatments for GSM: Fractional CO_2 Laser

- Laser therapy for the treatment of GSM, vaginal laxity, and incontinence remains controversial
  - Currently not FDA approved for the treatment of GSM
- Several small open-label studies have shown efficacy of fractional CO_2 laser treatments for GSM with three treatments spaced 6 weeks apart
- Vaginal symptom and sexual function scores increased significantly at 3 months; some note continued symptom improvement at 1 year
- Trials comparing laser therapy to low-dose vaginal estrogen therapy (ET) are ongoing
- Results of randomized, blinded, sham-controlled trial of laser therapy for GSM are needed before widespread use of this very costly technology with unknown long-term effects

Hutchinson-Colas J, et al. *Maturitas*. 2015;82(4):342-345; Sokol ER, et al. *Menopause*. 2016;23(10):1102-1107;Sokol ER, et al. *Menopause*. 2017;24(7):810-814; The NAMS 2020 Genitourinary Syndrome of Menopause Position Statement Editorial Panel. *Menopause.* 2020;27(9):976-992.

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)

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Government-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	17B-estradiol 0.01% (0.1 mg active ingredient/g)	Estrace vaginal cream[a]	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
	Estrone 0.1% (1 mg active ingredient/g)	Estragyn vaginal cream[b]		0.5-4 g/d, intended for short-term use; progestogen recommended	Variable
Vaginal inserts	17B-estradiol inserts	Imvexxy[a]	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[a]	60 mg/d	1 tablet by mouth/d	N/A

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

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

Hormone Treatments: Low-dose Vaginal Estrogen

- Low-dose vaginal/local estrogen
  - Restores vaginal blood flow, decreases vaginal pH, improves thickness and elasticity of vulvovaginal tissues
- Many different formulations: vaginal ring, tablets, inserts, creams
- Improvements occur within a few weeks, with full efficacy in 2-3 months
- Serum levels typically in postmenopause range
- Large observational studies show no increased risk of endometrial cancer, breast cancer, or CVD
- Addition of a progestogen generally is not indicated
- Women who are obese at increased risk for endometrial cancer; endometrial surveillance or intermittent progestogen withdrawal might be considered
- ***Any vaginal bleeding should be evaluated***

Rahn DD, et al. *Obstet Gynecol*. 2014;124(6):1147-1156; Handa VL, et al. *Obstet Gynecol*. 1994;84(2): 215-218; Santen RJ. *Climacteric*. 2015;18(2):121-134; Crandall C, et al. *Menopause*. 2018;25(1):11-20; The NAMS 2020 Genitourinary Syndrome of Menopause Position Statement Editorial Panel. *Menopause*. 2020;27(9):976-992.

Hormone Treatments: Dehydroepiandrosterone

- 0.5%/6.5 mg DHEA vaginal suppository
- Indication: FDA approved for moderate to severe dyspareunia secondary to VVA
- Directions: inserted once daily at bedtime
- Phase 3 RCT showed significantly improved
  - Vaginal maturation index (VMI)
  - Vaginal pH
  - Signs of atrophy
  - Vaginal dryness
  - Dyspareunia
- Serum steroid levels remained within the normal postmenopause range
- Only adverse event (AE): vaginal discharge because of melting of the vehicle
- Safety: endometrial safety confirmed at 1 year

Labrie F, et al. *Menopause*. 2016;23(3):243-256; Portman DJ, et al. *Menopause*. 2015;22(12):1289-1295; The NAMS 2020 Genitourinary Syndrome of Menopause Position Statement Editorial Panel. *Menopause.* 2020;27(9):976-992.

Hormone Treatments: Ospemifene

- Oral selective estrogen receptor modulator: estrogen agonist/antagonist
- Indication: FDA approved for moderate to severe dyspareunia associated with VVA
- Directions: daily oral administration (60 mg)
- Improves
  - VMI
  - Vaginal pH
  - Symptoms of VVA
- Safety
  - No endometrial hyperplasia or cancer (at 52 weeks)
  - Can increase VMS
  - May increase the risk of venous thromboembolism (VTE)
- Antiestrogenic effects on breast but not approved for women with breast cancer
- Favorable effects on bone

Portman DJ, et al. *Menopause*. 2013;20(6):623-630; Bachmann GA, et al. *Menopause*. 2010;17(3):480-486; Simon J, et al. *Maturitas*. 2014;77(3):274-281; Soe LH, et al. *Int J Womens Health*. 2013;5:605-611; The NAMS 2020 Genitourinary Syndrome of Menopause Position Statement Editorial Panel. *Menopause.* 2020;27(9):976-992.

Clinical Decision Making

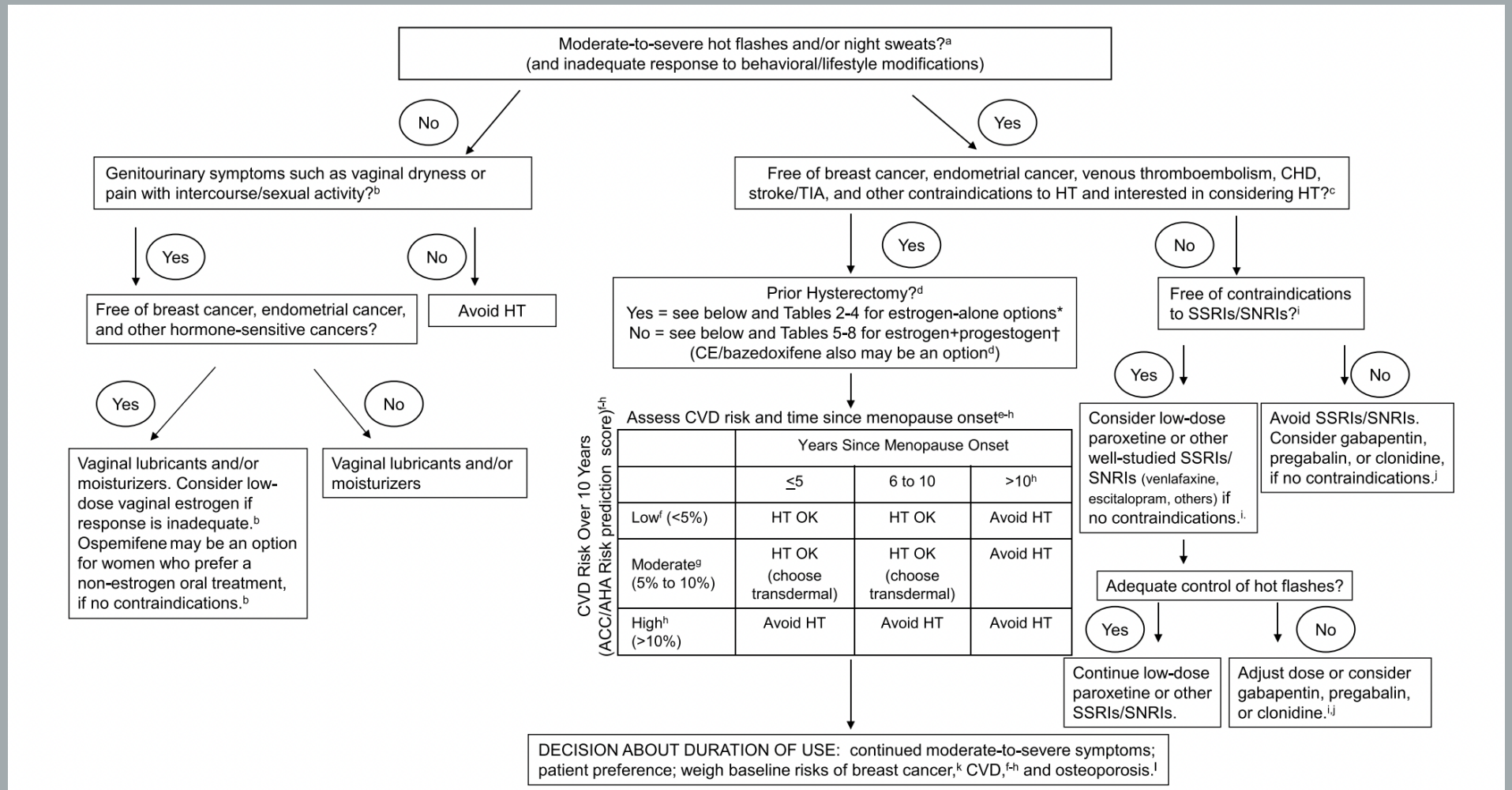

FIG. 1. Algorithm for menopausal symptom management and hormonal/non-hormonal therapy decision making. Algorithm footnotes appear at the end of the article.

https://www.menopause.org/docs/default-source/2014/menopro-app-algorithm-2014.pdf

Patient Education

MenoNotes

- Free information sheets written by menopause experts that provide clear, easy-to-understand explanations of important menopause-related topics
  - Menstrual Calendar
  - Depression
  - Hormone Therapy
  - Sleep Problems
  - Vaginal dryness
  - Bioidentical hormone therapy
  - Hot flashes

http://www.menopause.org/publications/consumer-publications/-i-menonotes-i-

Thank You

Questions?

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Authorized use of the NAMS Menopause A to Z Slide Set was utilized for portions of this presentation