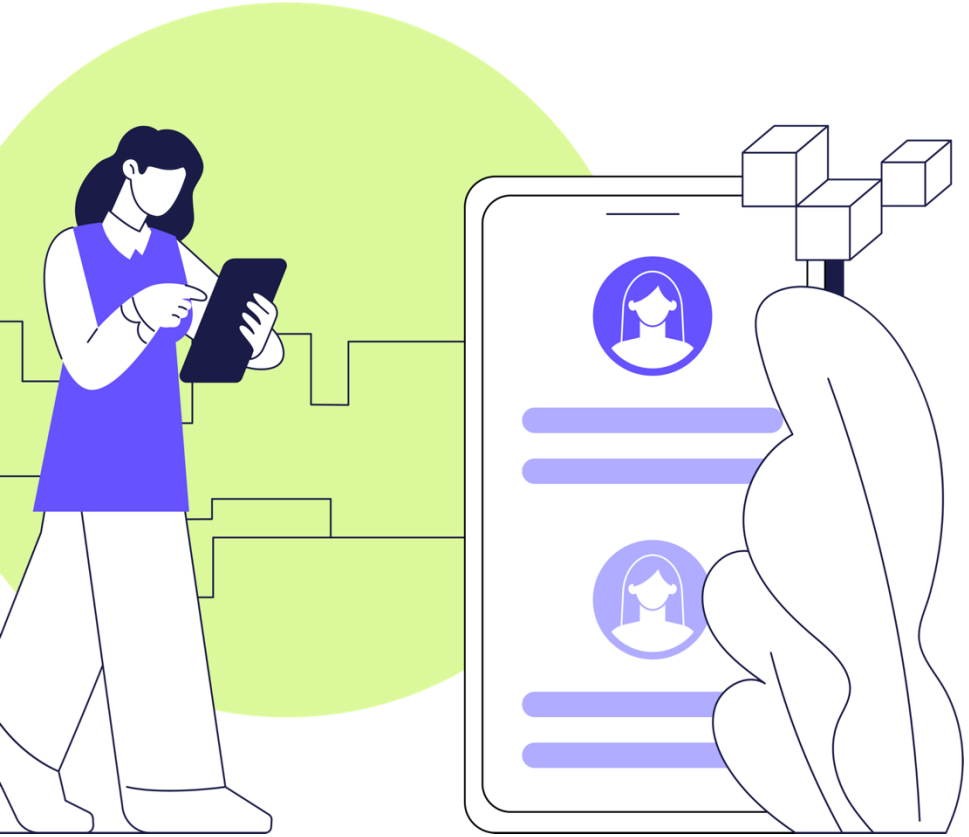
Menopause A–Z

The Menopause Society™

Acknowledgments

The Menopause Society is grateful to Mayne Pharma for the unrestricted grant funding for development of this slide set. The company had no input into the slide content.

Contents



SECTION 1

Menopause Basics

5. Menopause Demographics
6. Definitions and Terminology
7. Primary Ovarian Insufficiency, Premature Menopause, and Early Menopause

The Menopause Society™

Menopause Demographics

Menopause

- A normal, natural event, 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.
- Normally occurs between the ages of 40 and 58 years.

Women worldwide are living longer

- Many women will spend nearly 40% of their lives in postmenopause.
- More than 60% survive at least until aged 80 years.

Arias E, et al. United States Life Tables, 2015. *Nat Vital Stat Rep* 2018;67:1-64.

Definitions and Terminology

Natural menopause	Permanent cessation of menses for 12 months from loss of ovarian follicular activity.[a]
Induced menopause	Surgical or iatrogenic loss of ovarian function (eg, bilateral oophorectomy, chemotherapy, pelvic radiation, other forms of ovarian toxicity).
Primary ovarian insufficiency	Loss of normal ovarian function before age 40 y, resulting in irregular menstrual cycles and reduced fertility.
Premature menopause	FMP before age 40 y.
Early menopause	FMP before age 45 y.
Late menopause	FMP after the age 55 y.
Perimenopause/Menopause transition/Climacteric	The time frame “around menopause” marked by intermenstrual cycle irregularities or other menopause-related symptoms (hot flashes, sleep problems, vaginal dryness); ends after 1 y of amenorrhea.
Postmenopause	Stage of life after FMP.

[a]Assessed by symptoms or measurement of endocrine markers in those without a uterus, using hormone contraceptives, or with history of uterine ablation.

Crandall CJ, et al, eds. *Menopause Practice: A Clinician’s Gui*de, 6th ed. The North American Menopause Society; 2019.

Primary Ovarian Insufficiency, Premature Menopause, and Early Menopause

Primary ovarian insufficiency (POI)

- Characterized by hypergonadotropic hypogonadism that can be transient.
- Affects 1% of women aged younger than 40 years.

Premature menopause

- Permanent ovarian failure.

Early menopause

- Occurs between the ages of 40 and 45 years in approximately 3% of the population.

Etiology of POI, premature menopause, and early menopause

- Most cases are idiopathic; however, other etiologies include genetic, autoimmune, iatrogenic, infectious, and metabolic.

European Society for Human Reproduction and Embryology (ESHRE) Guideline Group on POI, et al. *Hum Reprod* 2016;31:926-937. doi: 10.1093/humrep/dew027

SECTION 2

Menopause Stages and Physiology

The Menopause Society™

Stages of Reproductive Aging

Chronologic aging

- Natural process of physiologic deterioration that is genetically determined and environmentally modifiable.

Reproductive aging

- Progressive loss of oocytes by ovulation and atresia.
  - Not correlated with chronologic aging.
  - Ovaries contain a finite number of oocytes during fetal development.
    - At 20 weeks' gestation: 6 to 7 million oocytes.
    - At birth: 1 to 2 million oocytes.
    - At puberty: 300,000 to 500,000 oocytes.
    - At menopause: 300 to 400 oocytes, most of which are incompetent

Harlow SD, et al. *Menopause* 2012;19:387-395. doi: 10.1097/gme.0b013e31824d8f40; Soules MR, et al. *Menopause* 2001;8:402-407. doi: 10.1097/00042192-200111000-00004

Stages of Reproductive Aging Workshop

- In 2001, the Stages of Reproductive Aging Workshop (STRAW) established a nomenclature for reproductive aging based on menstrual cycle.
- STRAW+10 updated and modified the model in 2011.
    - Considered the gold standard for categorizing reproductive aging and divides the reproductive lifespan into three broad phases, further broken down into seven stages centered on the FMP (Stage 0).
    - Reproductive Phase: Early (Stage −5), Peak (Stage −4), and Late (Stage –3).
    - The Menopause Transition (MT): Early (Stage –2) and Late (Stage –1).
    - Postmenopause Phase: Early (Stage +1) and Late (Stage +2).
- Applies to menstruating women regardless of demographics, age, body mass index (BMI), and lifestyle characteristics.

Harlow SD, et al. *Menopause* 2012;19:387-395. doi: 10.1097/gme.0b013e31824d8f40; Soules MR, et al. *Menopause* 2001;8:402-407. doi: 10.1097/00042192-200111000-00004

STRAW+10

- Each stage has clinical criteria, endocrine parameters, and characteristic markers.
- Menstrual cycle is the principal criteria in STRAW.
- Criteria cannot be applied if there is a history of primary ovarian insufficiency, irregular menstrual cycles, hysterectomy, or endometrial ablation.
    - Endocrine markers can be used to assess reproductive aging in those clinical situations.

Menarche — FMP (0)

STAGE	-5	-4	-3b	-3a	-2	-1	+1a	+1b	-1c	-2
TERMINOLOGY	REPRODUCTIVE				MENOPAUSE 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 FSH AMH Inhibin B			Low Low	Variable Low Low	↑ Variable Low Low	↑ >25 IU/L** Low Low	↑ Variable Low Low		Stabilizes Very 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 piluitary standard

Harlow SD, et al. *Menopause* 2012;19:387-395. doi: 10.1097/gme.0b013e31824d8f40

Measures of Ovarian Reserve

Follicle-stimulating hormone (FSH) in conjunction with estradiol (days 2-5 of menstrual cycle, not taking hormones)

- Most common for measuring ovarian reserve.
  - FSH >10 IU/L + estradiol < 60 pg/mL.
  - FSH <10 IU/L + estradiol >100 pg/mL.

Antimüllerian hormone (AMH)

- Produced by the granulosa cells of preantral and small antral follicles.
- Measure any day of the cycle or while taking hormones.
- Not recommended as a screening tool in general population.
- <1 ng/mL.

Antral follicle count (AFC)

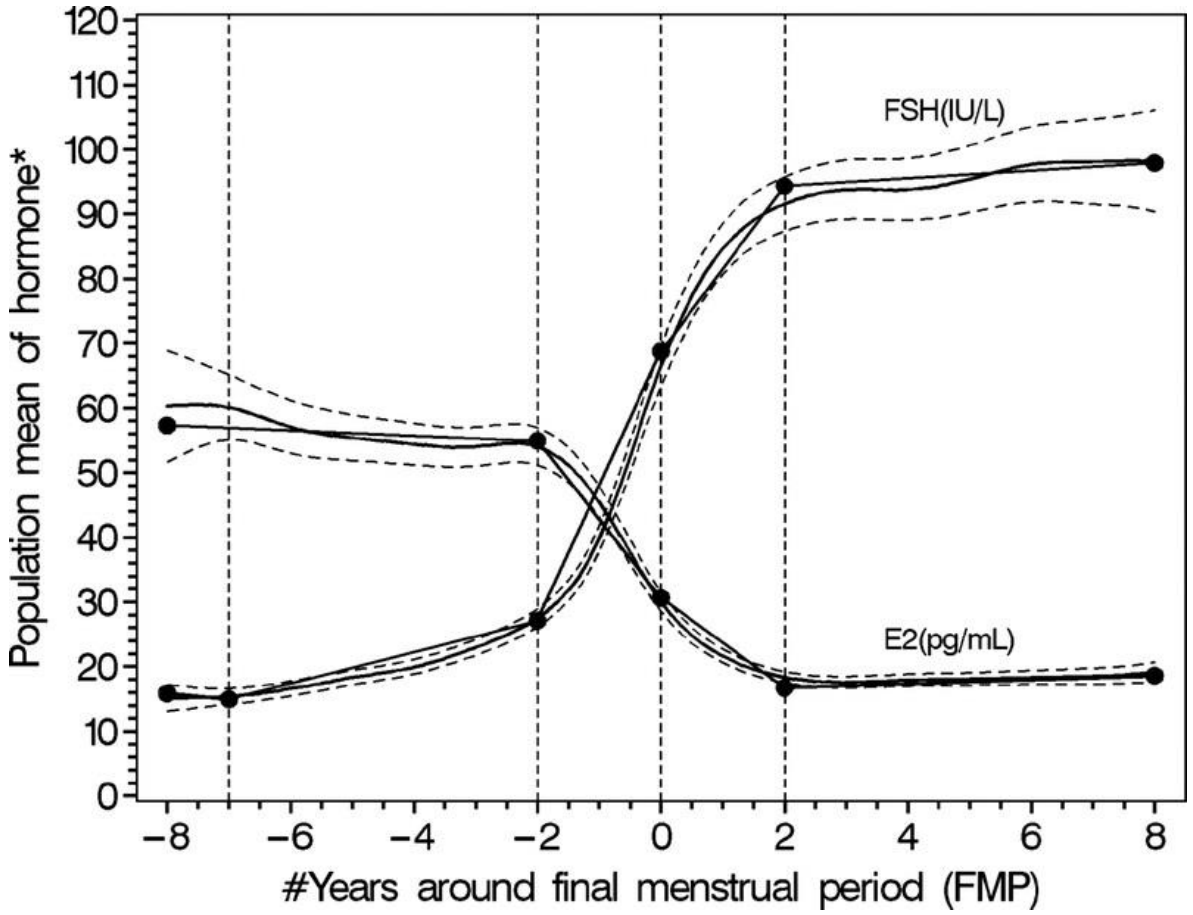
- Number of ultrasound-detected follicles 2 mm to 10 mm in both ovaries.
- <7 follicles.

AFC and AMH

- Useful markers of ovarian response to controlled ovarian stimulation.

Finkelstein JS, et al. J *Clin Endocrinol Metab* 2020;105:e1862-e1871. doi: 10.1210/clinem/dgz283; Practice Committee for the American Society for Reproductive Medicine. *Fertil Steril* 2020;14:1151-1157. doi: 10.1016/j.fertnstert.2020.09.134

Physiology of the Menopause Transition



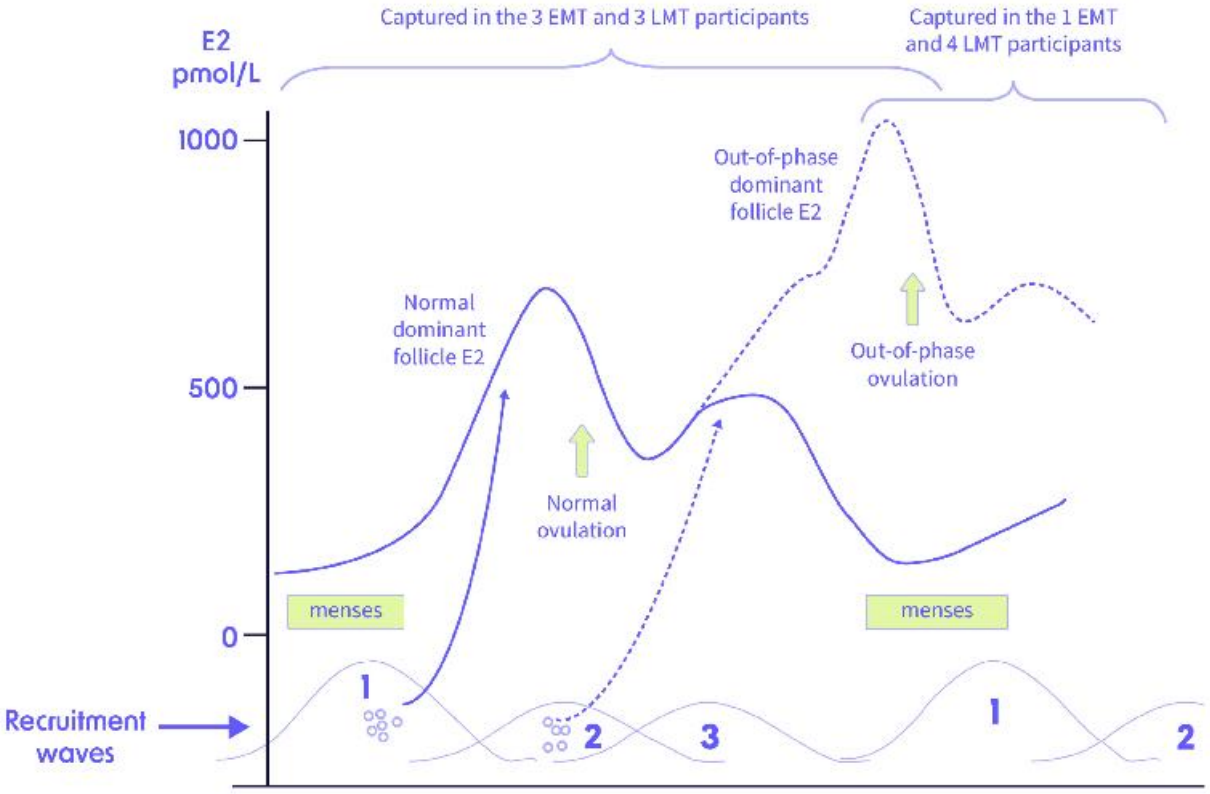
- ↓Ovarian sensitivity to gonadotropin stimulation.
- ↓Estradiol production.
- ↓Negative feedback to hypothalamic-pituitary-adrenal axis results in ↑FSH and ↑luteinizing hormone (LH).

- Curves reflect changes in estradiol and FSH (units of hormone are marked in the corresponding curves) during the MT.

Figure reproduced from Randolph JF, Zheng H. Change in follicle-stimulating hormone and estradiol across the menopausal transition: effect of age at the final menstrual period. *J Clin Endocrinol Metab* 2011;96:746-754; by permission of Oxford University Press on behalf of the Endocrine Society. All rights reserved.

Harlow SD, et al. *Menopause* 2012;19:387-395. doi: 10.1097/gme.0b013e31824d8f40

Physiology of the Menopause Transition



Adapted from Hale GE, Hughes C, Burger H, et al. Atypical estradiol secretion and ovulation patterns caused by luteal out-of-phase (LOOP) events underlying irregular ovulatory menstrual cycles in the menopausal transition. *Menopause* 2009;16:50-59; by permission of Wolters Kluwer Health on behalf of The Menopause Society. All rights reserved.

Early Menopause Transition

- Persistent cycle irregularity by ≥7 d.
- Decline in inhibin B and AMH because of reduction in follicles (low AFC).
- Diminished ovarian reserve. Lower AMH and inhibin B promotes growth of remaining follicular pool, accelerating follicular atresia.
- Early follicular FSH is variable.
- Luteal out-of-phase (LOOP) events occur in about one in four cycles.
- May or may not have mild vasomotor symptoms (VMS).
- May have pronounced premenstrual syndrome.

Late Menopause Transition

- Amenorrhea > 60 d.
- Menstrual cycles have variable cycle length.
- Variable estradiol levels with increased prevalence of anovulation.
- FSH levels are ≥25 IU/L because of few remaining oocytes.
- Negligible AMH and AFC.
- LOOP cycles occur in a third of women; VMS and other signs of menopause likely.

Hale GE, et al. *Menopause* 2009;16:50-59. doi: 10.1097/GME.0b013e31817ee0c2; Harlow SD, et al. *Menopause* 2012;19:387-395. doi: 10.1097/gme.0b013e31824d8f40; Santoro N, et al. J *Clin Endocrinol Metab* 2008;93:1711-1721. doi: 10.1210/jc.2007-2165; Soules MR, et al. *Menopause* 2001;8:402-407. doi: 10.1097/00042192-200111000-00004

Luteal Out-of-Phase Events

- Symptoms from elevated estradiol:
  - Mastalgia
  - Migraine
  - Menorrhagia
  - Growth of fibroids
  - Endometrial hyperplasia
- Increased risk of reproductive cancers (especially with longer MT).
- Pregnancy can occur, with increased incidence of twins.
- Obesity is associated with elevated estradiol concentrations because of aromatization of androgen to estrogen.

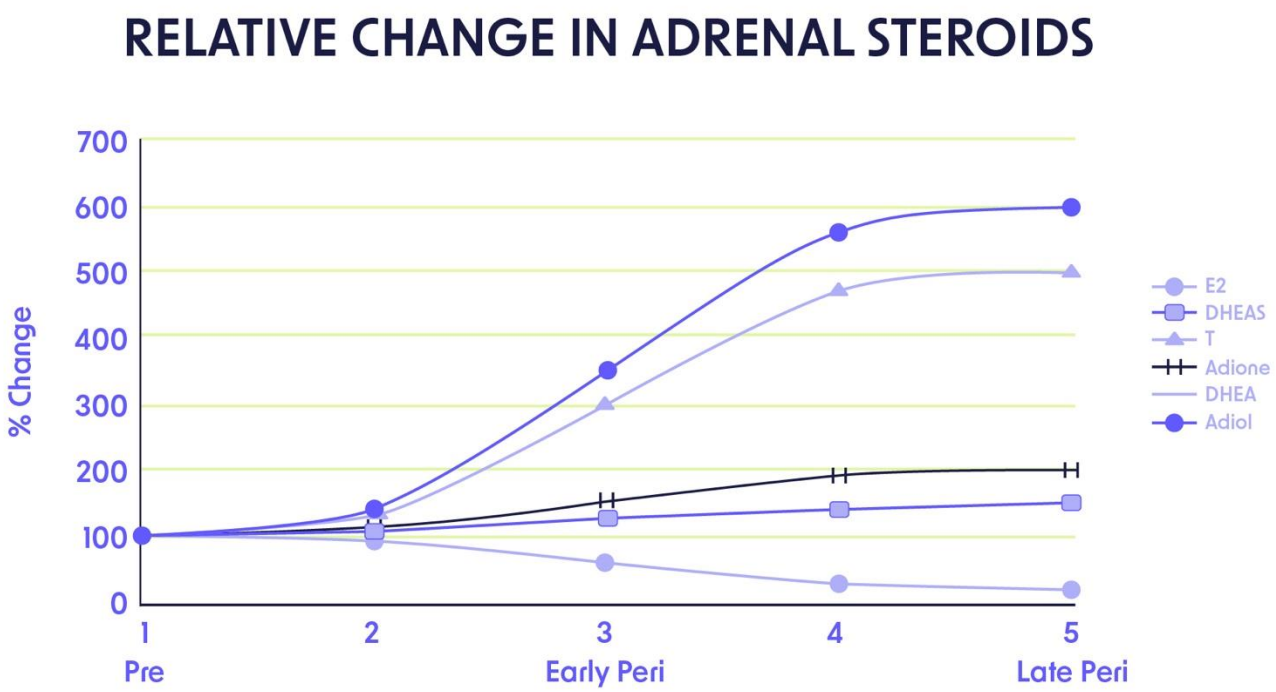
Freeman EW, et al. *Menopause* 2010;17:718-726. doi: 10.1097/gme.0b013e3181cec85d; Hale GE, et al. *Menopause* 2009;16:50-59. doi: 10.1097/GME.0b013e31817ee0c2; Hale GE, et al. *J Steroid Biochem Mol Biol* 2014;142:121-131; doi: 10.1016/j.jsbmb.2013.08.015 Randolph JF Jr, et al. *J Clin Endocrinol Metab* 2004;89:1555-1561. doi: 10.1210/jc.2003-031183; Randolph JF Jr, et al. *J Clin Endocrinol Metab* 2011;96:746-754. doi: 10.1210/jc.2010-1746

Adrenal Physiology and Menopause

- Adrenal gland is composed of adrenal cortex and adrenal medulla.
- Adrenal cortex produces
  - Cortisol (glucocorticoid).
  - Aldosterone (mineralocorticoid).
  - Androgens, sex steroids: dehydroepiandrosterone (DHEA), dehydroepiandrosterone sulfate (DHEAS), androstenedione, testosterone.
- Adrenal medulla produces and secretes catecholamines: epinephrine, norepinephrine, and some dopamine.
- Adrenal androgens are enzymatically converted to estrogens in the peripheral tissues.
- Although cortisol increases with age, androgens decrease.
- Significance in the drop in androgens with natural menopause is not correlated with menopause symptoms.
- Checking androgen concentrations is not recommended because there are no serum androgen concentrations that define female androgen insufficiency.

Crandall CJ, et al, eds. *Menopause Practice: A Clinician's Guide*, 6th ed. The North American Menopause Society; 2019; Davis SR, et al. *JAMA* 2005;294:91-96. doi: 10.1001/jama.294.1.91

Hypothalamic-Pituitary-Adrenal Axis and the Menopause Transition



- 85% of those in the late perimenopause and early menopause experience
  - Marked rise in DHEA and androstenediol.
  - Moderate rise in DHEAS, testosterone, and androstenedione.
- Adrenal androgen levels return to premenopause level within 1 to 2 years after FMP.
- Marked rise in cortisol is associated with rise in FSH in late perimenopause.
- Changes in cortisol patterns associated with mood, sleep, and vasomotor symptoms (VMS).

McConnell DS, et al. *Menopause* 2012;19:658-663. doi: 10.1097/gme.0b013e31823fe274; Woods NF, et al. *Menopause* 2006;13:212-221. doi: 10.1097/01.gme.0000198490.57242.2e; Reed SD, et al. *Clin Endocrinol* 2016; 84:672–679. doi: 10.1111/cen.12995

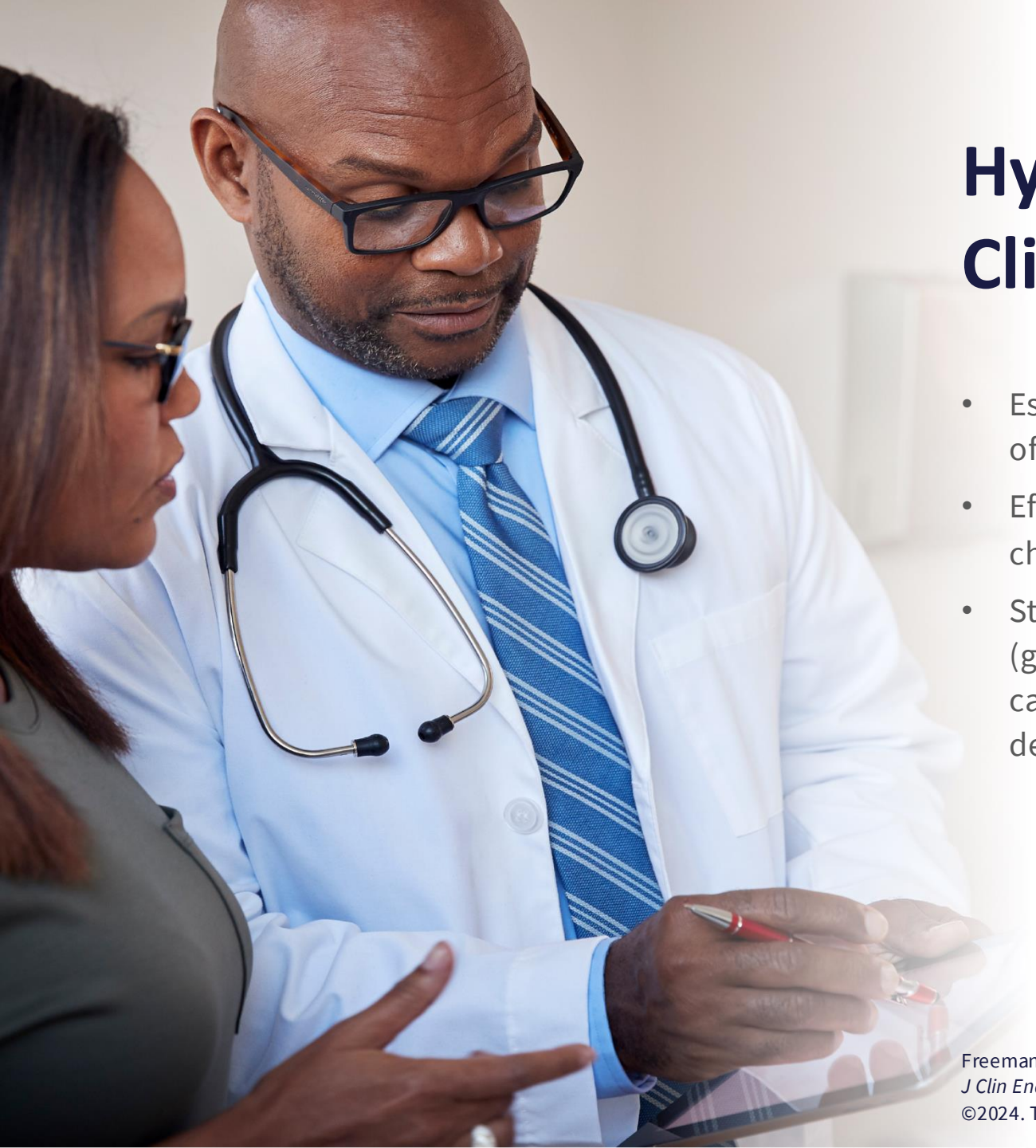
Dehydroepiandrosterone Sulfate and the Menopause Transition

- Study of Women's Health Across the Nation (SWAN) confirmed well-established age-related fall in circulating DHEAS levels.
- Systematic review and meta-analysis of DHEA use in postmenopausal women with normal adrenal function found no evidence of improvement in sexual symptoms, serum lipids, serum glucose, weight, or bone mineral density (BMD).
- DHEA supplementation for postmenopausal women is not routinely recommended.

Crawford S, et al. *J Clin Endocrinol Metab* 2009;94:2945-2951. doi: 10.1210/jc.2009-0386; Davis SR, et al. *J Clin Endocrinol Metab* 2011;96:1642-1653. doi: 10.1210/jc.2010-2888; Elraiyah T, et al. *J Clin Endocrinol Metab* 2014;99:3536-3542. doi: 10.1210/jc.2014-2261

SECTION 3

Menopause Symptoms



Hypoestrogenism and Clinical Symptomatology

- Estrogen deficiency is often associated with a variety of clinical symptoms.
- Effects from estrogen deficiency versus effects from chronologic aging can be difficult to untangle.
- Studies of drugs that suppress estrogen synthesis (gonadotropin-releasing hormone agonists or antagonists) can help to differentiate chronologic aging from estrogen deficiency effects.

Freeman EW. *Obstet Gynecol* 2007;110:230-240. doi: 10.1097/01.AOG.0000270153.59102.40; Santoro N, et al. *J Clin Endocrinol Metab* 2021;106:1-15. doi: 10.1210/clinem/dgaa764

Principal Symptoms and Health Concerns in Menopause

- Principal symptoms affecting quality of life (QOL): VMS, mood changes, cognitive changes, sleep disturbances, increased weight, change in body habitus, genitourinary syndrome of menopause (GSM), sexual dysfunction, and changes to skin and hair.
- Health concerns: osteoporosis, cardiovascular disease (CVD), and cancer.
- Symptoms often start before the FMP during the MT.
- A multitude of symptoms may occur with varying degrees of bother.
- **THERE IS NO ONE MENOPAUSE SYNDROME!**

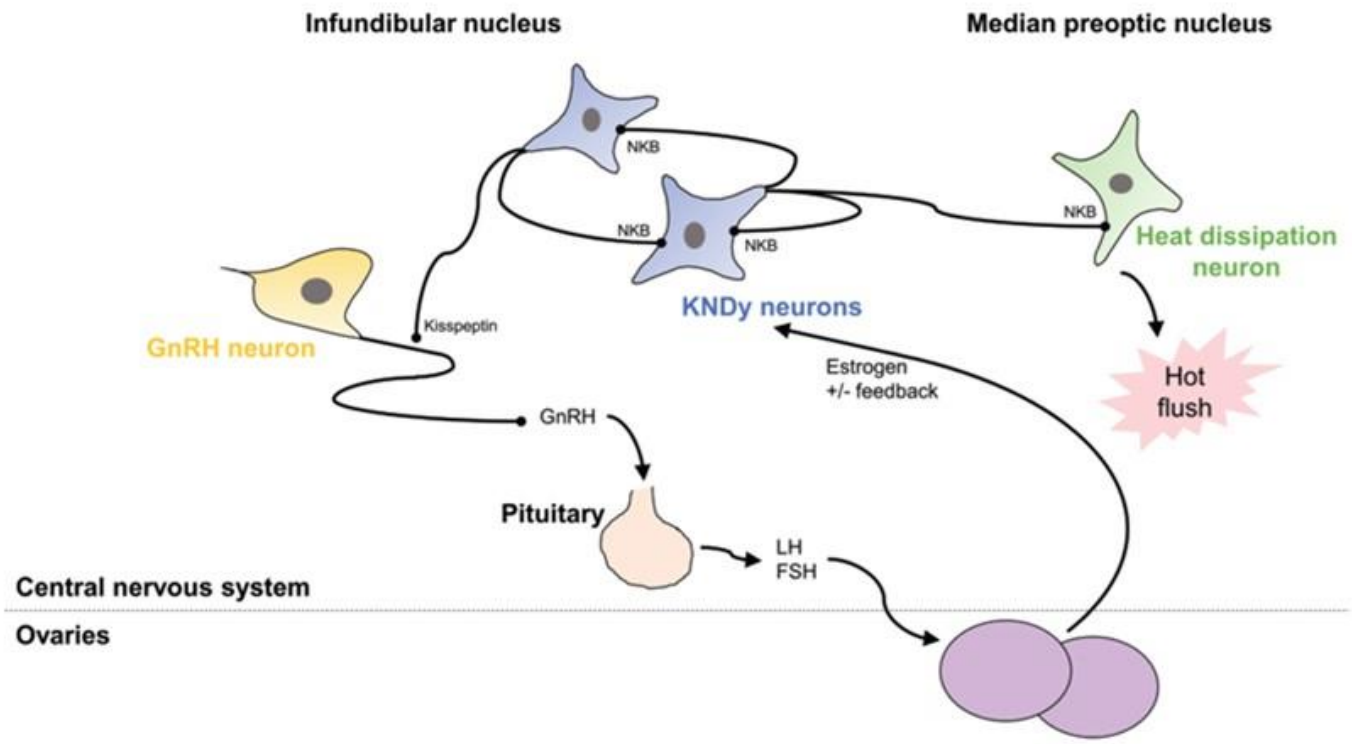
Avis NE, et al. *Am J Med* 2005;118:37-46. doi: 10.1016/j.amjmed.2005.09.05; Green R, et al. *Womens Health (Lond)* 2009;5:127-133. doi: 10.2217/17455057.5.2.127; Neugarten BL, et al. *Psychosom Med* 1965;27:266-273; doi: 10.1097/00006842-196505000-00009; Sowers M, et al. SWAN: A multicenter, multiethnic, community-based cohort study of women and the menopausal transition. In: Lobo RA, et al, eds. *Menopause: Biology and Pathobiology.* Academic Press 2000:175-188.

Vasomotor Symptoms

- Most common symptom during the MT and in menopause.
- Hot flashes during the day and night sweats.
- Often can be accompanied by perspiration, chills, anxiety, and heart palpitations.
- Characterized by sudden intense sensation of heat in the upper body, particularly the face, neck, and chest that last approximately 30 seconds to 5 minutes.
- The number of episodes and degree of bother varies.
- VMS are most bothersome during late perimenopause and early menopause.

ACOG Practice Bulletin Number 141: management of menopausal symptoms. *Obstet Gynecol* 2014;123:202-216. doi: 10.1097/01.AOG.0000441353.20693.78; Avis NE, et al. *JAMA Intern Med* 2015;175:531-539. doi: 10.1001/jamainternmed.2014.8063; Freeman EW. *Obstet Gynecol* 2007;110:230-240. doi: 10.1097/01.AOG.0000270153.59102.40; Gold EB, et al. *Am J Epidemiol* 2000;152:463-473. doi: 10.1093/aje/152.5.463; Green R, et al. *Womens Health (Lond)* 2009;5:127-133. doi: 10.2217/17455057.5.2.127

Pathophysiology of Vasomotor Symptoms



Reproduced from Santoro N, Roeca C. The menopause transition: signs, symptoms, and management options. *J Clin Endocrinol Metab* 2021;106:1-15; by permission of Oxford University Press on behalf of the Endocrine Society. All rights reserved.

Freedman RR. *Semin Reprod Med* 2005;23:117-125. doi: 10.1055/s-2005-869479; Santoro N, et al. *J Clin Endocrinol Metab* 2021;106:1-15. doi: 10.1210/clinem/dgaa764

- Pathophysiology is multifactorial.
- Involves complex interplay between central nervous system and peripheral physiologic processes.
- Kisspeptin-neurokinin B-dynorphin (KNDy) neurons that control the gonadotropin-releasing hormone (GnRH) pulse generator are activated by decreasing estradiol serum concentrations in the menopause transition. This causes an activation cascade to the adjacent thermoregulatory center causing VMS.
- Blockade of neurokinin receptors on KNDy and thermoregulatory neurons reduces or eliminates VMS.
- Small increases in temperature trigger thermoregulatory mechanisms causing the sensation of a hot flush (vasodilation, sweating, and decreased skin resistance) due to a narrowing of the normal thermoregulatory zone.

Prevalence of Vasomotor Symptoms

- **VMS affect up to 80% of women during the MT.**
- Varies by menopause phase:
  - Premenopause: 21% reported VMS.
  - Perimenopause: 41% reported VMS.
  - Postmenopause: 42% reported VMS.

Freeman EW, et al. *Climacteric* 2007;10:197-214. doi: 10.1080/13697130601181486; Gold EB, et al. *Am J Epidemiol* 2000;152:463-473. doi: 10.1093/aje/152.5.463; Gold EB, et al. *Am J Public Health* 2006;95:1226-1235. doi: 10.2105/AJPH.2005.066936; Thurston RC, et al. *Obstet Gynecol Clin North Am.* 2011;38:489-501. doi: 10.1016/j.ogc.2011.05.006

Duration of Vasomotor Symptoms

- Median duration of VMS of 7.4 years centered around FMP (SWAN) but may continue for 10 years or more:
  - African American women (10.1 y)
  - Hispanic women (8.9 y)
  - Non-Hispanic White women (6.5 y)
  - Chinese women (5.4 y)
  - Japanese women (4.8 y)
- Earlier onset of menopause, depression, anxiety, stress, less college education, financial strain, single, smoker, poor social situation, and BMI greater than 30 kg/m^2 are associated with longer duration of symptoms.
- Approximately 10% experience VMS for more than 20 years.

Avis NE, et al. *JAMA Intern Med* 2015;175:531-539. doi: 10.1001/jamainternmed.2014.8063; Richard-Davis G, et al. *JAMA Intern Med* 2015;175:540-541. doi: 10.1001/jamainternmed.2014.8099

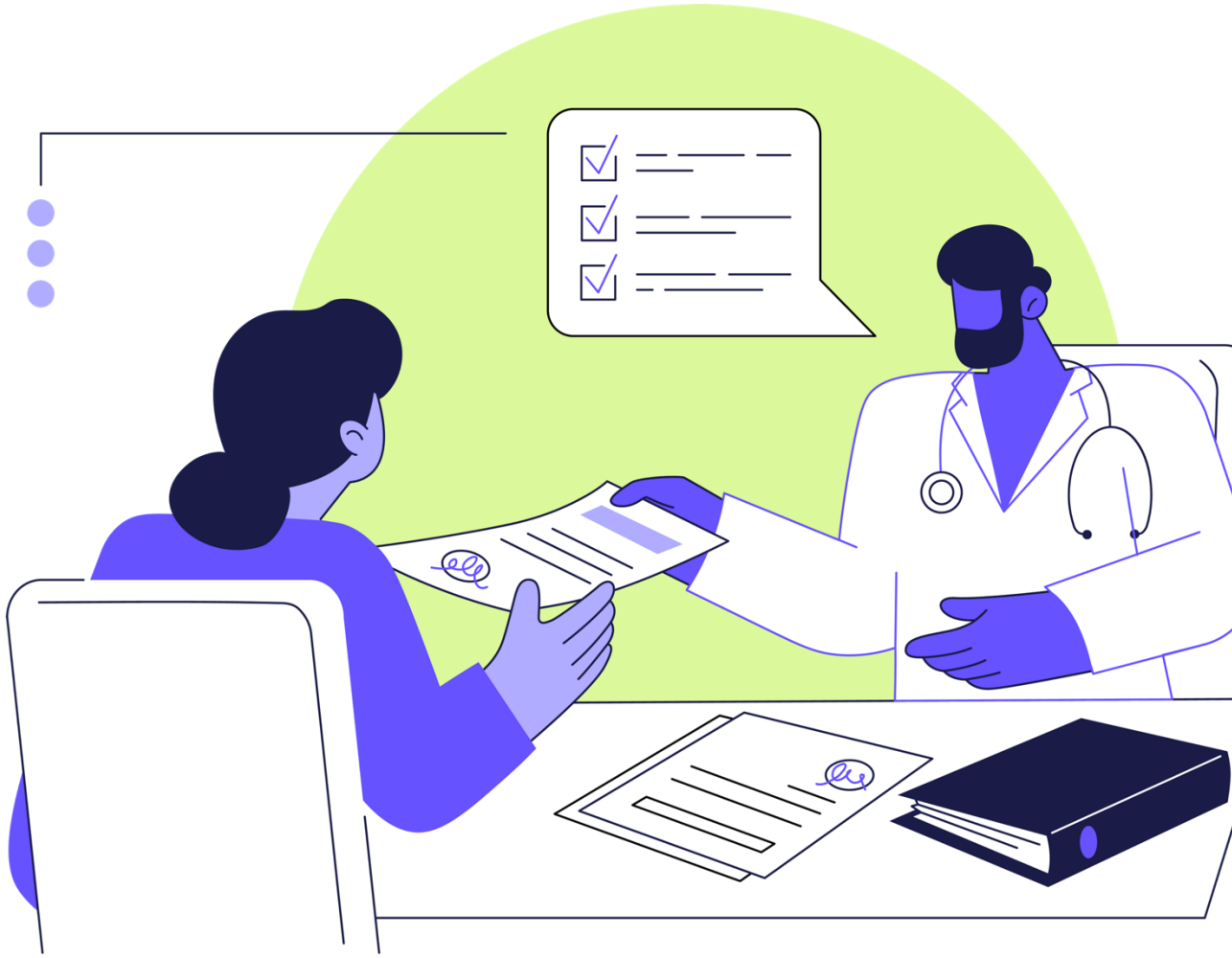
Risk Factors for Vasomotor Symptoms

- Obesity (or weight gain).
- Smoking (tobacco or nicotine).
- Low socioeconomic position.
- Low education attainment.
- High-fat or high-sugar diets.
- Race or ethnicity.
- Oophorectomy.
- Medical comorbidities (thyroid disease, diabetes mellitus [DM], obstructive sleep apnea [OSA], chronic pain conditions).
- High anxiety levels.

Gold EB, et al. *Am J Epidemiol* 2000;152:463-473. doi: 10.1093/aje/152.5.463; Gold EB, et al. *Am J Public Health* 2006;96:1226-1235. doi: 10.2105/AJPH.2005.066936; MacDonald PC, et al. *Am J Obstet Gynecol* 1978;130:448-455. doi: 10.1016/0002-9378(78)90287-9

Vasomotor Symptoms Not Related to Menopause

- Thyroid dysfunction, infections, malignancy, pheochromocytoma, and carcinoid syndrome.
- Warning signs that trigger evaluation:
  - New-onset VMS in late menopause.
  - Younger women (premenopause or menopause transition) with persistent VMS accompanied by nausea, vomiting, diarrhea, weight loss, fever, cough, wheezing, palpitations, tachycardia, flushing, or persistent headache.



Crandall CJ, et al. *JAMA* 2023;329:405-420. doi: 10.1001/jama.2022.24140

Genitourinary Syndrome of Menopause

- Collection of signs and symptoms associated with estrogen deficiency that can involve the vagina, vulva, bladder, and urethra.
- Symptoms must be bothersome and not caused by alternative diagnoses.
- Often chronic and progressive and unlikely to improve without treatment.
- Vulvovaginal atrophy (VVA) is a component of GSM that describes the appearance of genital tissues.
- The presence of VVA is not indicative of symptoms.

Portman DJ, et al. *Maturitas* 2014;79:349-354. doi: 10.1016/j.maturitas.2014.07.013; The NAMS 2020 GSM Position Statement Editorial Panel. *Menopause* 2020;27:976-992. doi: 10.1097/GME.0000000000001609

Prevalence of Genitourinary Syndrome of Menopause

- 40% to 50% of menopausal women are bothered by vulvovaginal symptoms, and 30% to 40% report urinary symptoms.
- Prevalence of GSM in the general population is not known; determining whether the signs and symptoms included in GSM are attributable to the endocrine changes at menopause or are because of aging is challenging.
- Approximately half of sexually active menopausal women experience bothersome symptoms of GSM.
- Most bothersome symptoms are vaginal dryness and dyspareunia.
- Menopausal women with sexual dysfunction are four times more likely to have GSM symptoms.
- Negatively affects sexual intimacy and QOL.

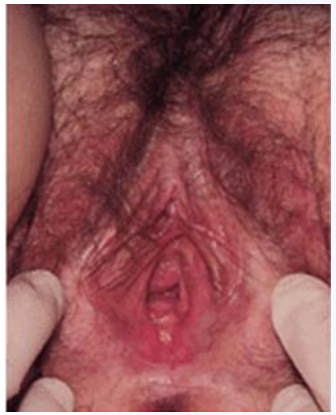
Gold EB, et al. *Am J Epidemiol* 2000;152:463-473. doi: 10.1093/aje/152.5.463; Levine KB, et al. *Menopause* 2008;15: 661-666. doi: 10.1097/gme.0b013e31815a5168; Palma F, et al. *Maturitas* 2016;83:40-44. doi: 10.1016/j.maturitas.2015.09.001; Reed SD. *Clin Obstet Gynecol* 2024;67:1–3. doi: 10.1097/GRF.0000000000000843; Santoro N, et al. *J Sex Med* 2009;6:2133-2142. doi: 10.1111/j.1743-6109.2009.01335.x; Simon JA, et al. *Menopause* 2013;20:1043-1048. doi: 10.1097/GME.0b013e318287342d; The NAMS 2020 Genitourinary Syndrome of Menopause Position Statement Editorial Panel. *Menopause* 2020;27:976-992. doi: 10.1097/GME.0000000000001609

Signs of Hypoestrogenism

- A measurement tool for GSM is under development.

Signs of hypoestrogenism

Vulva	• Thinning loss of pubic hair • Thinning or fusion of labia • Clitoral hood retraction or fusion • Posterior fissuring
Vagina	• Introital retraction • Pallor or erythema, petechiae • Loss of rugae • Loss of hymenal remnants • Leukorrhea • pH>5 • Loss of vaginal and cervical secretions
Urethra	• Prominence of urethral meatus/caruncle



Christmas MM, et al. *Menopause* 2020;27:1070-1080. doi: 10.1097/GME.0000000000001570; Phillips NA, et al. *Menopause* 2021;28:579-588. doi: 10.1097/GME.0000000000001728

Symptoms Associated With Genitourinary Syndrome of Menopause

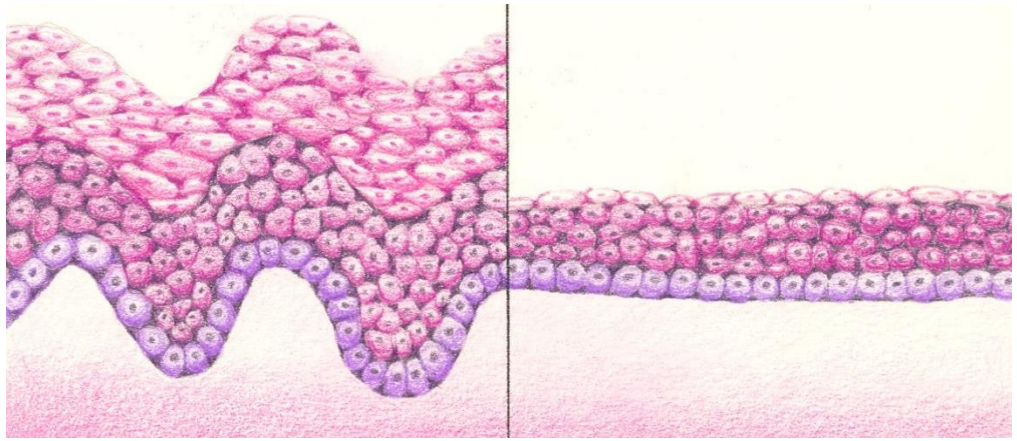
Symptoms of GSM

Genital symptoms	• Vulvovaginal dryness • Vulvovaginal itching, burning, or irritation • Vaginal discharge
Urinary symptoms	• Dysuria • Nocturia • Urinary frequency or urgency • Recurrent urinary tract infection
Sexual symptoms	• Decreased lubrication/arousal with sexual activity • Pain with introital insertion during sexual activity • Dyspareunia • Decreased or delayed orgasm • Postcoital bleeding

Doust J, et al. *Clin Obstet Gynecol* 2024;67:4-12. doi: 10.1097/GRF.0000000000000834; Phillips NA, et al. *Menopause* 2021;28:579-588. doi: 10.1097/GME.0000000000001728; Shifren JL, et al. *Menopause* 2019;26:341-349. doi: 10.1097/GME.0000000000001275

Pathophysiology of Genitourinary Syndrome of Menopause

- Estrogen maintains blood flow to the vulvovaginal tissue; stimulates collagen, hyaluronic acid, and mucopolysaccharides within the epithelium.
- Estrogen is associated with vaginal pH < 4.5 and healthy microbiota.
- Estrogen receptors (ERs) are found throughout the vagina, vulva, urethra, and trigone of the bladder.



Loss of estrogen results in

- Thinning of the vulvar tissue and superficial epithelium.
- Loss of vaginal rugae, labia minora, and vaginal elasticity.
- Narrowing of the vaginal canal.
- Poor distension.
- Decrease in glycogen, lactobacilli, and lactic acid.
- Decreased blood flow.
- Higher vaginal pH leading to an increase in lymphocytes and plasma cells.
- Vaginal introitus narrowing with shorter proximity to urethral meatus.

Constantine GD, et al. *Curr Med Res Opin* 2014;30:143-148. doi: 10.1185/03007995.2013.850068; Mac Bride MB, et al. *Mayo Clin Proc* 2010;85:87-94. doi: 10.4065/mcp.2009.0413; Muhlesisen AL, et al. *Maturitas* 2016;91:42-50. doi: 10.1016/j.maturitas.2016.05.015; Weber MA, et al. *Menopause* 2016;23:833-838. doi: 10.1097/GME.0000000000000634

Other Causes of Genitourinary Symptoms

- Lichen sclerosus, planus, or simplex.
- Desquamative inflammatory vaginitis.
- Contact dermatitis.
- Vulvovaginal candidiasis and vaginitis.
- Cicatricial pemphigoid.
- Idiopathic overactive bladder.
- Detrusor overactivity.
- Vulvodynia/Vestibulodynia.
- Psychological disorders.
- Malignancy and treatments (ie, surgery, chemotherapy, radiation therapy).
- Trauma.
- Foreign body.
- Urinary tract infection.

Christmas MM, et al. *Clin Obstet Gynecol* 2024;67:101-114. doi: 10.1097/GRF.0000000000000833; The NAMS 2020 Genitourinary Syndrome of Menopause Position Statement Editorial Panel. *Menopause* 2020;27:976-992. doi: 10.1097/GME.0000000000001609

Other Common Menopause Symptoms

- Sleep disruption.
- Mood changes.
- Cognitive changes.
- Muscle and joint pain.
- Skin and hair changes.
- Weight gain.
- Headaches or migraines.
- Decreased libido.

Sleep Disturbances and Menopause

- Difficulty sleeping (the symptom) and insomnia (the disorder) are common in menopause.
- During the MT, women with VMS are more likely to report disrupted sleep.
  - Night sweats may cause sleep disturbance.
  - Sleep disturbances can be present whether women sense hot flashes or not.
- SWAN: 38% of women aged 40 to 55 years reported difficulty sleeping.
  - Highest rates of sleeplessness in late perimenopause (45%) or surgical menopause (47%).
- Contributing factors: night sweats, aging, stress, social/psychologic factors, certain drugs or alcohol, poor sleep health and medical comorbidities.
  - Primary or secondary to other conditions (OSA, restless legs syndrome, thyroid disease, DM, anxiety).

Baker FC, et al. *Nat Sci Sleep* 2018;9:73-95. doi: 10.2147/NSS.S125807; Joffe H, et al. *Semin Reprod Med* 2010;28:404-421. doi: 10.1055/s-0030-1262900; Zolfaghari S, et al. *Menopause* 2020;27:295-304. doi: 10.1097/GME.0000000000001462

Effect of Sleep Dysfunction on Quality of Life and Health

- Associated with fatigue, irritability, chronic illness (eg, chronic pain).
- Negative effects on mood; worsening depression.
- Associated with weight gain.
    - The more abnormal the electroencephalogram, the higher correlation with metabolic syndrome (MetS) and increased adiposity.
- Higher association with CVD.

Baker FC, et al. *Sleep Med Clin* 2018;13:443-456. doi: 10.1016/j.jsmc.2018.04.011;
Kravitz HM, et al. *Sleep* 2008;31:979-990.

Mood Disorders and Menopause

- Depression with or without anxiety is one of the most debilitating conditions worldwide.
- Depression disproportionately affects women more than men.
- *Windows of vulnerability:* Concept that women with hormone sensitivity may be more affected by the erratic hormone fluctuations with menstrual cycle changes, postpartum, and perimenopause.
- Depressive symptoms, anxiousness, decreased motivation, irritability, and decreased enjoyment from usual activities are most often described during the MT.

Bloch M, et al. *Gen Hosp Psychiatry* 2006;28:3-8. doi: 10.1016/j.genhosppsych.2005.08.006; Lokuge S, et al. *J Clin Psychiatry* 2011;72: e1563-e1569. doi: 10.4088/JCP.11com07089; Rubinow DR, et al. *Depress Anxiety* 2015;32:539-549. doi: 10.1002/da.22391; Vivian-Taylor J, et al. *Maturitas* 2014;79:142-146. doi: 10.1016/j.maturitas.2014.05.014; Wittchen HU, et al. *Psychol Med* 2002;32:119-132. doi: 10.1017/s0033291701004925; Yonkers KA, et al. *Lancet* 2008;371:1200-1210. doi: 10.1016/S0140-6736(08)60527-9

Prevalence of Mood Disorders During the Menopause Transition

- A 45% to 70% risk of depressive symptoms for perimenopausal women compared with a 25% to 30% risk for premenopausal women.
- Three longitudinal cohort studies, SWAN, the Penn Ovarian Aging Study, and the Seattle Midlife Women's Health Study, documented increased risk for depressive symptoms during the MT.
- The Harvard Moods and Cycle Study found a 2-fold increase for the development of depressive symptoms and for clinical depression in perimenopausal women compared with premenopausal women.
- A systematic review showed that women with bipolar disorder had an increase in bipolar and depressive symptoms (41%-91%) during perimenopause.

Bromberger JT, et al. *Am J Public Health* 2004;94:1378-1385. doi: 10.2105/ajph.94.8.1378; Bromberger JT, et al. *Menopause* 2013;20:488-495. doi: 10.1097/GME.0b013e3182730599; Cohen LS, et al. *Arch Gen Psychiatry* 2006;63:385-390. doi: 10.1001/archpsyc.63.4.385; Freeman EW, et al. *JAMA Psychiatry* 2014;71:36-43. doi: 10.1001/jamapsychiatry.2013.2819; Joffe H, et al. *Arch Gen Psychiatry* 2012;69:484-492. doi: 10.1001/archgenpsychiatry.2011.1578; Perich T, et al. *Bipolar Disorders* 2017;19:434-443. doi: 10.1111/bdi.12530; Schmidt PJ, et al. *Am J Psychiatry* 2004;161:2238-2244. doi: 10.1176/appi.ajp.161.12.2238

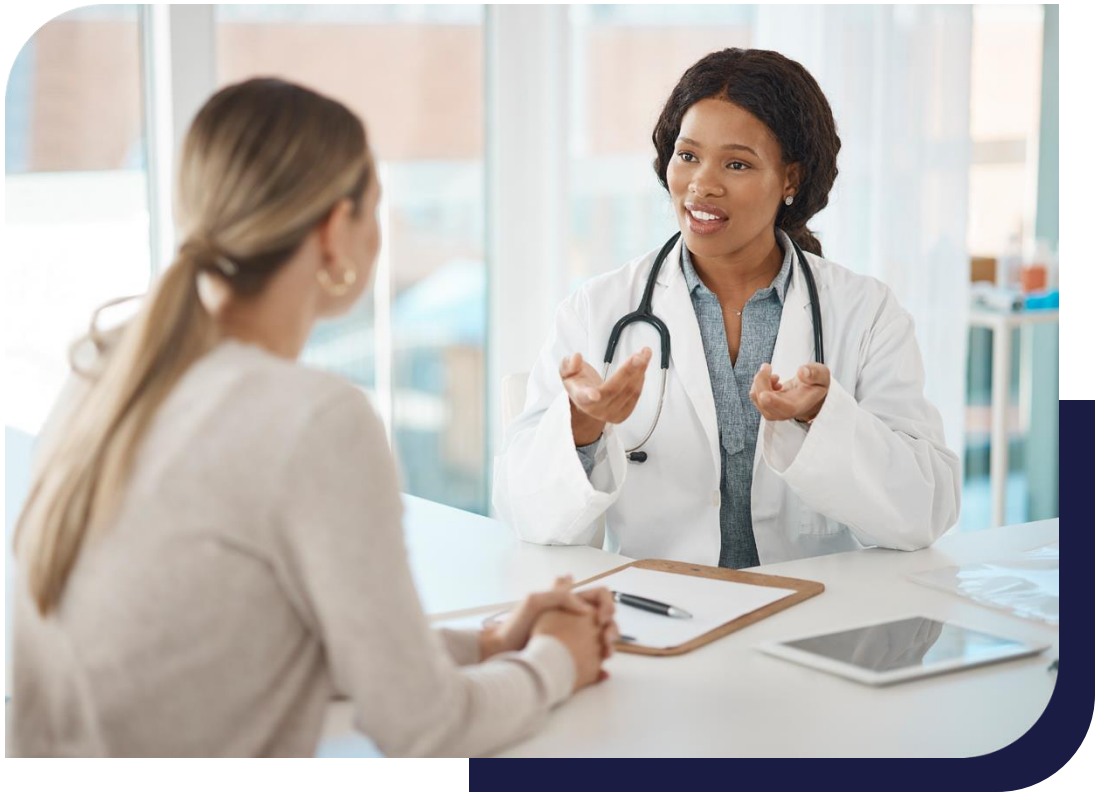
Factors in the Expression and Experience of Depression

- Personal history of depression (most predictive factor).
- Overall poor health.
- Presence and severity of VMS.
- Sleep disturbances.
- Cognitive changes.
- Surgical menopause.
- Changes in weight, appearance, and energy.
- Ethnicity.
- Lifestyle behaviors (ie, sedentary lifestyle and smoking).
- Stressful life events.

Bromberger JT, et al. *Am J Public Health* 2004;94:1378-1385. doi: 10.2105/ajph.94.8.1378; Joffe H, et al. *Semin Reprod Med* 2010;28:404-421. doi: 10.1055/s-0030-1262900; Pérez-López FR, et al. *Menopause* 2014;21:159-164. doi: 10.1097/GME.0b013e31829479bb

Psychosocial Stressors That Contribute to Mood Changes

- Sandwich generation (caring for both children and aging parents).
- Changes to physical health in self and partner.
- Role changes (empty nest).
- Death of parents.
- Possible changes in marital status.
- Other transitions, such as kids leaving the home.



Maki PM, et al. *J Womens Health (Larchmt)* 2019;28:117-134. doi: 10.1089/jwh.2018.27099.mensocrec

Cognitive Changes

- Cognitive decline leading to dementia is a common concern during the MT and beyond.
- Evidence that verbal episodic memory and processing speed can decline during the MT.
  - Most affected functions: forgetfulness, word recall, ability to retrieve information, and concentration.
  - Ability for new learning and responding to information is least affected.
- Any transient issue with cognition appears to resolve after menopause.

Karlamangla AS, et al. *PLoS One* 2017;12:e0169008. doi: 10.1371/journal.pone.0169008; Lehert P, et al. *Climacteric* 2015;18:678-689. doi: 10.3109/13697137.2015.1078106; Maki PM, et al. *Menopause* 2008;15:848-856. doi: 10.1097/gme.0b013e31816d815e

Prevalence of Cognitive Changes

- In population-based studies, 44% to 62% of women in the MT report subjective cognitive decline.
- Alzheimer disease, the most common form of dementia, affects women more than men and is the fifth-leading cause of death.
- Women account for two-thirds of clinically diagnosed cases of dementia.
- In the longitudinal SWAN study of more than 3,300 midlife women, 41% of postmenopausal women reported cognitive impairment compared with only 31% of premenopausal women.

Conde DM, et al. *World J Psychiatry* 2021;11:412-428. doi: 10.5498/wjp.v11; Gold EB, et al. *Am J Epidemiol* 2000;152:463-473. doi: 10.1093/aje/152.5.463; Stefanowski B, et al. *Maturitas* 2023;168:53-61. doi: 10.1016/j.maturitas.2022.10.012

Factors in the Expression and Experience of Cognitive Changes

- Somatic aging is the biggest contributor to cognitive decline.
- Depression, anxiety, and sleep disturbance are associated with cognitive decline.
- Studies show a correlation between hot flashes and memory performance.
- Bilateral oophorectomy before menopause associated with a higher risk of cognitive impairment than natural menopause (age-matched).
- Bilateral oophorectomy at 45 years of age or younger is associated with increased risk of dementia.
- Other factors with cognitive decline and dementia: cardiovascular factors, DM, low education, obesity, physical inactivity, low social contact, excessive alcohol consumption, traumatic brain injury, and pollution.

Lehert P, et al. *Climacteric* 2015;18:678-689. doi: 10.3109/13697137.2015.1078106; Maki PM, et al. *Menopause* 2008;15:848-856. doi: 10.1097/gme.0b013e31816d815e; Santoro N, et al. *J Clin Endocrinol Metab* 2021;106:1-15. doi: 10.1210/clinem/dgaa764; Stefanowski B, et al. *Maturitas* 2023;168:53-61. doi: 10.1016/j.maturitas.2022.10.012

Muscle and Joint Pain and Menopause

- “Arthritis of the Menopause.”
- Musculoskeletal pain, arthralgia, and arthritis are all more common postmenopause.
- May be transient and self-limiting.
- If chronic in nature, rule out other causes:
    - Tendinitis, fibromyalgia, spondylosis, arthritis (either inflammatory or degenerative), or vitamin D deficiency, hypothyroidism, hyperparathyroidism, medication-related (statins or bisphosphonates), scleroderma, Sjogren syndrome.

Barnabei VM, et al. *Obstet Gynecol* 2005;105:1063-1073. doi: 10.1097/01.AOG.0000158120.47542.18;
Welton AJ, et al. *BMJ* 2008;337:a1190. doi: 10.1136/bmj.a1190

Prevalence of Muscle and Joint Pain at Menopause

- More than 50% of women report arthralgia at menopause.
    - Increases with obesity and inactivity.
- Often unrecognized because of rise in osteoarthritis (OA) with age.
    - 30% of adults aged older than 45 years have x-ray findings of OA.
- Fibromyalgia is 10 times more common in women than men, with more than 50% developing symptoms after menopause onset.

Maliano M. *Maturitas* 2010;67:29-33. doi: 10.1016/j.maturitas.2010.04.009

Role of Estrogen in Arthralgia

- Estrogen has a complex involvement in joint health:
  - Positive effects on cartilage metabolism.
  - Positive effects on balancing inflammatory reactions.
- Arthralgias seen in other settings of acute estrogen withdrawal (aromatase inhibitor use, surgical menopause).
- Conservative treatment with exercise, weight loss, analgesics.
  - If persistent, severe, or unresponsive, HT may alleviate arthralgia.
  - WHI: Women on HT have less joint pain or stiffness compared with placebo.
  - WHI: Estrogen-alone use resulted in sustained reduction in frequency of joint pain and fewer joint replacements.

Chlebowski RT, et.al. *Menopause* 2013;20:600-608. doi: 10.1097/GME.0b013e31828392c4; Cirillo DJ, et al. *Arthritis Rheum* 2006;54:3194-204. doi: 10.1002/art.22138; Watt FE. *Post Reprod Health* 2018;24:34-43. doi: 10.1177/2053369118757537

Skin Changes and Menopause

- Hypoestrogenism is associated with changes in the structure and function of the skin.
- Approximately 60% of women seen in menopause clinics report skin problems.
- Common symptoms reported by menopausal women include
  - Dryness.
  - Pruritis.
  - Thinning.
  - Wrinkles.
  - Sagging.
  - Poor wound healing.
  - Poor wound healing.
  - Reduced vascularity.
  - Decreased elasticity.
  - Premalignant or malignant lesions.
  - Pigmentation changes.
  - Lower self-esteem.

Kamp E, et al. *Clin Exp Dermatol* 2022;47:2117-2122. doi: 10.1111/ced.15308;
Zouboulis CC, et al. *Climacteric* 2022;25:434-442. doi: 10.1080/13697137.2022.2050206

Factors Affecting Skin Changes

Intrinsic factors

- Genetics.
- Aging.
- 30% decline in skin collagen in the first 5 years after menopause, about 2% per year decline over next 20 years.

Extrinsic factors

- Ultraviolet light.
- Smoking.
- Alcohol consumption.
- Pollution.
- Poor diet (nutrient deficiencies).
- Sleep deprivation.
- Decline in estrogen.

Brincat M, et al. *Br Med J (Clin Res Ed)* 1983;287(6402):1337-1338. doi: 10.1136/bmj.287.6402.1337; Reus TL, et al. *Mech Ageing Dev* 2020;185:111193. doi: 10.1016/j.mad.2019.111193; Verdier-Sévrain S, et al. *Exp Dermatol* 2006;15:83-94. doi: 10.1111/j.1600-0625.2005.00377.x

Effect of Estrogen on Skin

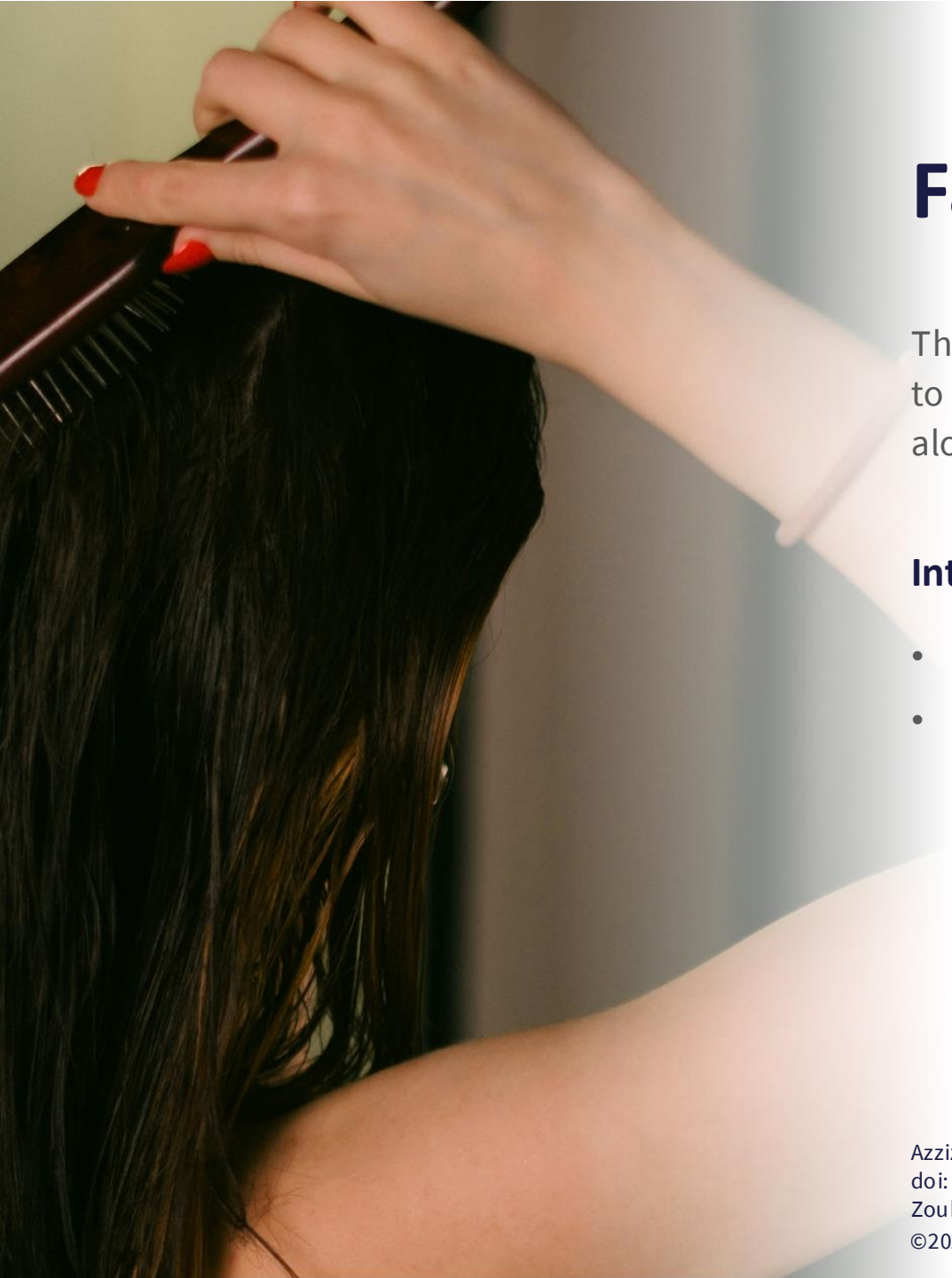
- Estrogen receptors present in significant numbers in skin.
- Estrogen decrease is associated with
  - Decrease in cellular growth factors.
  - Decreased ability to repair enzymes.
  - Decrease in dermal vasculature.
  - Less elasticity, dryness, skin-barrier disruption, dermal thinning.
- Estrogen therapy (ET) may benefit wound healing through modifying inflammation.
- ET has beneficial effects on skin thickness, collagen, and elasticity, and improved skin moisture, with fewer wrinkles.
- ET melasma is not related to pregnancy melasma.
  - Related to visible light or sun exposure.
  - Easier to prevent than treat.

Brincat M, et al. *Br Med J (Clin Res Ed)* 1983;287(6402):1337-1338. doi: 10.1136/bmj.287.6402.1337; Lephart ED, et al. *Dermatol Ther* 2021;11:53-69. doi: 10.1007/s13555-020-00468-7; "The 2022 Hormone Therapy Position Statement of The North American Menopause Society" Advisory Panel. *Menopause* 2022;29:767-794. doi: 10.1097/GME.0000000000002028; Verdier-Sévrain S, et al. *Exp Dermatol* 2006;15:83-94. doi: 10.1111/j.1600-0625.2005.00377.x

Hair Changes and Menopause

- Hair loss and thinning often coincide with menopause for many women.
- Not everyone experiences changes in their hair with menopause, and symptoms vary widely in those that do.
- Common symptoms include
  - Reduced hair growth on scalp.
  - Telogen effluvium (increased hair shedding on scalp).
  - Hirsutism (unwanted hair growth on facial areas).
- Hair growth aberrations can have a negative effect on body image, self-esteem, QOL, and emotional well-being.

Rinaldi F. et.al. *Biomedicines* 2023;11:3041. doi: 10.3390/biomedicines11113041



Factors Affecting Hair Changes

The exact mechanism of female pattern hair loss is unclear; however, it seems to be related to an inflammatory process and altered hormone imbalance, along with environmental and genetic factors.

Intrinsic factors

- Genetics.
- Aging.

Extrinsic factors

- Environmental factors (ie, ultraviolet light exposure, free radical damage).
- Systemic diseases (ie, hypothyroidism).
- Medications.
- Poor diet and nutritional deficiencies.
- Decline in estrogen.

Azziz R. *Obstet Gynecol* 2003;101:995-1007. doi: 10.1016/s0029-7844(02)02725-4; Ramos PM, et al. *An Bras Dermatol* 2015;90:529-543. doi: 10.1590/abd1806-4841.20153370; Yip L, et al. *Australas J Dermatol* 2011;52:81-88. doi: 10.1111/j.1440-0960.2011.00745.x; Zouboulis CC, et al. *Climacteric* 2022;25:434-442. doi: 10.1080/13697137.2022.2050206

Weight Changes and Menopause

- Obesity (BMI ≥30 kg/m^2) in the United States disproportionately affects women.
- US National Health and Nutrition Examination Survey 2018: 43% of menopausal women have obesity.
  - Two-thirds of women aged 45 to 59 years and three-quarters aged 60 years and older are overweight (BMI>25 kg/m^2).
  - Half of both age groups have obesity (BMI >30 kg/m^2).
- Weight gain at midlife is related mostly to aging and lifestyle, not menopause or HT.

Flagal KM, et al. *JAMA* 2016;315:2284-2291. doi: 10.1001/jama.2016.6458; Ford ES, et al. *JAMA* 2014;312:1151-1153. doi: 10.1001/jama.2014.8362; Hales CM et al. *NCHS Data Brief* 2020;1-8; Hurtado MD, et al. *Curr Obes Rep* 2024;13:352-363. doi: 10.1007/s13679-024-00555-2; Kapoor E, et al. *Mayo Clin Proc* 2017; 92:1552-1558. doi: 10.1016/j.mayocp.2017.08.004

Factors Affecting Weight Gain

- Sleep disturbance is associated with increased cortisol levels, lower thyrotropin, lower leptin, reduced glucose tolerance, and decreased energy expenditure that contributes to weight gain.
- Decreased resting metabolic rate results in weight gain because of
  - Decrease in lean muscle mass; increase in fat mass.
  - Alterations in gut microbiome are associated with estrogen deficiency, which may affect absorption and metabolism.
  - Loss of ovarian function and the cessation of the luteal phase of menstrual cycle.
  - Decreased physical activity (secondary to physical limitations, fatigue, work demands, mood changes).

Becker SL, et al. *Menopause* 2021;28:327-331. doi: 10.1097/GME.0000000000001702; Hurtado MD, et al. *Curr Obes Rep* 2024;13:352-363. doi: 10.1007/s13679-024-00555-2; Kapoor E, et al. *Mayo Clin Proc* 2017; 92:1552-1558. doi: 10.1016/j.mayocp.2017.08.004; Simkin-Silverman LR, et al. *Ann Behavior Med* 2003;26:212-220. doi: 10.1207/S15324796ABM2603_06

Health Risks Associated With Weight Gain at Midlife

- Menopause is associated with an increase in central adiposity as well as visceral fat and decrease of lean body mass, regardless of age.
  - Abdominal (central) obesity more consistently associated with obesity related comorbidities than BMI.
- Medical comorbidities associated with obesity in menopause include
  - MetS.
  - Type 2 DM.
  - CVD.
  - Aortic plaque.
  - Hepatic steatosis.
  - Breast cancer.
- Obesity is also associated with an increase in severity and frequency of VMS in the MT.

Brown WJ, et al. *Obes Res* 2005;13:1431-1441. doi: 10.1038/oby.2005.173; Crawford SI, et al. *Menopause* 2000;7:96-104. doi: 10.1097/00042192-200007020-00005; Douchi T, et al. *Maturitas* 2002;42:301-306. doi: 10.1016/s0378-5122(02)00161-5; Milewicz A, et al. *Climacteric* 2004;4:273-283; Neeland IJ, et al. *Obesity (Silver Spring)* 2013;21:E439-E447. doi: 10.1002/oby.20135

Headaches

- Approximately half of the adult population worldwide is affected by a headache disorder.
- Migraine is the second most prevalent neurologic disease in the United States and is three times more common in women than men.
- Categories of headache (no underlying cause) disorders include

Primary headaches

- Migraine.
- Tension-type.
- Trigeminal autonomic cephalalgias (ie, cluster).

"Other" primary headache disorders

- Cough-, exercise-, cold-, or sex-induced.
- Thunderclap.
- Stabbing.

Secondary headaches

- A symptom of another underlying cause.

GBD 2017 US Neurological Disorders Collaborators, et al. *JAMA Neurol* 2021;78:165-176. doi: 10.1001/jamaneurol.2020.4152; Law HZ, et al. *Plast Reconstr Surg Glob Open* 2020;8:e2790. doi: 10.1097/GOX.0000000000002790; Lipton RB, et al. *Headache* 2018;58:1408-1426. doi: 10.1111/head.13407; Lipton RB, et al. *Headache* 2022;62:122-140. doi: 10.1111/head.14259; van Lohuizen R, et al. *Expert Rev Neurother* 2023;19:1-21. doi: 10.1080/14737175.2023.2296610

Headaches and Menopause

- Abrupt decreases in estradiol, such as those that occur during the menstrual period and in postpartum, and perimenopause, play a role in the incidence of headaches.
- The prevalence or intensity of headaches often increases, especially in women with a history of menstrual migraines during the MT.
- Women who have migraines without aura note a decrease during natural menopause.
- Women with pure menstrual migraines often have complete resolution with menopause.
- Variable estrogen levels exacerbate migraines, whereas stable low-dose estrogen can ameliorate them.

Charles A. *N Engl J Med* 2017;377:553-561. doi: 10.1056/NEJMcp1605502; Freitag F. *Med Clin North Am* 2013;97:281-292. doi: 10.1016/j.mcna.2012.12.003; Headache Classification Committee of the International Headache Society (IHS) The International Classification of Headache Disorders, 3rd Edition. *Cephalalgia* 2018;38:1-211. doi: 10.1177/0333102417738202; Monteith TS, et al. *Curr Pain Headache Rep* 2009;13:463-469. doi: 10.1007/s11916-009-0075-0; Nappi RE, et al. *Cells* 2022;15;11:1355. doi: 10.3390/cells11081355; Peck KR, et al. *Headache* 2018;58:648-660. doi: 10.1111/head.13294; Zhao L, et al. *JAMA Intern Med* 2017;177.4: 508-515. doi: 10.1001/jamainternmed.2016.9378

Sexual Dysfunction and Menopause

- Sexual concerns frequently present during midlife because of hormone and biopsychosocial factors.
- Sexual concerns in midlife women remain underdiagnosed and undertreated.
- 40% to 50% of women report at least one sexual problem.
    - Low desire with or without distress reported by 48.5% of women aged 45 to 64 years.
- Sexual dysfunction is commonly associated with
    - Emotional issues.
    - Social functioning problems.
    - Relationship conflict and nonspecific medical conditions.

Biddle AK, et al. *Value Health* 2009;12:763-772. doi: 10.1111/j.1524-4733.2008.00483.x; Clayton AH, et al. *Mayo Clin Proc* 2018;93: 467-487. doi: 10.1016/j.mayocp.2017.11.002; Johannes CB, et al. *J Clin Psychiatry* 2009;70:1698-1706. doi: 10.4088/JCP.09m05390gry; Kingsberg SA, et al. *Menopause* 2022;29:1083-1085. doi: 10.1097/GME.0000000000002049; Laumann EO, et al. *JAMA* 1999;281:537-544. doi: 10.1001/jama.281.6.537;Shifren JL, et al. *Obstet Gynecol* 2008;112:970-978. doi: 10.1097/AOG.0b013e3181898cdb.

Classification of Female Sexual Dysfunction

	DSM-IV	DSM-V
Desire/Arousal	• Hypoactive sexual desire disorder. • Female arousal disorder.	• Female sexual interest/arousal disorder.
Pain	• Dyspareunia. • Vaginismus.	• Genitopelvic pain/penetration disorder.
Orgasm	• Female orgasmic disorder.	• Female orgasmic disorder.

Abbreviations: DSM-IV, *Diagnostic and Statistical Manual of Mental Disorders*, 4th ed; DSM-V, *Diagnostic and Statistical Manual of Mental Disorders*, 5th ed.

IsHak WW, et al. *Reprod Sys Sexual Disorder* 2013;2:2.

Factors Associated With Sexual Dysfunction

Physiological

- Neurologic problems.
- Cardiovascular disease.
- Cancer.
- Urogenital disorders.
- Medications.
- Fatigue.
- Hormone loss or abnormality.
- Chronic pain.

Psychological/ Emotional

- Anxiety/Stress.
- Self-image.
- Depression.
- History of abuse or trauma.
- Alchohol/ Substance abuse.

Sociocultural Influences

- Limited sex education.
- Conflict with religious, personal, or family values.
- Societal taboos.

Interpersonal Relationships

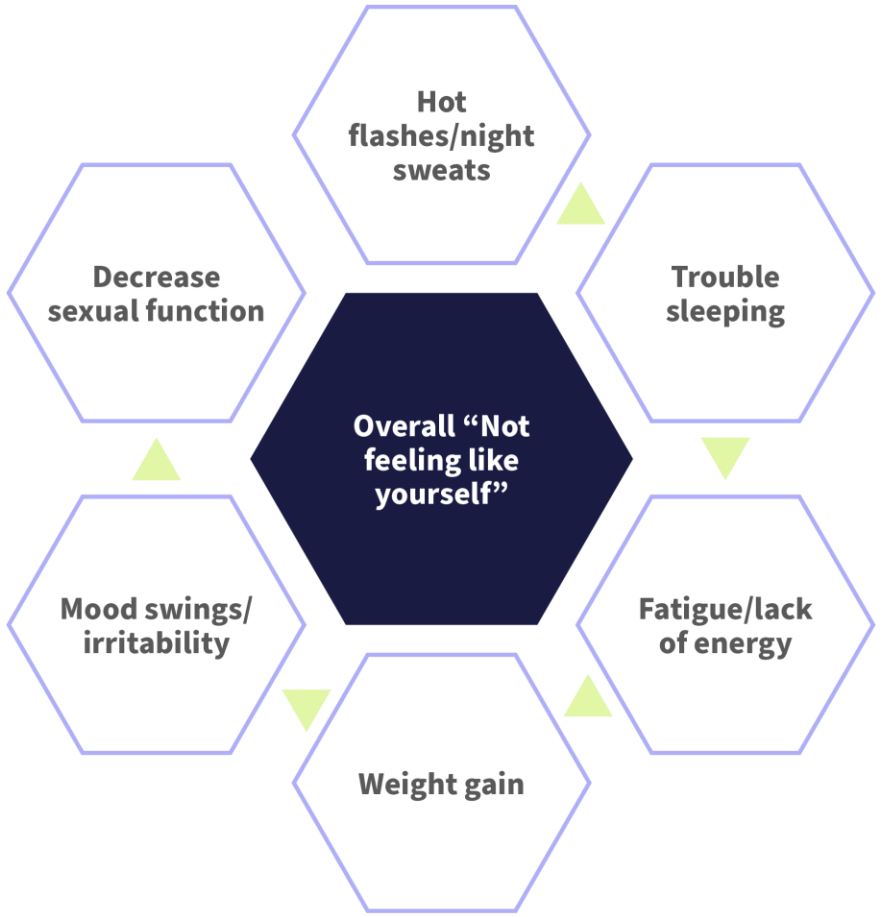
- Partner performance and technique.
- Lack of a partner.
- Relationship quality, conflict, communication.
- Logistics, lack of privacy.

Altof SE, et al. *J Sex Med* 2005;2:793-800. doi: 10.1111/j.1743-6109.2005.00145.x; Clayton AH, et al. *Mayo Clin Proc* 2018;93:467-487. doi: 10.1016/j.mayocp.2017.11.002; Kingsberg SA, et al. *J Sex Med* 2017;14:1463-1461. doi: 10.1016/j.jsxm.2017.05.018; Rosen RC, et al. *Obstet Gynecol Clin North Am* 2006;33:515-526. doi: 10.1016/j.ogc.2006.09.005

Menopause Symptoms and Sexual Desire

- The loss of sex hormones can be associated with low libido and decrease in orgasm response.
- No serum androgen concentrations define female androgen insufficiency; therefore, checking androgen concentrations is not recommended and should not be used to guide treatment.
- Hypoestrogenism can lead to structural changes to the vagina, vulva, and bladder, leading to decreased vaginal lubrication, dryness, and pain with penetration.

Menopause symptoms that negatively affect sexual desire



Christmas M, et al. *Obstet Gynecol Clin N Am* 2024;51:341-364. doi: 10.1016/j.ogc.2024.02.007; Goldstein I, et al. *Mayo Clin Proc* 2017;92:114-128. doi: 10.1016/j.mayocp.2016.09.01; Kingsberg SA, et al. *CNS Drugs* 2015;29:915-933. doi: 10.1007/s40263-015-0288-1; Pfaus JG. *J Sex Med* 2009;6:1506-1533. doi: 10.1111/j.1743-6109.2009.01309.x

Abnormal Uterine Bleeding

- Menstrual flow outside of normal volume, duration, regularity, or frequency.
- Umbrella term that encompasses heavy menstrual bleeding and intermenstrual bleeding.
- Accounts for one-third of visits to the gynecologist and 70% of all gynecologic consults in the perimenopause and postmenopause years.

Committee on Practice Bulletins—Gynecology. *Obstet Gynecol* 2012;120:197-206.
doi: 10.1097/AOG.0b013e318262e320

Classification of Abnormal Uterine Bleeding

FIGO Classification System (PALM-COEIN) for Causes of Abnormal Uterine Bleeding

PALM

Structural causes of AUB detected by physical examination, imaging, or tissue sampling.

- ***P***olyps.
- ***A***denomyosis.
- ***L***eiomyomas (fibroids).
- ***M***alignancy.

COEIN

Represents nonstructural, hormone, or systemic causes of AUB.

- ***C***oagulopathy.
- ***O***vulatory dysfunction/Anovulatory bleeding.
- ***E***ndometrial.
- ***I***atrogenic.
- ***N***ot yet classified.

Abbreviations: AUB, abnormal uterine bleeding; FIGO, International Federation of Gynecology and Obstetrics.

Munro MG, et al. *Int J Gynaecol Obstet* 2011;113:3-13. doi: 10.1016/j.ijgo.2010.11.011

Perimenopausal Abnormal Uterine Bleeding

- Irregular ovulation and insufficient progesterone during the MT leads to premature and irregular shedding of endometrium.
- For some, bleeding can be heavy and prolonged, contributing to compromised health and impaired QOL.
- Although AUB during the MT is common, it is important to differentiate between normal physiology and underlying pathology.
- Even when bleeding is not heavy or prolonged, unscheduled bleeding can significantly affect QOL. Treatment should be offered.
- Any bleeding, including spotting postmenopause, warrants evaluation.

Dreisler E, et al. *Maturitas* 2024;184:107944. doi: 10.1016/j.maturitas.2024.107944

SECTION 4

Clinical Assessment and Screening

The Menopause Society™

Clinical Assessment and Screening: Key Components for Menopause History

Symptoms effect on QOL and function

- Including, but not limited to, hot flashes, night sweats, genitourinary symptoms, decreased libido, insomnia, and changes in mood and cognition.
- Screening questionnaires can elicit symptoms and degree of bother or interference (eg, The Menopause Transition Scale [MTS])

Menstrual history

- Last menstrual period, frequency, duration, amount of flow, intermenstrual bleeding, history of polycystic ovary syndrome or endometriosis; age at menarche and final menses.

Type of menopause

- Natural vs induced.

Medications

- Specifically take note of anticoagulants, hormones, selective estrogen receptor modulators (SERMs), chemotherapy, antipsychotics, antidepressants, steroids, and opioids because they may influence symptoms.

Anderson NJ, et al. *Menopause* 2022:868-876. doi:10.1097/GME.0000000000001975

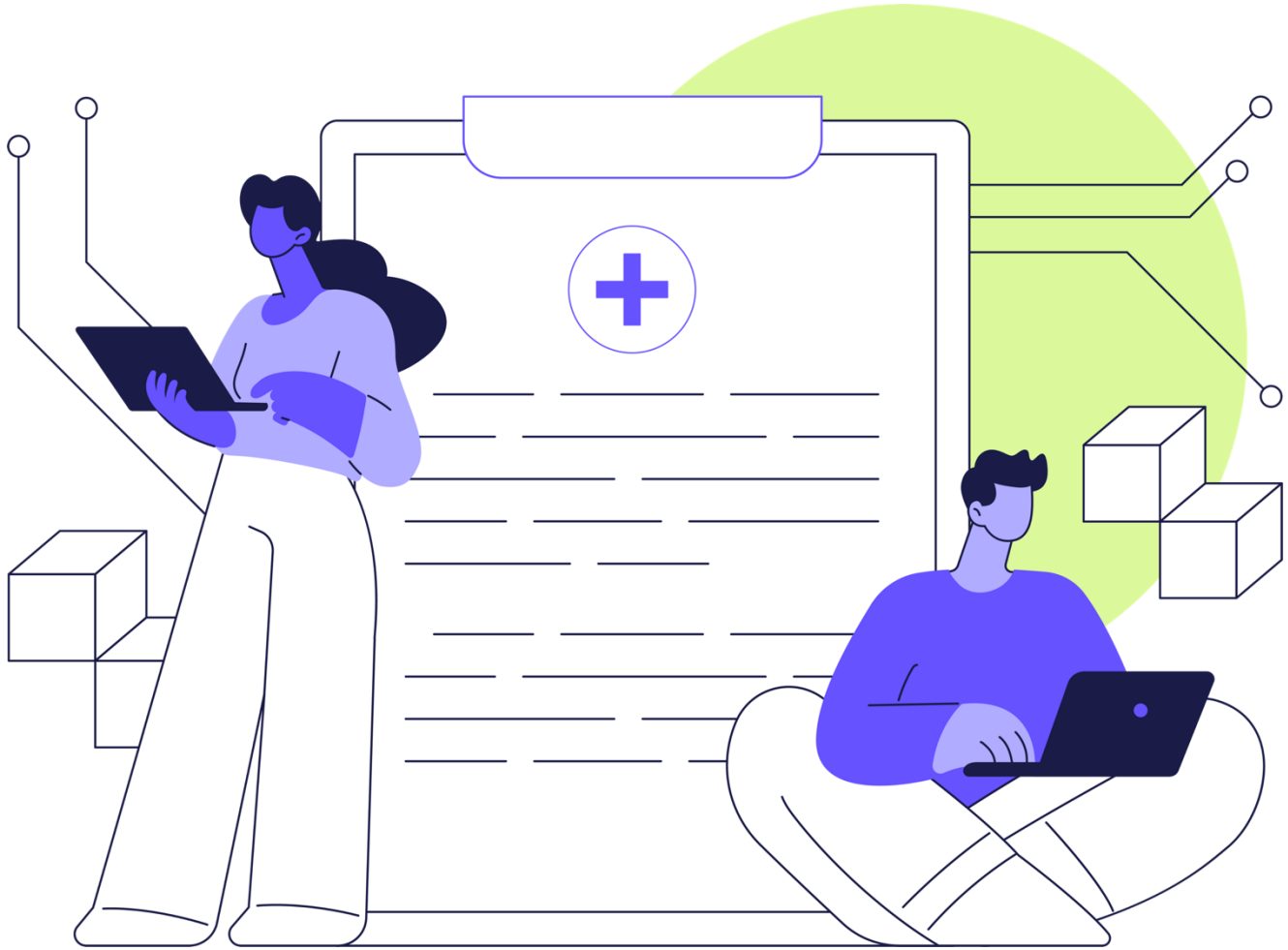
Clinical Assessment and Screening: Key Components for Menopause History (cont)

Menopause Transition Scale			
Please circle the answer that is closest to how you have felt in the last 2 wk.			
SYMPTOM	**EASY (3)**	**MODERATE (2)**	**HARD (1)**
Hot Flashes/ Night Sweats	Rare to none, no sweating, predictable, barely distracting	Somewhat frequent, sweating, predictable, somewhat distracted from activity	Frequent, sweating, unpredictable, very distracting from activity
Weight	Stable, healthy or overweight, losing	Overweight or not losing	Obese or gaining
Energy	Good, rested in AM, mostly good days	Moderate, mostly rested in AM, good and bad days	Tired, mostly not rested in AM, mostly bad days
Libido	Both partners initiate, both satisfied, relationship good predictable, no dysfunction	Only partner initiates, OK once going, relationship mostly OK	No one initiating, no desire, relationship stressed
Moods	Good mood-rare mild anxiety/ depressed mood, no one notices,	Some anxiety/depressed mood, others notice, not predictable, some dysfunction	Mostly anxious or depressed, others notice, not predictable, poor function in daily activities
Vaginal Dryness	Minor to no dryness, rare to no bladder symptoms, no pain with intercourse	Some dryness, some bladder symptoms, mild pain with intercourse	Mostly dryness, always bladder symptoms, mostly pain with intercourse
Vaginal Bleeding	None or light, predictable, not interfering with daily activities	Moderate to heavy, predictable, some interference with daily activities	Heavy, not predictable, interfering with daily activities

From Anderson NJ, et al. *Menopause* 2022:868-876. doi:10.1097/GME.0000000000001975

Risk Factor Assessment

- Medical history.
- Surgical history.
- Family history: hormone-sensitive cancers, clotting disorders, heart disease or stroke, osteoporosis.
- Social history: includes tobacco use, drug use, vaping, alcohol use, and exercise.
- Sexual history: current partners, sexually transmitted infections, protection, numbers of pregnancies and outcomes, history of infertility.



ACOG Committee Opinion No 755: well-woman visit. *Obstet Gynecol* 2018;12:e181-e186. doi: 10.1097/AOG.0000000000002897

Physical Examination

- Height
- Weight
- Waist-hip ratio
- Blood pressure
- Breast and pelvic examinations

Testing and Imaging

- Generally, measuring serum hormone concentrations is not recommended to diagnose the MT or to guide treatment success.
- Hormone concentrations are variable and don’t stabilize until 3 to 6 years after the FMP.
- Checking FSH, LH, estradiol, testosterone, prolactin, thyroid-stimulating hormone (TSH), AMH, or genetic testing may be indicated.
    - In those aged younger than 40 years and amenorrheic or with fertility concerns.
    - When the uterus is absent or a progestin intrauterine device is present, unable to assess bleeding or menopause status.
    - In those with an atypical presentation of VMS or VMS accompanied by symptoms not commonly associated with menopause, an evaluation for infection, thyroid dysfunction, malignancy, pheochromocytoma, or carcinoid syndrome may also be warranted.

Crandall C, et al. *JAMA* 2023;329:405-420. doi:10.1001/jama.2022.24140

Preventive Screening in Midlife

Osteoporosis

- Initiate screening with dual-energy x-ray absorptiometry (DXA) at age 65 years if no risk factors. Initiate earlier than age 65 with one of these risk factors:
    - FRAX score: 10-year risk of 8.4% or higher of a major fracture.
    - Postmenopausal with history of a fragility fracture, low body weight (BMI <21kg/m^2), high-risk medication use, or underlying medical comorbidity associated with bone loss.

Cholesterol

- Women aged 55 to 65 years should have lipid panel every 1 to 2 years.
- Adults aged older than 65 years should be screened annually. Those aged younger than 55 years, every 5 years.

Diabetes

- US Preventive Services Task Force (USPSTF) recommends testing with hemoglobin A_{1c} every 3 years in adults aged 35 to 70 years who are overweight (BMI ≥ 25mg/m^2) or obese (BMI≥ 30kg/m^2).

International Society for Clinical Densitometry. 2019 ICSD Official Positions—Adult. Accessed May 28, 2024; US Preventive Services Task Force, et al. *JAMA* 2018;319:2521-2531. doi: 10.1001/jama.2018.7498; NIH Heart, Lung, and Blood Institute: Blood cholesterol: diagnosis. Last updated April 18, 2024. Accessed May 27, 2024; US Preventive Services Task Force. *JAMA* 2021:326:736-743. doi:10.1001/jama.2021.12531

Preventive Cancer Screening in Midlife

- Breast cancer screening recommendations (USPSTF and the American College of Obstetricians and Gynecologists [ACOG]):
  - Biennial screening ages of 40 to 74 years (USPSTF).
  - Every 1 to 2 years age 40 to 75 years (ACOG).
  - Insufficient evidence to recommend continued screening over age 75 years or that supplemental screening indicated with dense breast tissue (USPSTF).
- Cervical cancer screening recommendations (USPSTF and American Cancer Society):
  - Aged 30 to 65 years:
    - Primary human papillomavirus (HPV) testing every 5 years.
    - Cotesting every 5 years (cytology + HPV testing).
    - Cytology alone every 3 years.
  - Aged older than 65 years:
    - No screening necessary after adequate negative prior screening.
  - Prior hysterectomy: no screening necessary in those without a history of cervical intraepithelial neoplasia (CIN) 2+ or more in the past 25 years or cervical cancer ever.

Markus JZ, et al. *J Low Genit Tract Dis* 2021;25:187-191. doi: 10.1097/LGT.0000000000000614; US Preventive Services Task Force. *JAMA*. 2021;325:962-970. doi: 10.1001/jama.2021.1117; US Preventive Services Task Force. *JAMA* 2021;325:1965-1977. doi: 10.1001/jama.2021.6238; US Preventive Services Task Force. *JAMA* 2024. doi:10.1001/jama.2024.5534

Preventive Cancer Screening in Midlife (cont)

- Colon cancer screening recommendations (USPSTF):
  - Begin screening at age 45 years.
    - Annual screening options: fecal immunochemical test, Guaiac-based fecal occult blood test.
    - Every 3 years: Cologuard.
    - Every 5 years: flexible sigmoidoscopy, computed tomography (CT), virtual colonoscopy.
    - Every 10 years: colonoscopy.
  - Screening is no longer recommended for people aged older than 85 years.
- Lung cancer screening recommendations (USPSTF):
  - Annual low-dose CT screening in asymptomatic persons aged 55 to 80 years with a 30-pack/year history, current smokers, or quit within the past 15 years.

Markus JZ, et al. *J Low Genit Tract Dis* 2021;25:187-191. doi: 10.1097/LGT.0000000000000614; US Preventive Services Task Force. *JAMA*. 2021;325:962-970. doi: 10.1001/jama.2021.1117; US Preventive Services Task Force. *JAMA* 2021;325:1965-1977. doi: 10.1001/jama.2021.6238; US Preventive Services Task Force. *JAMA* 2024. doi:10.1001/jama.2024.5534

Recommended Immunizations in Midlife

- Vaccines play a major role in reducing morbidity and mortality from vaccine-preventable diseases.
- Vaccination assessment should be evaluated regularly based on risk factors and age.

Vaccine	<45 y	50-64 y	≥65 y
COVID-19	1 or more doses of updated vaccine		
Influenza inactivated or recombinant	1 dose annually		
Respiratory syncytial virus (RSV)		≥60 years recommended based on shared decision-making	
Tetanus, diphtheria, pertussis (Tdap)	Tdap booster every 10 years		
Varicella (VAR)	2 doses if born in 1980 or later with additional risk factors		
Zoster recombinant (RZV)		2 doses	
Human papillomavirus (HPV)	2-3 doses, depending on age at initial vaccination		
Pneumococcal (PCV 15, 20, 23)	Recommended based on risk factors (ie, alcoholism, tobacco use, coronary heart disease, liver disease, lung disease, diabetes, autoimmune disorders, immunodeficiency, sickle cell disease).		Recommended based on shared decision-making

ACOG Committee Opinion No 772: immunization, infectious disease, and public health preparedness expert work group. *Obstet Gynecol* 2019;133:e254-e259. doi: 10.1097/AOG.0000000000003130;
CDC Immunization Schedules. 2024. www.cdc.gov/vaccines/schedules/index.html. Accessed June 7, 2024.

SECTION 5

Hormone Therapy Considerations

75. Hormone Contraception
76. Transitioning from Hormone Contraception to Hormone Therapy
77. FDA Indications for Hormone Therapy Use
78. Categories of Hormone Therapy
79. Types of Estrogen Therapy
81. Oral Estrogen Therapy
82. Transdermal and Topical Estrogen Therapy
83. Vaginal Estrogen Therapy
84. Alternative Vaginal Therapy—Dehydroepiandrosterone Sulfate
85. Types of Progesterone Therapy
86. Alternative Progesterone Option
87. Selective Estrogen Receptor Modulators
88. Bazedoxifene
89. Ospemifene
90. Other Commercially Available Selective Estrogen Receptor Modulators
91. Bioidentical Hormone Therapy
92. Custom-Compounded Hormone Therapy Pros and Cons
93. Testosterone Indications and Prescribing
94. Contraindications to Hormone Therapy
95. Transdermal vs Oral Hormone Therapy Delivery and Risk for Adverse Outcomes
96. Potential Hormone Therapy Adverse Events
97. Timing of Hormone Therapy Initiation
98. Monitoring Hormone Therapy
99. Stopping Systemic Hormone Therapy and Duration of Use
100. Use of Hormone Therapy in Gene-Positive Carriers

Hormone Contraception

- Despite a decline in fertility during perimenopause, pregnancy is still possible until menopause is reached.
- Hormone contraception is the best option for those with bothersome perimenopausal symptoms, including AUB, and for those who wish to avoid pregnancy.
    - Low-dose combination estrogen-progestin contraceptives (pills, patch, ring) are only appropriate for healthy, lean, nonsmoking perimenopausal women without other contraindications.
    - Progestin-only contraception can be used when contraceptive doses of estrogen are contraindicated (ie, tobacco users, hypertension, history of venous thromboembolism [VTE]).
    - Long-acting, reversible contraceptive methods such as the levonorgestrel-releasing intrauterine systems (LNG-IUS) and the etonogestrel subdermal implant provide long-term protection from pregnancy and can be used to treat AUB.
    - Depot medroxyprogesterone acetate (MPA) injection may be associated with weight gain and lower BMD, which makes it less ideal in this patient population.

Curtis KM, et al. *N Engl J Med* 2017;376:461-468. doi: 10.1056/NEJMcp1608736; Curtis KM, et al. *MMWR Recomm Rep* 2016;65:1-66. doi: 10.15585/mmwr.rr6504a1; Curtis KM, et al. *MMWR Recomm Rep* 2016;65:1-103. doi: 10.15585/mmwr.rr6503a1; Trussell J, et al. *Contraceptive Technology*. 21st ed. Ayer; 2018:95-128.

Transitioning From Hormone Contraception to Hormone Therapy

- Individualization is required.
- May continue contraception until typical age of menopause (51-52 y) or when 90% of women reach menopause (55 y).
- Can transition from hormone contraception to HT if still symptomatic.
- Hot flashes may reappear transiently because birth control has higher hormone concentrations than HT.

Curtis KM, et al. *MMWR Recomm Rep* 2016;65:1-66. doi: 10.15585/mmwr.rr6504a1; Kaunitz AM. *N Engl J Med* 2008;358:1262-1270. doi: 10.1056/NEJMcp0708481

FDA Indications for Hormone Therapy Use

- VMS, including hot flashes and night sweats.
- Prevention (not treatment) of bone loss or osteoporosis.
- Treatment of premature hypoestrogenism because of
  - Hypogonadism.
  - Bilateral oophorectomy.
  - POI.
- GSM.

"The 2022 Hormone Therapy Position Statement of The North American Menopause Society" Advisory Panel. *Menopause* 2022;29:767-794. doi: 10.1097/GME.0000000000002028

Categories of Hormone Therapy

Estrogen therapy (ET)

- Unopposed systemic estrogen for postmenopausal women who have undergone hysterectomy or vaginally in low doses for women with vaginal symptoms regardless of presence of uterus.

Estrogen-progestogen systemic therapy (EPT)

- For postmenopausal women with a uterus.
- Progestogen reduces the risk of endometrial adenocarcinoma because of unopposed estrogen.

Progesterone systemic therapy (PT)—off-label

- In those with VMS with contraindications to ET.

Tissue selective estrogen complex (TSEC)

- For postmenopausal women with a uterus who prefer a progestogen-free option.

Selective estrogen-receptor modulators (SERMs)

- Commercially available formulations for treatment of dyspareunia, osteoporosis prevention or treatment, and breast cancer reduction.
- Estrogen antagonist has a similar effect to progestogen on the uterine lining.

Dehydroepiandrosterone (DHEA)

- For postmenopausal women with moderate to severe dyspareunia secondary to GSM.

Liu JH, ed. Prescription Therapies. *Menopause Practice: A Clinician's Guide*, 6th ed. The North American Menopause Society; 2019:277-317.

Types of Estrogen Therapy

Conjugated equine estrogens (CEE)

- On the US market since 1940s.
- The most used in randomized, controlled trials (RCTs).
- More is known about efficacy and safety than any other estrogen product.
- Purified from urine of pregnant mares, consists of 20 estrogens, including estrone and 17β-estradiol.
- FDA approved for VMS, GSM, and prevention of osteoporosis.

Synthetic conjugated estrogens (CE)

- US government does not view as a generic equivalent to CEE; approved generic equivalent in Canada.
- FDA approved for VMS.

Micronized 17β-estradiol

- Most widely used estrogen in Europe, now more widely used in the United States.
- Only estrogen available in a US government-approved, bioidentical formulation.
- FDA approved for VMS, GSM, and prevention of osteoporosis.

Ethinyl estradiol

- Widely used in combination contraceptives.

Gaspard U, et al. *Menopause* 2020;27:848-857. doi: 10.1097/GME.0000000000001561; Gerard C, et al. *Drugs R D* 2023;23:77-92. doi: 10.1007/s40268-023-00419-5; Liu JH, ed. Prescription Therapies. *Menopause Practice: A Clinician's Guide*, 6th ed. The North American Menopause Society; 2019:277-317; Santoro N, et al. *J Clin Endocrinol Metab* 2021;106:1-15. doi:10.1210/clinem/dgaa764; "The 2022 Hormone Therapy Position Statement of The North American Menopause Society" Advisory Panel. *Menopause* 2022;29;767-794. doi:10.1097/GME.0000000000002028

Types of Estrogen Therapy (cont)

Esterified estrogens

- Oral products of synthetic estrogen mixtures containing 75% to 85% sodium estrone sulfate.
- FDA approved for VMS.

Estetrol

- Naturally occurring estrogen produced in fetal liver during pregnancy.
- Has been shown to inhibit ovulation and treat VMS.
- Combination of estetrol and drospirenone, used in oral contraceptives.
- Not FDA approved for VMS, GSM, or osteoporosis prevention.

Gaspard U, et al. *Menopause* 2020;27:848-857. doi: 10.1097/GME.0000000000001561; Gerard C, et al. *Drugs R D* 2023;23:77-92. doi: 10.1007/s40268-023-00419-5; Liu JH, ed. Prescription Therapies. *Menopause Practice: A Clinician's Guide*, 6th ed. The North American Menopause Society; 2019:277-317; Santoro N, et al. *J Clin Endocrinol Metab* 2021;106:1-15. doi:10.1210/clinem/dgaa764; "The 2022 Hormone Therapy Position Statement of The North American Menopause Society" Advisory Panel. *Menopause* 2022;29;767-794. doi:10.1097/GME.0000000000002028

Oral Estrogen Therapy

- Historically, the most widely used form in North America.
- Because of first-pass uptake in the gastrointestinal tract and hepatic metabolism
  - Increase in high-density lipoprotein cholesterol.
  - Associated with 25% increase in triglycerides.
  - Increase in some hepatic globulins, coagulation factors, and inflammatory factors.
  - Decrease in E-selectin, an endothelial adhesion molecule, which may affect coronary artery disease.
  - Increase in sex hormone-binding globulin (SHBG).

Canonico M, et al. *Stroke* 2016;47:1734-1741. doi: 10.1161/STROKEAHA.116.013052; Goodman MP. *J Womens Health (Larchmt)* 2012;21:161-169. doi: 10.1089/jwh.2011.2839; Laliberte F, et al. *Menopause* 2011;18:1052-1059. doi: 10.1097/gme.0b013e3182175e5c; Renoux C, et al. *BMJ* 2010;340:c2519. doi: 10.1136/bmj.c2519; Santen RJ. *Climacteric* 2015;18:121-134. doi: 10.3109/13697137.2014.947254; Shifren JL, et al. *J Clin Endocrinol Metab* 2008;93:1702-1710. doi: 10.1210/jc.2007-2193; Suckling J, et al. *Cochrane Database Syst Rev* 2006;(4):CD001500. doi: 10.1002/14651858.CD001500.pub2

Transdermal and Topical Estrogen Therapy

- Patch, gel, spray, and emulsion forms are available.
- Not subjected to first-pass hepatic metabolism.
- Associated with more stable serum levels.
- Minimal effect on SHBG; therefore, less of a negative effect on sexual functioning.
- Risk of skin-to-skin transfer of small amounts.
- Adequately powered studies show increase in VTE and stroke with oral ET but not transdermal.

Canonico M, et al. *Stroke* 2016;47:1734-1741. doi: 10.1161/STROKEAHA.116.013052; Goodman MP. *J Womens Health (Larchmt)* 2012;21:161-169. doi: 10.1089/jwh.2011.2839; Laliberte F, et al. *Menopause* 2011;18:1052-1059. doi: 10.1097/gme.0b013e3182175e5c; Renoux C, et al. *BMJ* 2010;340:c2519. doi: 10.1136/bmj.c2519; Santen RJ. *Climacteric* 2015;18:121-134. doi: 10.3109/13697137.2014.947254; Shifren JL, et al. *J Clin Endocrinol Metab* 2008;93:1702-1710. doi: 10.1210/jc.2007-2193; Suckling J, et al. *Cochrane Database Syst Rev 2006*;(4):CD001500. doi: 10.1002/14651858.CD001500.pub2

Vaginal Estrogen Therapy

- Cream, tablet, insert, and rings (low dose for local therapy and two higher doses for systemic therapy) available.
- Small amounts of estrogen administered locally effective for treating vaginal atrophy.
- Endometrial protection is not needed with low doses of local estrogen.
- Endometrial protection with a progestogen is needed with systemic dose estrogen rings.

Canonico M, et al. *Stroke* 2016;47:1734-174. doi: 10.1161/STROKEAHA.116.013052; Goodman MP. *J Womens Health (Larchmt)* 2012;21:161-169. doi: 10.1089/jwh.2011.2839; Laliberte F, et al. *Menopause* 2011;18:1052-1059. doi: 10.1097/gme.0b013e3182175e5c; Renoux C, et al. *BMJ* 2010;340:c2519. doi: 10.1136/bmj.c2519; Santen RJ. *Climacteric* 2015;18:121-134. doi: 10.3109/13697137.2014.947254; Shifren JL, et al. *J Clin Endocrinol Metab* 2008;93:1702-1710. doi: 10.1210/jc.2007-2193; Suckling J, et al. *Cochrane Database Syst Rev* 2006;CD001500. doi: 10.1002/14651858.CD001500.pub2

Alternative Vaginal Hormone Option: Dehydroepiandrostero

- 6.5 mg 0.5% DHEA vaginal suppository.
- DHEA converted into estrogens and androgens in vaginal tissue.
- Inserted once daily at bedtime.
- Serum steroid levels remained within the normal postmenopausal range and not associated with recurrence of ovarian, endometrial, cervical, or breast cancer.
- Only adverse event: vaginal discharge.
- Endometrial safety confirmed at 1 year.
- No head-to-head studies comparing DHEA and vaginal estrogen.
- FDA approved for moderate to severe dyspareunia secondary to GSM.

Casiano Evans E, et al. *Obstet Gynecol* 2023;142:555-570. doi: 10.1097/AOG.0000000000005288; Cipriani S, et al. *Climacteric* 2023;26:309-315. doi: 10.1080/13697137.2023.2213827; Labrie F, et al. *Menopause* 2016;23:243-256. doi: 10.1097/GME.0000000000000571; Portman DJ, et al. *Menopause* 2015;22:1289-1295. doi: 10.1097/GME.0000000000000470; Portman DJ, et al. *Climacteric* 2019;22:65-72. doi: 10.1080/13697137.2018.1535583; The NAMS 2020 GSM Position Statement Editorial Panel. *Menopause* 2020;27:976-992. doi: 10.1097/GME.0000000000001609

Types of Progesterone Therapy

Progesterone

- Micronized progesterone (MP) compound identical to endogenous progesterone.
- Bedtime dosing advised because of sedating effects.
- Only FDA-approved bioidentical progestogen.
- Contraindicated in women with peanut allergy.
- No systemic topical options, except compounded (not recommended).
- Vaginal progesterone (off-label use):
    - Used for infertility treatments.
    - Provides endometrial protection for postmenopausal systemic estrogen (expensive).

Progestins

- Synthetic products with progesterone-like activity.
- Classified into two groups based on structure.
- Chemical structure similar to progesterone (pregnanes).
- MPA is the most commonly used and studied in the United States for endometrial protection.
- Chemical structure similar to testosterone.
    - Norethindrone, levonorgestrel, norgestimate.
    - Most potent progestogen.

Capozzi, A. et al. *Minerva Obstet Gynecol* 2022;74:364-376. doi: 10.23736/S2724-606X.21.04881-8; Montplaisir J, et al. *Menopause* 2001;8:10-16. doi: 10.1097/00042192-200101000-00004; Schussler P, et al. *Psychoneuroendocrinology* 2008;33:1124-1131. doi: 10.1016/j.psyneuen.2008.05.013

Alternative Progesterone Option

- Progestin-containing intrauterine device.
- LNG 52 mg provides endometrial precancer and cancer protection.

Crandall CJ, et al. *JAMA* 329;2023:405-420. doi:10.1001/jama.2022.24140;
Luo L, et al. *Cochrane Database Syst Rev* 2018;12:CD009458. doi:
10.1002/14651858.CD009458.pub3; “The 2022 Hormone Therapy Position Statement of The North American Menopause Society” Advisory Panel. *Menopause* 2022;29:767-794. doi: 10.1097/GME.0000000000002028

Selective Estrogen-Receptor Modulators

- SERMs exhibit both agonist and antagonist properties, depending on target tissue.
- Like estrogen, may bind to hormone receptors ER-α and ER-β.
- Numerous commercially available SERMs.
  - Bazedoxifene (BZA), ospemifene, tamoxifen, raloxifene, and toremifene.
- Naturally occurring SERMs (bind predominately ER-β).
  - Phytoestrogens: isoflavones, coumestans, prenylflavonoids.
  - Food sources rich in phytoestrogens: nuts, oil-containing seeds, legumes, and soy-containing products.

Dutertre M, et al. *J Pharmacol Exp Ther* 2000;295:431-437; Yildiz F, ed. *Phytoestrogens in Functional Foods*. CRC: Boca Raton, Florida; 2006.

Bazedoxifene

- BZA is a third-generation SERM.
  - Estrogen agonist on bone.
  - Estrogen antagonist on breast and endometrial tissue.
- Also shown to improve sleep and vaginal dryness.
- Favorable safety profile in terms of risk of endometrial polyps, hyperplasia, carcinoma.
- Effect on breast density similar to placebo.
- Associated with 2-fold increased risk of VTE; avoid in women at high risk.
- Approved in Europe and Japan for treatment of osteoporosis.
- BZA and CEE (TSEC):
  - Used without progestogen in those with a uterus.
  - Indicated for those not wanting to use EPT for systemic symptoms.
  - FDA approved for treatment of VMS and prevention of osteoporosis.

Christiansen C, et al. *BMC Musculoskelet Disord* 2010;11:130. doi: 10.1186/1471-2474-11-130; Harvey HA, et al. *Breast* 2006;15:142-157. doi: 10.1016/j.breast.2005.09.007; Silverman SL, et al. *J Bone Miner Res* 2018;23:1923-1934. doi: 10.1359/jbmr.080710

Ospemifene

- Oral 60 mg tablet taken daily.
- Estrogen agonist on vaginal tissue.
- Modest increase in hot flashes compared with placebo (9.6% vs 3.4%).
- Estrogenic-type response on endometrium but not associated with increase in endometrial hyperplasia or cancer within first year.
- Associated with slight increased risk of hemorrhagic stroke and VTE (black box warning).
- FDA approved for treatment of moderate to severe dyspareunia.

Casiano Evans E, et al. *Obstet Gynecol* 2023;142:555-570. doi: 10.1097/AOG.0000000000005288

Other Commercially Available Selective Estrogen-Receptor Modulators

Raloxifene

(FDA approved for osteoporosis treatment of the spine).

- Second-generation SERM.
- Estrogen agonist on bone.
- Minimal effect on uterine endometrium.
- Antiestrogenic effects on breast.
- Lower risk of uterine cancer, VTE, and cataracts compared with tamoxifen.

Tamoxifen

(FDA approved for breast cancer prevention and treatment).

- Potent antiestrogen in breast tissue.
- Can reduce the risk of invasive ER+ breast cancer in high-risk women by 49%.
- Estrogen agonist on bone, liver, and uterus.

Toremifene

(FDA approved to treat advanced estrogen-sensitive breast cancer and as adjuvant treatment of early breast cancer.

- Related to tamoxifen.
- Weaker effect on endometrium compared with tamoxifen.
- May prolong QT interval in the heart (black box warning).

Bachmann GA, et al. *Menopause* 2010;17:480-486. doi: 10.1097/gme.0b013e3181c1ac01; Constantine GD, et al. *Menopause* 2015;222:36-43. doi: 10.1097/GME.0000000000000275; Cummings SR, et al. *JAMA* 1999;281:2189-2197. doi: 10.1001/jama.281.23.2189; Fisher B, et al. *J Natl Cancer Inst* 1998;90:1371-1388. doi: 10.1093/jnci/90.18.1371; Love RR, et al. *N Engl J Med* 1992;326:852-856. doi: 10.1056/NEJM199203263261302; Martino S, et al. *J Natl Cancer Inst* 2004;96:1751-1761. doi: 10.1093/jnci/djh319; Wurz GT, et al. *Clin Interv Aging* 2014:9:1939-1950. doi: 10.2147/CIA.S73753

Bioidentical Hormone Therapy

- Hormones that are chemically identical to hormones produced by ovaries during reproductive years, including estrone, estradiol, estriol, progesterone, testosterone, DHEA, and cortisol.
- Bioidentical is a marketing term not recognized by FDA and is often misused by compounding pharmacies who inaccurately market as “natural” and “safer” when there is no evidence to support these claims.
- The Menopause Society and ACOG have each released position statements against the use of compounded bioidentical hormones and do not endorse serum, saliva, or urine hormone testing to determine dosing.
- There are FDA-approved, extremely effective, bioidentical hormones that are monitored and regulated for purity and safety.

Bioidenticals: Sorting Myths From Facts [FDA Consumer Update]. January 9, 2008; Compounded Bioidentical Menopausal Hormone Therapy: ACOG Clinical Consensus No. 6. *Obstet Gynecol* 2023;142:1266-1273. doi: 10.1097/AOG.0000000000005395; Simon JA, et al. *Hormone Testing and Bioidentical Hormones*. 2007. www.menopause.org/docs/default-document-library/pg06monogrpah.pdf?sfvrsn=0. Accessed May 29, 2024; Pinkerton JV. *OBG Management*, 2009;21:42-52. “The 2022 Hormone Therapy Position Statement of The North American Menopause Society” Advisory Panel. *Menopause* 2022;29:767-794. doi: 10.1097/GME.0000000000002028

Custom-Compounded Hormone Therapy Formulations Pros and Cons

Pros

- Allows individualized dosing and combination therapy.
- Various modes of administration: subdermal implants (not recommended), sublingual tablets, rectal suppositories, and nasal sprays.
- For those with allergies or intolerance to FDA-approved therapies, can be prepared without binders, fillers, dyes, preservatives, or adhesives.

Cons

- Not FDA regulated.
- Do not require proof of claim and are not held to the same standard of manufacture.
- Not found to be safer than FDA-approved formulations in clinical trials.
- May even have harms associated with unknown pharmacokinetics (eg, pellets).
- Lack of monitoring of adverse events.
- Often not covered by third-party payers.

Compounded Bioidentical Menopausal Hormone Therapy: ACOG Clinical Consensus No. 6. *Obstet Gynecol* 2023;142:1266-1273. doi: 10.1097/AOG.0000000000005395; Crandall CJ, et al. *JAMA* 2023;329:405-420. doi:10.1001/jama.2022.24140; Rosenthal MS. *Menopause* 2008;15:1014-1022. doi: 10.1097/gme.0b013e318178862e; Cirigliano M. *J Womens Health (Larchmt)* 2007;16:600-631. doi: 10.1089/jwh.2006.0311; 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. doi: 10.1002/14651858.CD010407.pub2

Testosterone Indications and Prescribing

- Testosterone in doses less than one-tenth those used for males slightly improves sexual function (satisfactory sexual-event frequency, sexual desire, arousal, orgasm, responsiveness) and self-image and reduces sexual concerns and distress in postmenopausal women with hypoactive sexual desire disorder (HSDD).
  - Meta-analyses show no severe adverse events (AEs) with physiologic testosterone use.
  - AEs and safety concerns may occur with higher doses.
  - Long-term safety of testosterone therapy has not been established.
  - Total serum testosterone concentration should not be used to diagnose HSDD.
  - No FDA-approved formulations for postmenopausal women.
  - Often not covered by third-party payers.

Davis SR, et al. *Climacteric* 2019; 22:429-434. doi: 10.1080/13697137.2019.1637079; Islam RM, et al. *Lancet Diabetes Endocrinol* 2019;7:754-766. doi: 10.1016/S2213-8587(19)30189-5

Contraindications to Hormone Therapy

- Unexplained vaginal bleeding.
- Prior estrogen-sensitive cancers (breast/ovarian/endometrial).
- Triple-negative breast cancer; however, use of HT in symptomatic individuals may be considered if 5 years from diagnosis and treatment has been completed.
- History of coronary artery disease, stroke, myocardial infarction (MI).
- History of or inherited high risk for VTE.
- Severe active liver disease.
- Peanut allergy (MPA).

"The 2022 Hormone Therapy Position Statement of The North American Menopause Society" Advisory Panel. *Menopause* 2022;29:767-794. doi:10.1097/GME.0000000000002028

Transdermal Versus Oral Hormone Therapy Delivery and Risk for Adverse Outcomes

- Risk of blood clots with HT has been shown with oral ET and is greater with EPT than ET.
- In observational studies with transdermal ET there is little, if any, increased risk of blood clots. There is a slight risk when oral progestogen is added.
- Those with an active or history of VTE:
  - First-line is nonhormone therapy.
  - If nonhormone therapy is not effective, providers should consult with patient's hematologist before providing low-dose transdermal HT and discuss risks and benefits.
  - May use HT while undergoing anticoagulation treatment.

Canonico M, et al. *Circulation* 2007;115:840-845. doi: 10.1161/CIRCULATIONAHA.106.642280; LaVasseur C, et al. *Res Pract Thromb Haemost* 2022;6:e12763. doi: 10.1002/rth2.12763; Martinelli I, et al. *Blood* 2016;127:1417-1425. doi: 10.1182/blood-2015-08-665927; Sammaritano LR, et al. *Arthritis Rheumatol* 2020;*72*:529-556. doi: 10.1002/art.41191; Sobel TH, et al. *Menopause* 2022;29:483-490. doi: 10.1097/GME.0000000000001938

Potential Hormone Therapy Adverse Events

- 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.

"The 2022 Hormone Therapy Position Statement of The North American Menopause Society" Advisory Panel. *Menopause* 2022;29:767-794; doi:10.1097/GME.0000000000002028

Timing of Hormone Therapy Initiation

- Timing hypothesis.
  - Less CVD risk associated with HT use and potential CHD and cognitive 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.
  - Use of HT within 10 years of the onset of menopause was associated with a lower CHD risk than if it was started ≥20 years from the FMP.
  - Women aged 50 to 59 y in the ET arm had a more favorable all-cause mortality outcome and fewer MIs.
- Early Estrogen Prevention Study and the Early Versus Late Intervention Trial With Estradiol suggested cardiovascular (CV) safety of HT initiated early in menopause based on favorable CV biomarkers; underpowered to assess primary CV outcomes.

Ali N, et al. *Cureus* 2023;15:e43053. doi: 10.7759/cureus.43053; Harman SM, et al. *Ann Intern Med* 2014;161:249-260. doi: 10.7326/M14-0353; Hodis HN, et al. *N Engl J Med* 2016;374:1221-1231. doi: 10.1056/NEJMoa1505241; Manson JE, et al. *JAMA* 2013;310:1353-1368. doi: 10.1001/jama.2013.278040; Manson JE, et al. *JAMA* 2017;318:927-938. doi: 10.1001/jama.2017.11217; Rossouw JE, et al. *JAMA* 2007;297:1465-1477. doi: 10.1001/jama.297.13.1465

Monitoring Hormone Therapy

- Annual return visits.
  - More frequent visits for new starts or those with AEs.
- Annual mammogram.
- Endometrial sampling or transvaginal ultrasound is not required unless persistent postmenopausal bleeding or AUB in the MT develops. Hysteroscopy may be indicated.
- Serum hormone concentrations are not indicative of symptom severity nor do they guide treatment success.
- Clinical goal:
  - Use the appropriate HT dose, duration, regimen, and route of administration.
  - Periodic reevaluation.

“The 2022 Hormone Therapy Position Statement of The North American Menopause Society” Advisory Panel. *Menopause* 2022;29:767-794; doi:10.1097/GME.0000000000002028

Stopping Systemic Hormone Therapy and Duration of Use

- Decision should be individualized based on symptom severity and risk-benefit ratio.
- Approximately 50% experience recurrence of symptoms with discontinuation.
- Up to 20% of postmenopausal women have VMS that persist for 20 or more years.
- An observational study using prescription drug and encounter records of 10 million Medicare recipients found
    - Use of ET at age 65 years and beyond linked to reduced overall mortality and reduction of breast, lung, and colorectal cancer; congestive heart failure; VTE; atrial fibrillation; MI; and dementia. Many of these findings are consistent with prior observational studies representative of a healthy-user effect.
    - Use of EPT was not associated with benefit in any of these outcomes with the exception of congestive heart failure.
    - Increased breast cancer mortality was observed with EPT.
- Using a systematic review methodology, the National Institute for Health and Care Excellence found no evidence for CVD prevention with HT at any age and a small increase or neutral effect of ET on breast cancer.
- USPSTF, using a systematic review approach, found no benefit for primary prevention of chronic diseases, including CVD, in postmenopausal women.
- Low-dose local ET may be continued as long as vaginal symptoms are present.

Baik SH, et al. *Menopause* 2024;363-371.doi. 10.1097/GME.0000000000002335; US Preventive Services Task Force. *JAMA* 2022;328:1740-1746. doi:10.1001/jama.2022.18625

Use of Hormone Therapy in Gene-Positive Carriers

- *BRCA* carriers who undergo risk-reducing bilateral salpingo-oophorectomy (RRBSO) before the age of 45 years have a 50% to 55% reduction in breast cancer risk.
  - Use of HT does not negate this risk reduction.
  - HT did not affect age at breast cancer diagnosis and time from RRBSO until diagnosis.
- Breast cancer risk by HT type and administration:
  - Breast cancer risk might be lower in those who receive ET compared with EPT (odds ratio [OR], 0.62; 95% confidence interval [CI], 0.29-1.21).
  - Use of transdermal ET combined with oral micronized progesterone appears to have similar safety to ET but oral MPA with estradiol may increase breast cancer risk.
  - In a large case-control study involving 43,000 cases and 430,000 age-matched controls (1:10) progestogens were differently associated with breast cancer risk.
    - MP use was not associated with risk, whereas the use of synthetic progestins was associated with increased risk (OR, 1.28; 95% CI, 1.22-1.35).

Abenhaim HA, et al. *Obstet Gynecol* 2022;139:1103-1110. doi: 10.1097/AOG.0000000000004723; Kotsopoulos J, et al. *JAMA Oncol* 2018;4:1059-1065. doi: 10.1001/jamaoncol.2018.0211. Manyonda I. et al. *Post Reprod Health* 2020;26:26-31. doi: 10.1177/2053369119876490; Marchetti C, et al. *Crit Rev Oncol Hematol* 2018;132:111-115. doi: 10.1016/j.critrevonc.2018.09.018; Rebbeck TR, et al. *J Clin Oncol* 2005;23:7804-7810. doi: 10.1200/JCO.200

SECTION 6

Treatment of Vasomotor Symptoms

The Menopause Society™

Recommended Evidence-Based Nonhormone Therapies

Lifestyle modifications

- Weight loss

Procedural interventions

- Stellate ganglion block

Mind-Body therapies

- Hypnosis
- Cognitive-behavioral therapy

Pharmacologic treatments

- Certain antidepressants
- Fezolinetant
- Gabapentinoids
- Oxybutynin

Lifestyle Modifications

- Weight loss is the only lifestyle modification associated with improvement in VMS based on limited evidence, with more of an effect in perimenopause and early postmenopause.
- Exercise and diet are integral to many health benefits and aid in weight loss; however, there is limited evidence from clinical trials confirming reduction in VMS.
    - Observational studies have shown an association with regular exercise and fewer reported VMS, but several *Cochrane* reviews concluded evidence was insufficient to recommend.
- Cooling techniques may help with coping with VMS but are not associated with reduction in VMS.
- There is no strong evidence that avoiding triggers (ie, alcohol, caffeine, spicy foods, hot liquids) improves VMS.

Cramer H, et al. *Maturitas* 2018;109:13-25. doi: 10.1016/j.maturitas.2017.12.005; Daley A, et al. *Cochrane Database Syst Rev* 2007 CD006108. doi: 10.1002/14651858.CD006108.pub2; Daley A, et al. *Cochrane Database Syst Rev* 2011:CD006108. doi: 10.1002/14651858.CD006108.pub3; Daley A, *Cochrane Database Syst Rev* 2014: CD006108. doi: 10.1002/14651858.CD006108.pub4; Guthrie JR, et al. *Obstet Gynecol* 1996;88:437-442. doi: 10.1016/0029-7844(96)00196-2; "The 2023 Nonhormone Therapy Position Statement of the North American Menopause Society" Advisory Panel. *Menopause* 2023;30:573-590. doi: 10.1097/GME.0000000000002200

US Government Regulation of Dietary Supplements

- Dietary supplements refer to a wide range of vitamins, minerals, herbs, or amino acids that are available without prescription and are not regulated by FDA.
- Manufacturers are permitted to make claims regarding their products' ability to alleviate symptoms; however, claims of disease benefit are not permissible.
- Labeling designations are generally reliable indicators of quality control in manufacturing (Identity, Quality, Purity, Strength, and Consistency).
    - US designations: "USP" and "NSF."
    - Canadian designations: "NPN" and "DIN."

Dietary Supplements

- Various vitamins, herbs, minerals, and amnio acids are widely marketed to improve VMS despite limited-to-no proven benefit.
- Because of limited rigorous, randomized, clinical trial data showing efficacy and lack of government regulation ensuring purity and safety, use of dietary supplements for management of VMS is not recommended.

"The 2023 Nonhormone Therapy Position Statement of the North American Menopause Society" Advisory Panel. *Menopause* 2023;30:573-590. doi: 10.1097/GME.0000000000002200

Mind-Body Therapies

- Various mind-body techniques are promoted as treatment for VMS, but only cognitive-behavioral therapy (CBT) and clinical hypnosis have some evidence for benefit.
  - CBT:
    - Brief therapy, typically four to six sessions, involving
      - Psychoeducation around the physiology of VMS, incorporating how thoughts and emotions affect the perception of physical sensations.
      - Training in strategies to manage VMS specifically geared toward challenging negative beliefs about VMS.
  - Individual or group-led therapy with a clinical psychologist or self-guided resources all have been found to reduce VMS bother and interference.
  - Two double-blind RCTs (MENOS 1 and MENOS 2), along with several other clinical trials found improvement in VMS bother and QOL in perimenopausal and postmenopausal women with and without breast cancer.
- Clinical hypnosis:
  - Involves induction of a deeply relaxed state and individualized mental imagery and suggestion to manage VMS.
  - Two RCTs performed by same investigator group in menopausal women have shown improvement over controls.

Atema V, et al. *J Clin Oncol* 2019;37:809-822. doi: 10.1200/JCO.18.00655; Ayers B, et al. *Menopause* 2012;19:749-759. doi: 10.1097/gme.0b013e31823fe835; Elkins G, et al. *J Clin Oncol* 2008;26:5022-5026. doi: 10.1200/JCO.2008.16.6389; Elkins GR, et al. *Menopause* 2013;20:291-298. doi: 10.1097/gme.0b013e3 1826ce3ed; Fenlon D, et al. *Psychooncology* 2020;29:1514-1523. doi: 10.1002/pon.5432; Green SM, et al. *Menopause* 2019;26:972-980. doi: 10.1097/GME.0000000000001363; Hardy C, et al. *Menopause* 2018:508-519. doi: 10.1097/GME.0000000000001048; Mann E, et al. *Lancet Oncol* 2012;13:309-318. doi: 10.1016/S1470-2045(11)70364-3; Norton S, et al. *Menopause* 2014;21:574-578. doi: 10. 1097/GME.0000000000000095; Sliwinski JR, et al. *J Evid Based Complementary Altern Med* 2017;22:652-659. doi: 10. 1177/2156587217708523; "The 2023 Nonhormone Therapy Position Statement of the North American Menopause Society" Advisory Panel. *Menopause* 2023;30:573-590. doi: 10.1097/GME.0000000000002200

Procedural Interventions

- Traditional acupuncture has the same efficacy as sham for VMS.
- Electroacupuncture shows promise but requires more rigorous studies.
- Stellate ganglion blockade may alleviate moderate to very severe VMS in select women but is associated with potential risk and benefit is not sustained beyond 6 months.
- Calibration of neural oscillations and chiropractic interventions have minimal to no clinical trials.

“The 2023 Nonhormone Therapy Position Statement of the North American Menopause Society” Advisory Panel. *Menopause* 2023;30:573-590. doi: 10.1097/GME.0000000000002200

Recommended Nonhormone Pharmacologic Therapies

Drug	Dose Range	Starting Dose	Efficacy	Adverse Events
Selective serotonin reuptake inhibitors				
Paroxetine salt	7.5 mg/d	Single dose	40%-65%	Nausea, dizziness, fatigue (don't use with tamoxifen)
Paroxetine	10 mg-25 mg/d	10 mg/d		
Citalopram Escitalopram	10 mg-20 mg/d	10 mg/d	50%-65%	Nausea, dizziness, fatigue, drowsiness, headache, dry mouth
Serotonin-norepinephrine reuptake inhibitors				
Desvenlafaxine	100 mg-150 mg/d	50 mg/d	50%-65%	Nausea, constipation, dry mouth, ↑blood pressure, insomnia
Venlafaxine	37.5 mg-150 mg/d	37.5 mg/d		

Crandall CJ, et al. *JAMA* 2023;329:405-420. doi: 10.1001/jama.2022.24140; Lederman S, et al. *Lancet* 2023;401:1091-1102. doi: 10.1016/S0140-6736(23)00085-5; "The 2023 Nonhormone Therapy Position Statement of the North American Menopause Society" Advisory Panel. *Menopause* 2023;30:573-590. doi: 10.1097/GME.0000000000002200

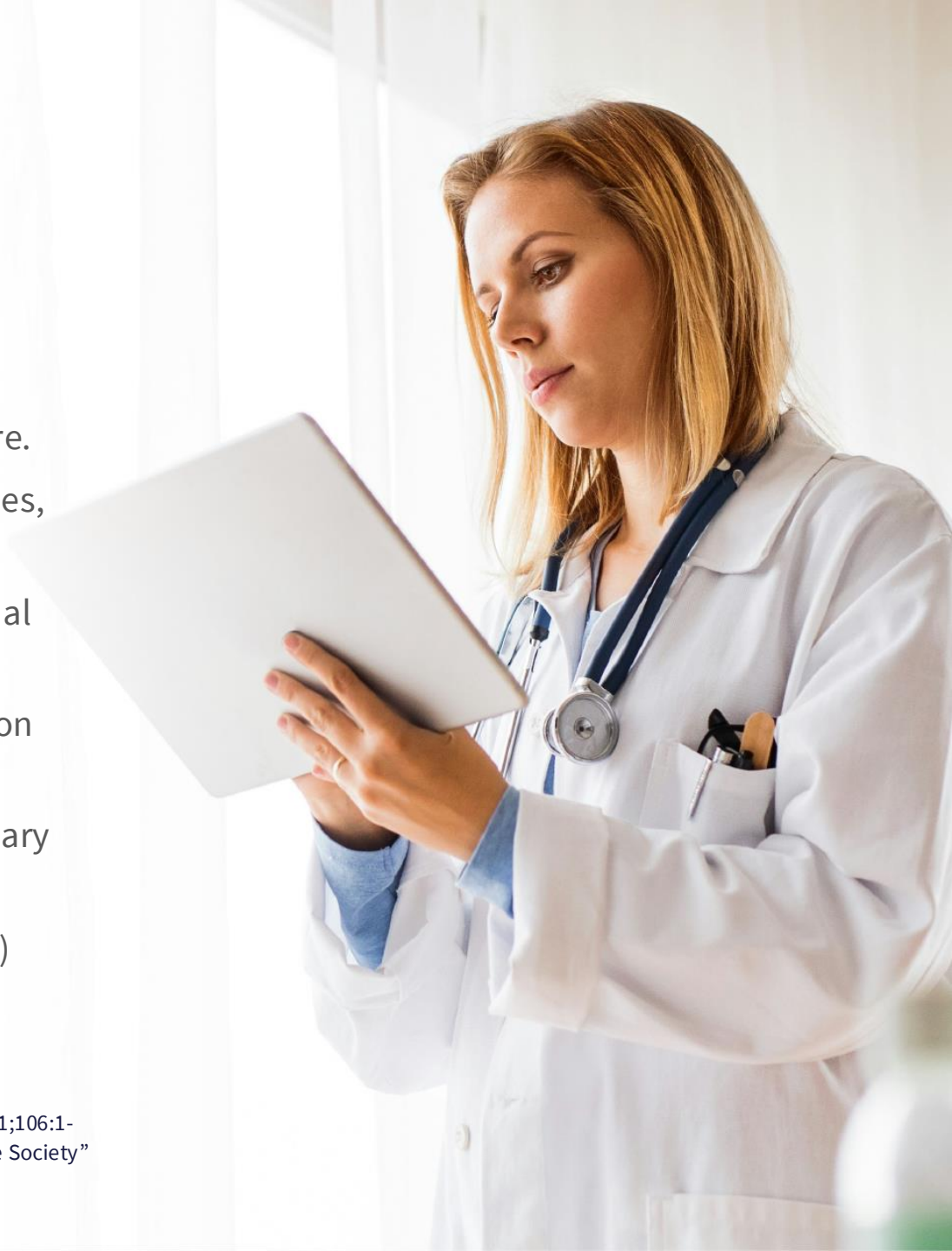
Recommended Nonhormone Pharmacologic Therapies (cont)

Drug	Dose Range	Starting Dose	Efficacy	Adverse Events
Gabapentinoid				
Gabapentin	900 mg-2,400 mg/d	100-300 mg (before bedtime)	40%-65%	Dizziness, headache, drowsiness, disorientation, unsteadiness
Anticholinergic				
Oxybutynin	2.5 mg-5 mg twice/d or 15 mg extended release/d	2.5 mg twice/d	70%	Dry mouth and eyes, constipation; long-term use may be associated with cognitive decline
Neurokinin B Antagonist				
Fezolinetant	45 mg/d	Single dose	50%-70%	Abdominal pain, diarrhea, insomnia, back pain, headache, ↑Liver enzymes

Crandall CJ, et al. *JAMA* 2023;329:405-420. doi: 10.1001/jama.2022.24140; Lederman S, et al. *Lancet* 2023;401:1091-1102. doi: 10.1016/S0140-6736(23)00085-5; "The 2023 Nonhormone Therapy Position Statement of the North American Menopause Society" Advisory Panel. *Menopause* 2023;30:573-590. doi: 10.1097/GME.0000000000002200

Hormone Therapy for Treatment of Vasomotor Symptoms

- Systemic HT reduces the frequency and severity of VMS by 75% or more.
- There are a variety of doses and formulations: oral, transdermal patches, topical sprays/gels, and vaginal rings.
- Transdermal HT bypasses the first-pass liver effect, and in observational studies was found to have lower risk for VTE than oral formulations.
- Transdermal HT has minimal effect on SHBG and may be a better option for those with sexual dysfunction.
- HT should be used at the lowest effective dose for the duration necessary to meet treatment goals.
- VMS after surgical menopause (bilateral salpingo-oophorectomy; BSO) often require higher doses of HT.



Crandall CJ, et al. *JAMA* 2023;329:405-420. doi: 10.1001/jama.2022.24140; Santoro N, et al. *J Clin Endocrinol Metab* 2021;106:1-15. doi: 10.1210/clinem/dgaa764; "The 2022 Hormone Therapy Position Statement of The North American Menopause Society" Advisory Panel. *Menopause* 2022;129:767-794. doi: 10.1097/GME.0000000000002028

Endometrial Protection

- Progestogens must be used in conjunction with ET for prevention of endometrial hyperplasia or cancer from unopposed systemic ET.
- A progestogen is not required in those who have undergone hysterectomy.
- Bazedoxifene, in a tissue-selective estrogen complex (TSEC; CEE + BZA) is an alternative to a progestogen.
- Combination, single dose formulations improve compliance and reduce the risk of irregular bleeding; however, dosing options are limited.
- When dosing adjustments or alternative formulations are preferred, ET and progestogen therapy (PT) may be administered separately.
    - Continuous dosing (highest rates of amenorrhea, lowest rates of hyperplasia).
        - ET and PT administered daily.
    - Cyclic dosing (associated with withdrawal bleeding).
        - Continuous-cyclic: ET administered daily; PT administered 12 days per month.
        - Long cycle/Continuous-cyclic: ET administered daily; PT add 14 days every 2 months (higher rate of endometrial hyperplasia or cancer).
        - Intermittent-combined: ET administered daily, PT in cycles of 3 days on and 3 days off.

"The 2022 Hormone Therapy Position Statement of The North American Menopause Society" Advisory Panel. *Menopause* 2022;129:767-794. doi: 10.1097/GME.0000000000002028; Crandall CJ, et al. *JAMA* 2023;329:405-420. doi: 10.1001/jama.2022.24140; Santoro N, et al. *J Clin Endocrinol Metab* 2021;106:1-15. doi: 10.1210/clinem/dgaa764

Combination Hormone Therapy Options for Vasomotor Symptoms

Oral Continuous-Cyclic		
CEE (E)+ MPA (P)	Premphase	0.625 mg E days 1-14, then 0.625 mg E + 0.5 mg P days 15-28
Oral Continuous-Combined		
17β-estradiol + progesterone	Bijuva	1 mg E + 100 mg P
CEE + MPA	Prempro	0.625 mg E + 2.5 mg or 5.0 mg P; 0.3 or 0.45 mg E + 1.5 mg P
Ethinyl estradiol + NETA	Femhrt	2.5 µg E + 0.5 mg P; 5 µg E + 1 mg P
17β-estradiol + NETA	Activella	0.5 mg E + 0.1 mg P; 1 mg E + 0.5 mg P
17β-estradiol + drospirenone	Angeliq	0.5 mg E + 0.25 mg P; 1 mg E + 0.5 mg P
CEE + BZA	Duavee	0.45 mg E + 20 mg BZA
Transdermal Continuous-Combined		
17β-estradiol + NETA	Combipatch	0.05 mg E + 0.1 4mg P; 0.05 mg E + 0.2 5mg P 2x/wk
17β-estradiol + LNG	ClimaraPro	0.045 mg E + 0.015 mg P once/wk

Abbreviations: BZA, bazedoxifene; CEE, conjugated equine estrogens; NETA, norethindrone acetate; LNG, levonorgestrel.

Liu JH, ed. Prescription therapies. *Menopause Practice: A Clinician's Guide*, 6th ed. The North American Menopause Society; 2019:277-317.

Estrogen Therapy Options for Vasomotor Symptoms

Oral Estrogen		
CEE	Premarin	0.3-1.25 mg
Synthetic CE-A[a]	Cenestin	0.3-1.25 mg
Synthetic CE-B[b]	Enjuvia	0.3-1.25 mg
Esterified estrogen	Menest	0.3-1.25 mg
17β-estradiol	Estrace, various generics	0.5-2.0 mg
Estradiol acetate	Femtrace	0.45-1.8 mg
Estropipate[c]	Ortho-Est, Ogen, various generics	0.625-5.0 mg

[a]Synthetic CE-A: mixture of 9 of the estrogens found in CE.

[b]Synthetic CE-B: includes the 9 estrogens found in CE and Δ–dehydroestrone sulfate.

[c]Formerly called piperazine estrone sulfate.

Liu JH, ed. Prescription therapies. *Menopause Practice: A Clinician's Guide*, 6th ed. The North American Menopause Society; 2019:277-317.

Estrogen Therapy Options for Vasomotor Symptoms (cont)

Transdermal Estrogen		
17β-estradiol matrix patch	Alora, Climara, Esclim, Fempatch, Menostar, Vivelle, Vivelle-Dot, various generics	0.014-0.1 mg delivered daily; applied once or twice/d
17β-estradiol reservoir patch	Estraderm	0.05-0.1 mg/d, applied twice/ wk
17β-estradiol transdermal gel	EstroGel, Elestrin, Divigel	0.52-0.75 mg/d
17β-estradiol topical emulsion	Estrasorb	2 packets/d
17β-estradiol transdermal spray	Evamist	1-3 sprays/d
Estradiol acetate ring	Femring	Device containing 12.4 mg or 24.8 mg releases 0.05 mg/d or 0.10 mg/d for 90 d

Liu JH, ed. Prescription therapies. *Menopause Practice: A Clinician's Guide*, 6th ed. The North American Menopause Society; 2019:277-317.

Progestogen Therapy Options for Endometrial Protection

Oral Tablets		
MPA	Provera, various generics	Continuous-combined: 2.5 mg/d Continuous-cyclic: 5 mg for 12-14 d
Norethindrone	Micronor, various generics	Continuous-combined: 0.35 mg/d Continuous-cyclic: 0.35-0.7 mg for 12-14 d
NETA	Aygestin, various generics	Continuous-combined: 0.5-1.0 mg/d Continuous-cyclic: 2.5 mg/d for 12-14 d
MP	Prometrium	Continuous-combined: 100 mg/d Continuous-cyclic: 200 mg/d for 12-14 d
Intrauterine System		
Levonorgestrel[a]	Mirena	20 µg/d

Abbreviations: MP, micronized progesterone; MPA, medroxyprogesterone acetate; NETA; norethindrone acetate.

[a]Not FDA approved for endometrial protection with estrogen therapy.

Liu JH, ed. Prescription therapies. *Menopause Practice: A Clinician's Guide*, 6th ed. The North American Menopause Society; 2019:277-317.

SECTION 7

Treatment of Genitourinary Symptoms

The Menopause Society™

Nonhormone Therapies for Genitourinary Syndrome of Menopause

- Vulvovaginal lubricants.
  - Short-term relief of dyspareunia because of atrophy.
  - Before or with sexual activity.
- Vulvovaginal moisturizers.
  - Improve hydration of vaginal mucosa.
  - On a regular basis regardless of sexual activity (ie, every 2-5/d, as needed).
- Pelvic floor physical therapy (PFPT).
- Vaginal dilators and vibrators.
  - Mechanically stretch vaginal tissues; help relax pelvic floor muscles.
  - Single, dynamic, expanding dilator was cleared by FDA in 2023.
- Regular vulvovaginal stimulation (including masturbation, partnered sex).
- Other considerations.
  - Topical lidocaine before dilation or vaginal penetration.
  - Botulinum neurotoxin A injections.
  - Vaginal laser therapy.
  - Autologous platelet rich plasma injections.

Christmas MM, et al. *Clin Obstet Gynecol* 2024;67:101-114. doi: 10.1097/GRF.0000000000000833; Our Bodies Ourselves Today Content Experts. July 2022. Saleh DM, et al. *J Cosmet Dermatol* 2022;21:4269-4275. doi: 10.1111/jocd.14873

Lubricants

- Lubricants can be used by both or all partners or applied to device before vaginal-penetrative activity.

Options	Benefits	Drawbacks
Water-based	• Compatible with latex and silicone • Less risk of vulvovaginal candidiasis • Inexpensive • Some products may not decrease sperm motility	• Hyperosmolar • Dries out quickly • May contain glycerin or parabens
Silicone-based	• Compatible with latex • Does not dry out as easily as water-based	• Iso-osmolar • More expensive • Difficult to wash off • Incompatible with silicone and rubber (ie, vibrators or dilators) • Impairs sperm motility • Some products may increase the risk of vaginal candidiasis
Oil-based (vegetable, olive, coconut, vitamin E)	• Inexpensive • Natural	• Erodes condoms • Impairs sperm motility • Increased colonization with candida species

Christmas MM, et al. *Clin Obstet Gynecol* 2024;67:101-114. doi: 10.1097/GRF.0000000000000833

Fractional CO_2 Laser

- Energy-based devices may improve vaginal health by causing microtrauma.
- Lasers are not FDA approved for treatment of GSM.
    - FDA (2018) warns of risks (vaginal burns, scarring, dyspareunia, and recurring pain).
- American Urogynecologic Society (2020): no consensus on best treatment plan or patient criteria, long-term outcomes unknown.
- Data regarding safety and efficacy of laser devices and RCTs are limited.
- Meta-analysis shows no benefit.
- Further evaluation is needed.

Alshiek J, et al. *Urogynecology (Phila)* 2022;28:633-648. doi: 10.1097/SPV.0000000000001241; Cruz VL, et al. *Menopause* 2018;25:21-28. doi: 10.1097/GME.0000000000000955; FDA News Release. August 2, 2018; Filippini M, et al. *J Sex Med* 2022;19):452-470. doi: 10.1016/j.jsxm.2021.12.010; Li FG, et al. *Am J Obstet Gynecol* 2023;229:278.e1-278.e9. doi: 10.1016/j.ajog.2023.05.005; Li FG, et al. *JAMA* 2021;326:1381-1389. doi: 10.1001/jama.2021.14892; Paraiso MFR, et al. *Menopause* 2020;27:50-56. doi: 10.1097/GME.0000000000001416; The NAMS 2020 GSM Position Statement Editorial Panel. *Menopause* 2020;27:976-992. doi:10.1097/GME.0000000000001609

Vaginal and Pelvic Floor Activity

- Regular stimulation of vulva and vagina promotes blood flow to genital area.
    - Natural secretions may help maintain vaginal health.
- 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.
- Genitopelvic pain and penetration disorder often requires multifactorial approach, including PFPT in conjunction with behavioral health modalities (ie, sex therapy, CBT, and hypnotherapy).

Christmas MM, et al. *Clin Obstet Gynecol* 2024;67:101-114. doi: 10.1097/GRF.0000000000000833

Pelvic Floor Physical Therapy

- PFPT addresses pelvic floor dysfunction because of hypertonicity of the pelvic floor muscles.
- PFPT specialists use an array of techniques to relax the pelvic floor.
  - Manual therapy involves stretch, massage, and myofascial release.
  - Exercise assisted with biofeedback.
  - Electrotherapy and vaginal dilators as needed.
- Involves internal and external work.
- Therapeutic course typically entails 4 to 8 hour-long weekly sessions with home exercises.
- Systematic review of two RCTs and 27 observational case series found 59% to 80% improvement in pelvic pain after PFPT.

Cosgriff L, et al. *Obstet Gynecol Clin N Am* 2024;51:241-257. doi: 10.1016/j.ogc.2024.02.001; Tu FF. et al. *Obstet Gynecol Surv* 2005;60:474-483. doi: 10.1097/01.ogx.0000162246.06900.9f; Wallace SL, et al. *Curr Opin Obstet Gynecol* 2019;31:485-93. doi: 10.1097/GCO.0000000000000584

Hormone Therapies for Genitourinary Syndrome of Menopause

- Local vulvovaginal ET (cream, pill, insert, ring).
- Systemic HT: ET or EPT (oral, transdermal patch, spray, emulsion, or ring).
- DHEA insert.
- Oral SERM.

Christmas MM, et al. *Clin Obstet Gynecol* 2024;67:101-114. doi: 10.1097/GRF.0000000000000833

Local Vaginal Estrogen Therapy

- Effective treatment for management of moderate to severe genitourinary symptoms because of hypoestrogenism.
- Recommended when there is inadequate response to nonprescription therapies.
- Local vaginal ET preferred over systemic HT because better efficacy and negligible systemic absorption leading to decreased oncologic and thromboembolic risk.
- Protection of the endometrial lining with progestogen is not needed.

Product Type	Brand name	Generic available	Loading dose	Maintenance dose
Vaginal cream				
17-β estradiol	Estrace	Estradiol	0.5-1 g daily for 1-2 wk	0.5-1 g 1-3 times wk
Conjugated estrogens	Premarin	No	0.5-1 g daily for 1-2 wk	0.5-1 g 1-3 times wk
Vaginal insert				
Estradiol hemihydrate	Vagifem	Yuvafem	10 µg daily for 2 wk	Twice wk
17-β estradiol	Invexxy	No	4 or 10 µg/d for 2 wk	Twice wk
Vaginal ring				
17-β estradiol	Estring	No	Device containing 2 mg releases 7.5 µg/d for 90 d	

"The 2022 Hormone Therapy Position Statement of The North American Menopause Society" Advisory Panel. *Menopause* 2022;29:767-794. doi: 10.1097/GME.0000000000002028

Other Hormone Therapies

- FDA has approved two daily nonestrogen therapies for the treatment of dyspareunia because of hypoestrogenism.

Product Type	Brand name	Generic available	Dosing
Vaginal insert			
DHEA (prasterone)	Intrarosa	No	6.5 mg/d
Oral tablet			
SERM (ospemifene)	Osphena	No	60 mg/d

Abbreviations: DHEA, dehydroepiandrosterone; SERM, selective estrogen receptor modulator.

The NAMS 2020 GSM Position Statement Editorial Panel. *Menopause* 2020;27:976-992. doi:10.1097/GME.0000000000001609

Prasterone

- Intravaginal DHEA insert metabolizes to active androgens in the peripheral vaginal tissues that then aromatize to form estrogens.
- Intracellular conversion to active hormone with limited systemic absorption and no estrogenic stimulation to the endometrium.
- Studies have shown improvement in vaginal lubrication, arousal, orgasm, and pain.
- Safety in patients after breast or other hormone-derived cancers has not been well established; however, limited safety data is reassuring.

Crean-Tate KK, et al. *Am J Obstet Gynecol* 2020;222:103-113. doi: 10.1016/j.ajog.2019.08.043; Labrie F. et al. *Menopause* 2016;23:243-256. doi: 10.1097/GME.0000000000000571; Portman D, et al. *Menopause* 2015;22:1289-1295. doi: 10.1097/GME.0000000000000571

Ospemifene

- SERM.
- Only oral product available on the market to treat moderate to severe dyspareunia.
- Ideal for those who wish to avoid intravaginal therapies.
- May increase VMS but they typically diminish after the first month.
- Preclinical trials demonstrate antiestrogenic effect on breast tissue.
- Not approved for use in US women with history of breast cancer.
- Used in women with a history of breast cancer who have completed treatment in Europe.
- Potential risk of hemorrhagic stroke and VTE (discontinue before surgery to prolonged immobilization).

Archer DF, et al. *Expert Rev Endocrinol Metab* 2019;14:301-314. doi: 10.1080/17446651.2019.1657008; The NAMS 2020 GSM Position Statement Editorial Panel. *Menopause* 2020;27:976-992. doi:10.1097/GME.0000000000001609

Systemic Hormone Therapy for Genitourinary Syndrome of Menopause

- Systemic ET is indicated when there is concomitant VMS or premature menopause or when osteoporosis prevention is also a consideration.
- Vaginal ring with systemic-dose ET is the best option because direct absorption to vaginal tissues and sufficient absorption to address systemic symptoms (eg, VMS).
- The other forms of systemic ET (eg, oral pill, transdermal patch, emulsion, mist) do not always improve GMS.
- If genitourinary symptoms persist after initiating systemic ET, addition of local vaginal ET is often effective.
- Endometrial protection with a progestogen or TSEC is required if uterus is present.
- Transdermal ET is recommended in those with low libido because oral ET is associated with increased SHBG and reduced testosterone bioavailability.
- Systemic ET or EPT is associated with new onset or exacerbation of urinary symptoms: urgency, frequency, incontinence.

Christmas MM, et al. *Menopause* 2023;30:672-685. doi: 10.1097/GME.0000000000002187; Cody JD, et al. *Cochrane Database Syst Rev* 2012;10:CD001405. doi:10.1002/14651858.CD001405.pub3; Hendrix SL, et al. *JAMA* 2005;293:935-948. doi: 10.1001/jama.293.8.935; "The 2022 Hormone Therapy Position Statement of The North American Menopause Society" Advisory Panel. *Menopause* 2022;29:767-794. doi: 10.1097/GME.0000000000002028; The NAMS 2020 GSM Position Statement Editorial Panel. *Menopause* 2020;27:976-992. doi:10.1097/GME.0000000000001609

Risk of Vaginal Estrogen Therapy in High-Risk Patients

- Use of vaginal ET confers the same “low” risk in those with nonhormone-dependent cancers as in those with no history of cancer.
- Vaginal ET use in those with estrogen-dependent neoplasia after consultation with oncologist.
- In large observational studies, vaginal ET has not been associated with an increased risk of VTE.

The NAMS 2020 GSM Position Statement Editorial Panel. *Menopause* 2020;27:976-992. doi:10.1097/GME.0000000000001609

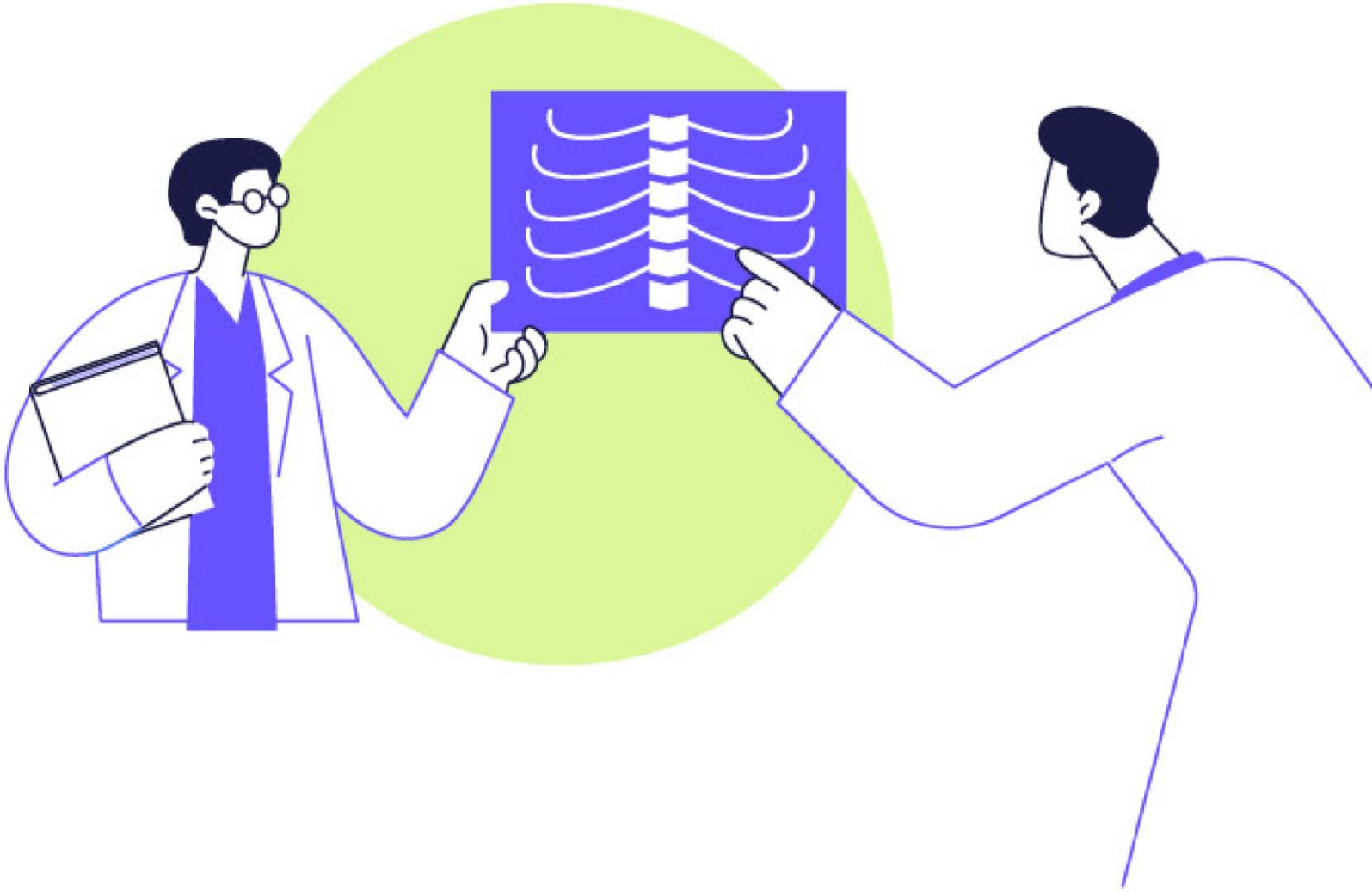
SECTION 8

Hormone Therapy Use in the Medically Complex Patient

The Menopause Society™

Cancer and Hormone Therapy

- Menopause is not associated with increased cancer risk.
- Because cancer rates increase with age, and in the United States cancer is the second-leading cause of death in women, regular screening is recommended.
- Many women are either cured of their cancer or are long-term survivors and require management of menopause symptoms.
- Use of HT in selected patients with cancer may be appropriate.



Breast Cancer and Hormone Therapy

- Observational evidence suggests that HT use does not further increase the risk of breast cancer in women at high risk because of a family history or after BSO for *BRCA 1* or *2* genetic variants.
- Systemic HT is generally not advised for survivors of breast cancer but may be considered when VMS are unresponsive to nonhormone options, with shared decision-making in conjunction with their oncologists.
- For survivors of breast cancer with GSM, low-dose vaginal ET or DHEA may be considered.
- Insufficient data are available to assess the risk of breast cancer with TSECs.

McVicker L, et al. *JAMA Oncol* 2024;10:103-108. doi: 10.1001/jamaoncol.2023.4508; Sussman T, et al. *J Oncol Pract* 2019;15:363-370. doi: 10.1200/JOP.18.00710

Endometrial Cancer and Hormone Therapy

- Endometrial cancer is the fourth most-common cancer in US women.
- 90% diagnosed with uterine cancer present with abnormal bleeding.
- Unopposed systemic ET in a postmenopausal woman with an intact uterus increases risk of endometrial cancer.
- Low-dose vaginal ET does not increase endometrial cancer risk.
- Use of systemic HT is an option in women with surgically treated, early stage, low-grade endometrial cancer in consultation with an oncologist if nonhormone therapies are ineffective.
- Vaginal or systemic HT are not advised with high-grade, advanced-stage endometrial cancers or with endometrial stromal sarcomas or leiomyosarcomas.

Edey KA, et al. *Cochrane Database Syst Rev* 2018;15:CD008830. doi: 10.1002/14651858.CD008830.pub3

Endometrial Hyperplasia and Hormone Therapy

- Risk of endometrial hyperplasia without atypia progressing to endometrial cancer is less than 5% over 20 years; however, with atypia, the risk rises to 28%.
- Endometrial hyperplasia in menopausal women with or without atypia can be managed with the LNG-IUS or continuous oral progestogen (eg, high operative risk or ongoing risk factors).
- The LNG-IUS has a higher disease regression rate, fewer AEs, and a favorable bleeding profile compared with oral progestogens.
- Hysterectomy is generally recommended for those with endometrial hyperplasia with atypia.
    - Systemic ET may be initiated if severe VMS after hysterectomy.
- Women taking HT should be encouraged to report any unscheduled vaginal bleeding promptly.
- Use of systemic ET alone in someone with intact uterus is associated with an increased risk of endometrial hyperplasia.
    - Endometrial protection with a progestogen is required.
    - A progestogen is not required with use of low-dose vaginal ET.

"The 2022 Hormone Therapy Position Statement of The North American Menopause Society" Advisory Panel. *Menopause* 2022;29:767-794. doi: 10.1097/GME.0000000000002028

Cervical Cancer and Hormone Therapy

- Over 20% of cervical cancers will occur in women aged older than 65 years.
- Nearly all develop in the setting of persistent infection.
- Radiation treatment of cervical cancer or treatment of advanced cancer often lead to iatrogenic menopause.
- Use of systemic HT has not been shown to have a harmful effect on a cervical cancer recurrence.
- HT should be initiated in those with moderate to severe VMS with or without GSM and with iatrogenic premature menopause without contraindications.
- Vaginal ET is not contraindicated.

Vargiu V, et al. *Climacteric* 2021;24:120-127. doi: 10.1080/13697137.2020.1826426

Ovarian Cancer and Hormone Therapy

- Leading cause of gynecologic cancer-related death.
- No satisfactory screening strategy.
- Use of oral contraceptives is associated with reduction in ovarian cancer risk.
- In women with a history of ovarian cancer, benefits of HT use generally outweighs risks, especially with bothersome VMS or early menopause.
- Use of HT is not advised in women with hormone-dependent ovarian cancers, including granulosa-cell tumors and low-grade serous carcinoma.
- HT use appears safe in women with *BRCA 1* and *BRCA 2* genetic variants who undergo RRBSO before the average age of menopause.
- Vaginal ET is not contraindicated.

Achimas-Cadariu PA, et al. *Cancers (Basel)* 2023;15:1-23. doi: 10.3390/cancers15020356; Angioli R, et al. *Crit Rev Oncol Hematol* 2018;124:51-60. doi: 10.1016/j.critrevonc.2018.02.005; Del Carmen MG, et al. *Gynecol Oncol* 2017;146:427-435. doi: 10.1016/j.ygyno.2017.06.013; Kuhle CL, et al. *Maturitas* 2016;92:86-96. doi: 10.1016/j.maturitas.2016.07.018

Lung Cancer and Hormone Therapy

- Leading cause of cancer-related death in women worldwide.
- The USPSTF recommends annual low-dose CT screening in asymptomatic persons aged 55 to 80 years with a 30-pack/year history, current smokers, or quit within past 15 years.
- There appears to be an overall neutral effect of HT on lung cancer incidence and survival.
- Smoking cessation should be encouraged, with increased lung cancer surveillance for older smokers, including current or past users of HT.

US Preventive Services Task Force. *JAMA* 2021;325:962–970. doi: 10.1001/jama.2021.1117

Colorectal Cancer and Hormone Therapy

- Third leading cause of cancer-related death in women worldwide.
- Begin screening tests in average-risk women at age 45 years.
- People aged older than 85 years should no longer get colorectal cancer screening.
- Observational studies suggest reduced incidence of colorectal cancer in current HT users, with reduced mortality.
- In the WHI, EPT but not ET reduced colorectal cancer risk, although cancers diagnosed in EPT users were diagnosed at a more advanced stage.
- There was no difference in colorectal cancer mortality with either EPT or ET.

US Preventive Services Task Force. *JAMA* 2021;325:1965-1977. doi: 10.1001/jama.2021.6238

Other Medical Comorbidities and Hormone Therapy

- Local vaginal ET is minimally absorbed (at recommended doses) with serum estrogen levels maintained within the normal postmenopause range.
- Because of minimal systemic absorption, local ET may be considered in those with a history of CVD, stroke, or VTE.
- HT is not US government approved for primary or secondary cardioprotection.
- Higher absolute risks of coronary heart disease (CHD), VTE, and stroke when HT is started in those aged older than 60 years or more than 10 years from the onset of menopause.

Cho L, et al. *Circulation* 2023;147:597-610. doi: 10.1161/CIRCULATIONAHA.122.061559; "The 2022 Hormone Therapy Position Statement of The North American Menopause Society" Advisory Panel. *Menopause* 2022;29:767-794. doi: 10.1097/GME.0000000000002028

Coronary Heart Disease and Hormone Therapy

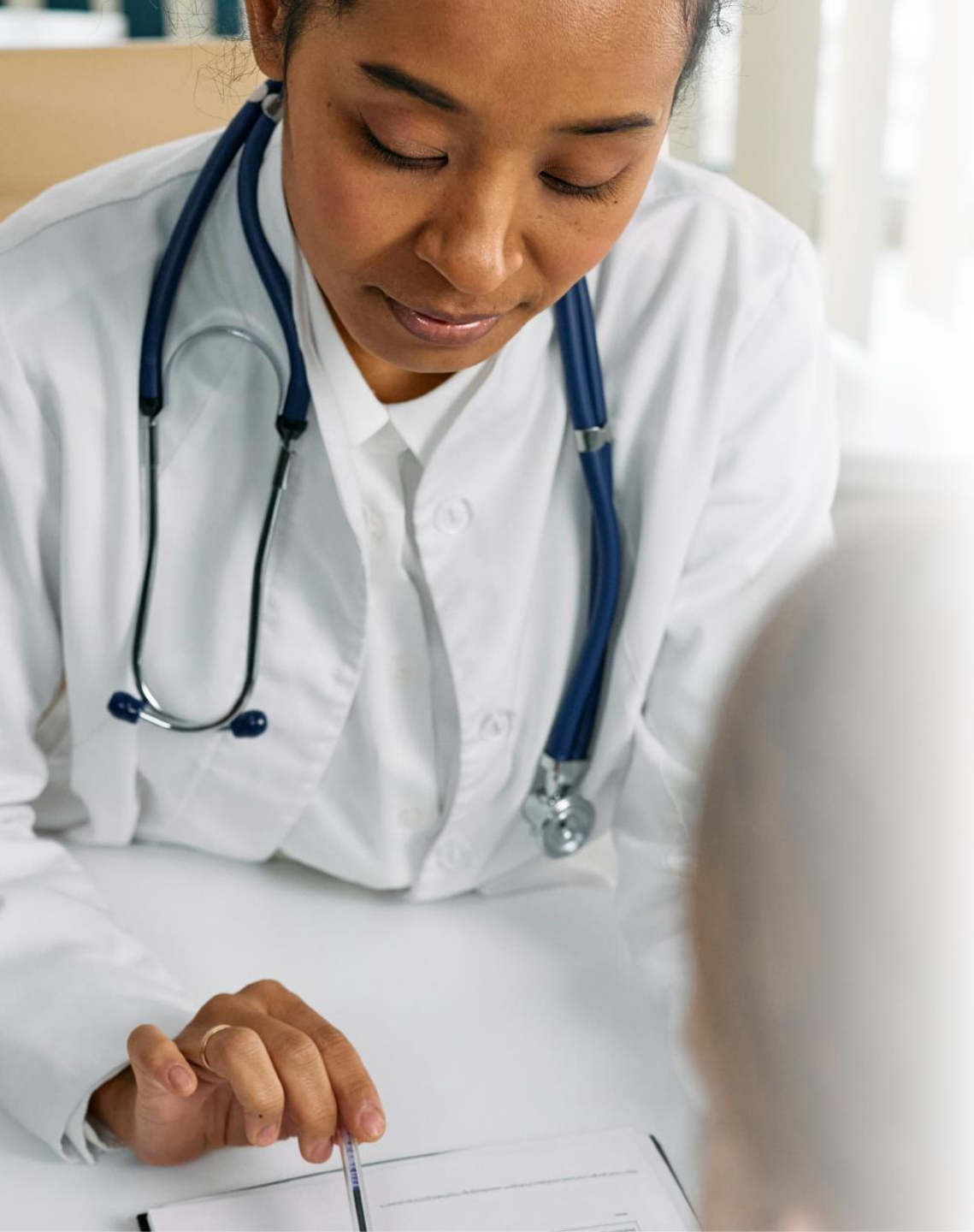
- Effects of HT on CHD vary depending on when HT is initiated in relation to a woman's age or time since menopause onset.
- Initiation of HT in recently postmenopausal women reduced or had no effect on subclinical atherosclerosis progression and coronary artery calcification in RCTs.
- Use of transdermal estradiol patch with or without oral progestogen has not been shown to increase blood pressure.
- Avoid HT use in those with dyslipidemia and preexisting CVD or those at high risk for CVD.

"The 2022 Hormone Therapy Position Statement of The North American Menopause Society" Advisory Panel. *Menopause* 2022;29:767-794. doi: 10.1097/GME.0000000000002028

Venous Thromboembolism and Hormone Therapy

- Systemic oral HT is associated with increased risk of VTE and is contraindicated in those with history of VTE.
- Systemic HT use in those with underlying thrombophilia without history of VTE is a relative contraindication.
- Those with a family history of VTE should undergo a thrombophilia workup before starting systemic HT.
- In observational studies, low-dose transdermal HT was not associated with increased VTE risk.
- Off-label use of low-dose transdermal HT may be considered in those with persistent VMS not responsive to nonhormone therapies, if adequately anticoagulated.

Cho L, et al. *Circulation*. 2023;147:597-610. doi: 10.1161/CIRCULATIONAHA.122.061559



Adult-Onset Diabetes Mellitus and Hormone Therapy

- HT reduces the diagnosis of new-onset type 2 DM by 30%, but it is not FDA approved for this indication.
- HT is not contraindicated in otherwise healthy women with preexisting type 2 DM and may be beneficial in terms of glycemic control when used for menopause-symptom management.
- Greater benefit with oral rather than transdermal estrogen.
- Progesterone has minimal effect on adult-onset DM.

Cho L, et al. *Circulation*. 2023;147:597-610. doi: 10.1161/CIRCULATIONAHA.122.061559; "The 2022 "Hormone Therapy Position Statement of The North American Menopause Society" Advisory Panel. *Menopause* 2022;29:767-794. doi: 10.1097/GME.0000000000002028

Systemic Lupus Erythematosus and Hormone Therapy

- It is unknown whether HT may mitigate risk.
- No reports of autoimmune symptom exacerbations when HT is used in patients with lupus erythematosus.
- HT should be avoided in patients with antiphospholipid antibodies.

Sammaritano LS, et al. *Arthritis Rheumatol* 2020;72:529-556. doi: 10.1002/art.41191

Liver Disease and Hormone Therapy

- Liver disease encompasses a wide array of conditions: acute (ie, alcoholic or viral hepatitis), chronic (ie, cirrhosis, metabolic associated steatohepatitis, nonalcoholic fatty liver disease, cholestatic), or liver lesions (ie, hemangiomas, adenomas, malignancy).
- These conditions and their treatment can affect menopause onset and symptoms:
  - Rapid bone loss is often a result of immunosuppressive therapy and chronic steroid use.
  - Increased risk of premature menopause, especially after liver transplantation.
- HT may be considered in those with premature menopause or those with moderate to severe VMS or GSM.
- Transdermal HT bypasses the first-pass metabolism of the liver and thus has less influence on lipid metabolism, especially triglycerides, and coagulation and inflammatory factors and may be safer in those with liver disease.
- HT may lead to growth of hemangiomas and is contraindicated if symptomatic.
- Some evidence suggests that transdermal HT may be protective against metabolic dysfunction-associated steatohepatitis.

Cyganek A, et al. *Prz Menopauzalny* 2016;15:1-5. doi: 10.5114/pm.2016.58765; Leon M, et al. *World J Gastroenterol* 2020;26:11-20. doi: 10.3748/wjg.v26.i1.11; van Malenstein H, et al. *Eur J Gastroenterol Hepatol* 2011;23:438-443. doi: 10.1097/MEG.0b013e328345c87d

Renal Disease and Hormone Therapy

- There are known nephroprotective effects of estrogen.
- Patients with end-stage renal disease (ESRD) are at increased risk for early menopause, osteoporosis, cognitive dysfunction, and CVD.
- HT appears safe postrenal transplant and with ESRD.
- Treatment with HT in ESRD is associated with improved quality of life, bone health, and CV biomarkers.
- Studies show a 30% reduction in ESRD incidence with HT use, regardless of duration.
- HT is associated with slight increased risk of arteriovenous access thrombosis.
- MP may be less thrombogenic than other formulations.

Ahmed SB, et al. *Nephrol Dial Transplant* 2016;31:1787-1795. doi: 10.1093/ndt/gfw08; Ahn SY, et al. *Sci Rep* 2021;11:15418. doi: 10.1038/s41598-021-93847-9; Pietrzak B, et al. *Transplant Proc* 2006;38:184-187. doi: 10.1016/j.transproceed.2005.12.001; Stehman-Breen C, et al. *Kidney Int* 1999;56:2243-2247. doi: 10.1046/j.1523-1755.1999.00793.x

Migraines and Hormone Therapy

- Migraine is not a contraindication to HT.
- Transdermal delivery is preferable.
- Progesterone may have a protective effect against migraine attacks by modulating nociception and downregulating ERs.

van Lohuizen R, et al. *Expert Rev Neurother* 2023;24:1-21. doi: 10.1080/14737175.2023.2296610

SECTION 9

Management of Mood Disorders and Cognitive Decline at Menopause

The Menopause Society™

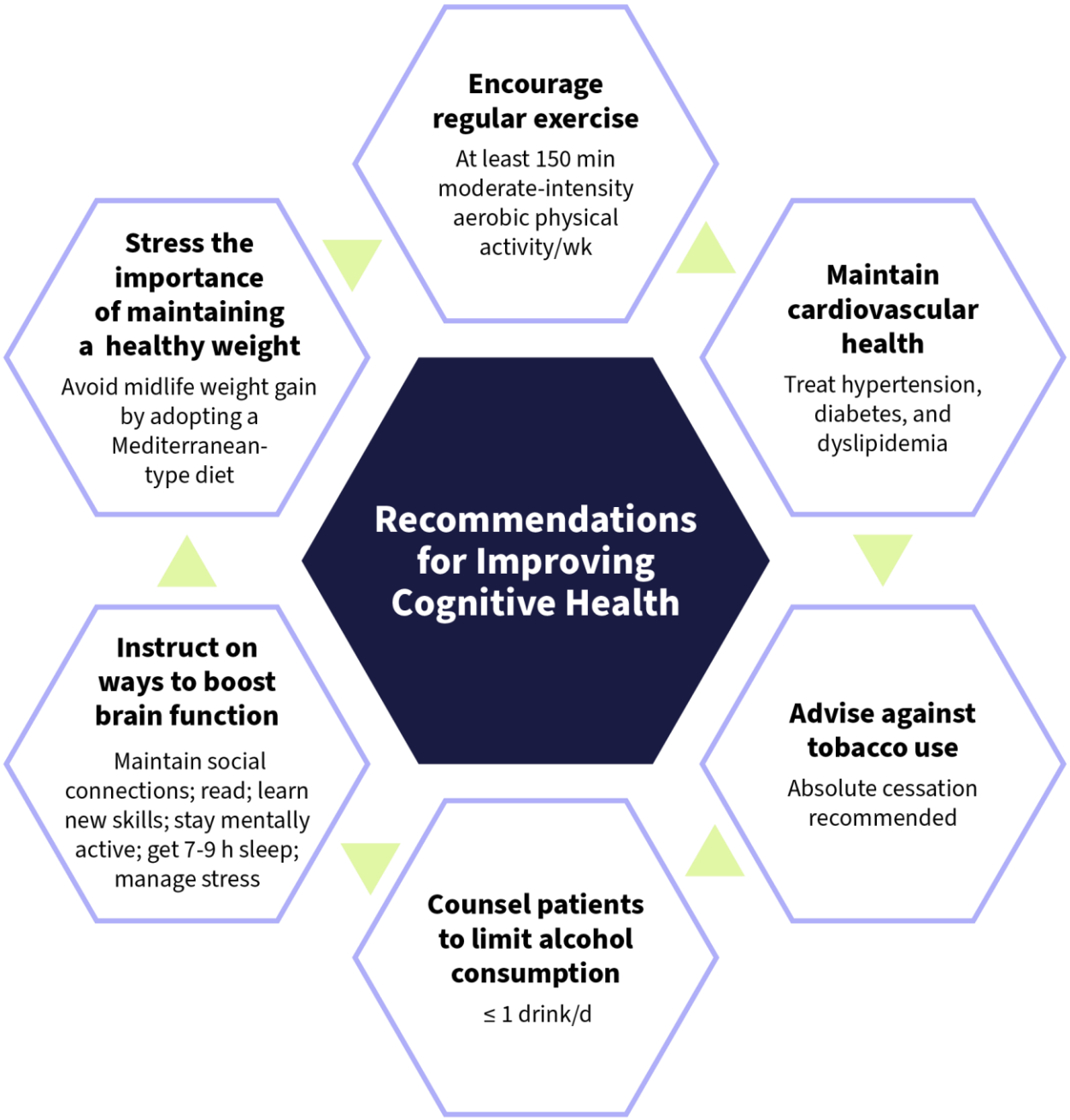
Cognitive Changes and Menopause

- Cognitive problems start in perimenopause, related to neuroendocrine changes.
    - Dementia before age 64 years is rare.
- Menopause brain fog refers to cognitive symptoms of memory and attention difficulties.
- Verbal learning and memory challenges are most common.
- MT memory dysfunction improves for most people postmenopause.
    - Cognitive vulnerabilities may continue because of social determinants and other factors.

Maki PM, et al. *Climacteric* 2022;25:570-578. doi: 10.1080/13697137.2022.2122792

Management of Cognitive Changes

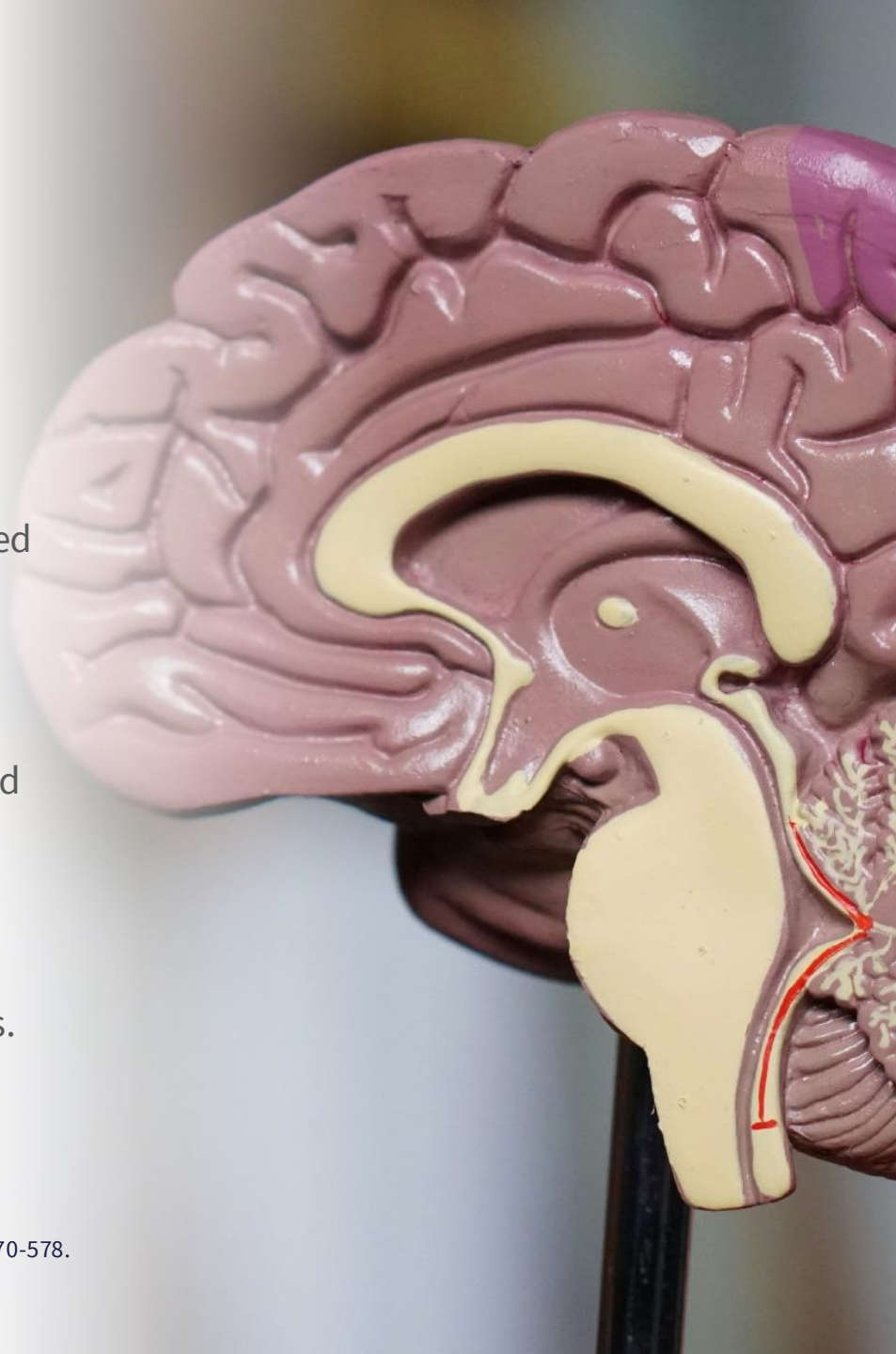
- Studies link cognitive issues to changes in estradiol levels as well as VMS, sleep disturbances, and mood symptoms of menopause.
- Addressing underlying menopause symptoms may improve cognition.
- Counsel patients on reducing dementia through modifiable interventions



Maki PM, et al. *Climacteric* 2022;25:570-578. doi: 10.1080/13697137.2022.2122792

Hormone Therapy and Cognition

- Studies show differential associations between HT and cognitive function, depending on formulation and timing of treatment:
  - HT was not found to affect cognitive domain scores and not recommended for treatment or prevention of cognitive dysfunction at any age.
  - Improved global cognition seen versus placebo in the subgroup of those in surgical menopause, mostly using ET.
  - ET initiated when aged younger than 65 years is associated with improved verbal memory and may help maintain cognitive function.
  - Treatment for more than 1 year is associated with worsening visual memory versus a shorter treatment duration.
  - Further research is needed with larger samples and homogenous designs.



Andy C, et al. *Front Endocrinol (Lausanne)* 2024;15:1350318. doi: 10.3389/fendo.2024.1350318; Maki PM, et al. *Climacteric* 2022;25:570-578. doi: 10.1080/13697137.2022.2122792

Mood Disorders and Menopause

- Depression and anxiety symptoms can be more severe and concerning during the MT.
- Classic depression symptoms that may or may not meet criteria for major depressive disorder (MDD), in combination with bothersome menopause-related symptoms and psychosocial stressors unique to this age group, can have significant effect on personal and professional relationships.
- History of MDD associated with higher risk of major depressive episodes during perimenopause compared with no history of MDD.
- Bipolar symptoms occur more frequently and can be more intense during MT compared with premenopause.

Conklin D, et al. *Womens Health Rep (New Rochelle)* 2021;2:430-442. doi: 10.1089/whr.2021.0025; Maki PM, et al. *J Womens Health (Larchmt)* 2019;28:117-134. doi: 10.1089/jwh.2018.27099.mensocrec; Perich T, et al. *Bipolar Disord* 2017;19:434-443. doi: 10.1111/bdi.12530; Truong D, et al. *Curr Psychiatry Rep* 2019;21:130. doi: 10.1007/s11920-019-1111-3

Estrogen and Mood Regulation

- Estrogen receptors are distributed throughout the brain.
  - Estrogen activity is found in the hypothalamus, prefrontal cortex, hippocampus, and brainstem.
    - Areas involved in mood and cognitive regulation.
- Clinical trials lack significant beneficial effects of estrogen on mood when administered to nondepressed perimenopausal, early postmenopausal, or late postmenopausal women.
- Efficacy of transdermal estradiol for depressive disorders in perimenopausal women with and without VMS observed in a few small studies.
- ET may augment clinical response to antidepressants during the MT.
- Studies do not support use of ET for treatment of depression in postmenopausal women.

Cohen LS, et al. *Am J Psychiatry* 2003;160:1519-1522. doi: 10.1176/appi.ajp.160.8.1519; Joffe H, et al. *J Clin Endocrinol Metab* 2011;96:E1044–E1054. doi: 10.1210/jc.2010-2503; Morrison MF, et al. *Biol Psychiatry* 2004;55:406-412. doi: 10.1016/j.biopsych.2003.08.011; Rasgon NL, et al. *Am J Psychiatry* 2001;158:1738. doi: 10.1176/appi.ajp.158.10.1738; Rudolph I, et al. *Climacteric* 2004;7:301-311. doi: 10.1080/13697130400001802; Soares CN, et al. *Arch Gen Psychiatry* 2001;58:529-534. doi: 10.1001/archpsyc.58.6.529

Nonhormone Interventions for Mood Disorders

- Antidepressants are first-line treatment for mood disorders in midlife, especially in those with
  - History of multiple depressive episodes in the past.
  - Current severe symptoms.
  - Significant functional impairments or suicidal ideation.
- Psychotherapy, including behavioral-based interventions, help reduce overall burden and functional impairment.

Soares CN. *Psychiatr Clin North Am* 2017;40:239-254. doi: 10.1016/j.psc.2017.01.007

SECTION 10

Management of Sleep Dysfunction at Menopause

The Menopause Society™

Sleep Hygiene Techniques

- Cool, dark, quiet room (add fan if needed).
- Sleep when tired or sleepy (avoid clock watching).
- Use the bedroom only for sleep and sexual activities.
- Lightweight sleepwear.
- Avoid heavy evening meals within 3 hours of bedtime.
- Avoid alcohol, caffeine, nicotine, chocolate.
- Exercise, but not within 3 hours of bedtime.
- Relaxation techniques (meditation, warm baths).
- Regular sleep and wake schedule, even on weekends.
- Avoid naps (unless a shift worker).
- Avoid bright lights and screens in the bedroom.

Kline CE, et al. *J Womens Health (Larchmt)* 2014;23:894-903. doi: 10.1089/jwh.2014.4730;
Morgenthaler T, et al. *Sleep* 2006;29:1415-1419.

Hormone Therapy and Sleep

- No form of HT is FDA approved to treat insomnia.
- Oral ET improves nighttime restlessness and awakening.
- Both ET and EPT appear to aid sleep quality by reducing hot flashes and night sweats.
- MP at bedtime is associated with improved sleep by stimulating benzodiazepine receptors, causing release of gamma-aminobutyric acid, a sedating neurotransmitter that facilitates sleep cycles.
- Effect of HT for OSA is controversial.

Kline CE, et al. *J Womens Health (Larchmt)* 2014;23:894-903. doi: 10.1089/jwh.2014.4730; Polo-Kantola P, et al. *Fertil Steril* 1999;71:873-880. doi: 10.1016/s0015-0282(99)00062-x

Cognitive-Behavioral Therapy—Insomnia

- Cognitive-behavioral therapy for insomnia (CBT-I) is first-line treatment for insomnia in menopausal women.
- Has been shown to be effective in treating menopause-related sleep disturbances, with long-lasting benefits.
- CBT-I practitioners conduct an evaluation to assess internal and external stimuli that cause sleep disturbances.
- Consists of a structured, skill-focused program that includes cognitive and behavioral techniques and sleep education.
- No head-to-head trials comparing the effect size of CBT-I and HT.

Hunter M, et al. *Managing Hot Flushes With Group Cognitive Behaviour Therapy: An Evidence-Based Treatment Manual for Health Professionals*. Routledge; 2014; McCurry SM, et al. *JAMA Intern Med* 2016;176:913-920. doi: 10.1001/jamainternmed.2016.1795; Perlis ML, et al. *Cognitive Behavioral Treatment of Insomnia: A Session-by-Session Guide*. Springer; 2008.

Nonpharmacologic Treatment Options for Sleep Disturbances

- Melatonin plays a major role in circadian rhythm, especially in sleep onset and in sleep maintenance through block arousal mechanism, but relationship between melatonin and menopause is unclear.
- Primary treatment for OSA is positive-airway pressure.
    - Oral appliances, implants, and surgical procedures for airway revision are also options.
- Aerobic exercise, mindfulness, and yoga show positive results, but research is needed to understand extent of them in menopausal patients.
- Patients may experience significant improvement in insomnia after more than 3 weeks of acupuncture treatment.

Drake CL, et al. *Sleep* 2019;42:zsy217. doi: 10.1093/sleep/zsy217; Guthrie KA, et al. *Sleep* 2018;41:zsx190. doi: 10.1093/sleep/zsx190; Kim SA, et al. *Am J Chin Med* 2021;49:1135-1150. doi: 10.1142/S0192415X21500543

Pharmacologic Therapies

Drug class	Drug options	Adverse events	Comments
Antidepressants			
Selective serotonin reuptake inhibitors	Citalopram Escitalopram Fluoxetine Paroxetine	Nausea, somnolence, dry mouth, increased sweating, tremor, diarrhea.	Some improve insomnia and also reduce VMS by 40%-60%.
Serotonin-norepinephrine reuptake inhibitors	Venlafaxine Desvenlafaxine Duloxetine Levomilnacipran		
Serotonin antagonist and reuptake inhibitor	Trazadone	Nausea, somnolence, dry mouth, sweating.	Adequate data supporting efficacy and safety in low-dose use for treatment of insomnia.
Tricyclic antidepressant	Doxepin	Somnolence, sedation, nausea, and upper respiratory tract infection.	Nightly use improves sleep and has no potential for abuse.
Dopamine agonist	Ropinirole HCL	Confusion, drowsiness, fatigue, nausea.	Used to treat restless leg syndrome and periodic limb movement disorder. Neither disorder responds to HT.

Jaffer KY, et al. *Innov Clin Neurosci* 2017;14:24-34.

Pharmacologic Therapies (cont.)

Drug class	Drug options	Adverse events	Comments
Sedative hypnotics			
Benzodiazepines	Alprazolam Diazepam Lorazepam Chlordiazepoxide	Daytime sedation, poor coordination, cognitive impairment, increased risk of driving accidents, falls.	Have been shown to improve sleep, although few studies have focused on women in menopause. Potential for abuse.
Z-drugs	Zolpidem Eszopiclone Zaleplon	Complex sleep behaviors, including sleepwalking, sleep-driving, and engaging in other activities while not fully awake; development of tolerance and rebound insomnia.	Approved by FDA to treat insomnia.
Orexin receptor antagonists	Suvorexant Daridorexant	Unusual dreams, diarrhea, dry mouth.	Indicated for the treatment of insomnia characterized by difficulties with sleep onset and/or sleep maintenance.

Jaffer KY, et al. *Innov Clin Neurosci* 2017;14:24-34.

SECTION 11

Management of Sexual Dysfunction at Menopause

The Menopause Society™

Treatment for Female Sexual Disorders

- Treatment is specific to the diagnoses, which frequently overlap.
- For HSDD, options may include sex education; individual or couples sex psychotherapy; treatment of contributory factors such as pain or hypo-orgasmia; and pharmacotherapy.
- FDA-approved medications for HSDD in premenopausal women include flibanserin and bremelanotide.
- Off-label testosterone can be considered for select postmenopausal women with HSDD.
- For arousal and orgasmic dysfunction, education about anatomy and physiology of orgasmic function, introduction of medical vibrator therapy, and psychosexual interventions are offered.
- For dyspareunia, in appropriate situations, vaginal moisturizers, lubricants, massagers (ie, dilators or vibrators), pharmacotherapy (ie, local ET, DHEA inserts, oral SERMs), or pelvic floor therapy may be considered.

Brotto L, et al. *J Sex Med* 2016;13:538-571. doi: 10.1016/j.jsxm.2016.01.019; Clayton AH, et al. *Mayo Clin Proc* 2018;93:467-487. doi: 10.1016/j.mayocp.2017.11.002; Davis SR, et al. *J Sex Med* 2019;16:1331-1337. doi: 10.1210/jc.2019-01603; FitzGerald MP, et al. *Int Urogynecol J Pelvic Floor Dysfunct* 2003;14:261-268. doi: 10.1007/s00192-003-1049-0; Goldstein I, et al. *Mayo Clin Proc* 2017;92:114-128. doi: 10.1016/j.mayocp.2016.09.018; Kingsberg SA, et al. *CNS Drugs* 2015;29:915-933. doi: 10.1007/s40263-015-0288-1; Kingsberg SA, et al. *J Sex Med* 2017;14:1463-1491. doi: 10.1016/j.jsxm.2017.05.018; Labrie F, et al. *Menopause* 2016;23:243-256. doi: 10.1097/GME.0000000000000571; Parish SJ, et al. *Menopause* 2023; 30:781-783. doi: 10.1097/GME.0000000000002190; Stahl SM, et al. *J Sex Med* 2011;8:15-27. doi: 10.1111/j.1743-6109.2010.02032.x

Nonmedication Treatments for Hypoactive Sexual Desire Disorder

Psychological contributors

- Mood (depression, irritability, shame or embarrassment, anxiety).
- Sleep disturbances.
- Developmental issues (trauma, abuse, childhood illness).
- Body image.
- Interpersonal issues.
    - Chronic (emotional estrangement).
    - Past relationship trauma and fear of vulnerability.
    - Partner sexual challenges or psychiatric illness.

Psychotherapy can

- Reduce performance anxiety.
- Restructure negative thoughts.
- Help regain confidence.
- Redirect focus to pleasure.
- Resolve interpersonal issues.
- Improve partner communication.

Kingsberg SA, et al. *Menopause* 2022;29:1083-1085. doi: 10.1097/GME.0000000000002049

Effects of Hormone Therapy on Sexual Function

- Relationship factors and physical and mental health are more important than estrogen levels or menopause status for sexual health.
- Benefits of HT on sexual function may be indirect.
- Improvement in vaginal dryness and dyspareunia can improve pain, hence improve desire.
- Improvement of bothersome hot flashes, night sweats, and related insomnia could improve sense of well-being, and in turn, sexual desire.

Clayton AH, et al. *Mayo Clin Proc* 2018;93:467-487. doi: 10.1016/j.mayocp.2017.11.002; Parish SJ, et al. *Menopause* 2023;30:781-783. doi: 10.1097/GME.0000000000002190; Santoro N, et al. *J Sex Med* 2016;13:305-316. doi: 10.1016/j.jsxm.2015.11.015

Testosterone Therapy for Hypoactive Sexual Desire Disorder

- HSDD is not diagnosed on the basis of low serum testosterone; it is a clinical diagnosis.
- Increasing testosterone levels within female physiologic range can improve sexual function in some women (satisfactory sexual event frequency, sexual desire, arousal, orgasm, responsiveness, self-image) and reduces sexual concerns and distress in postmenopausal women.
- Meta-analyses show no severe AEs with physiologic testosterone use.
- Monitoring total testosterone levels and response to treatment is recommended.
- Checking testosterone levels helps to exclude women with high baseline testosterone ranges and prevents androgen excess AEs.
- Long-term safety of testosterone therapy has not been established.

Clayton AH, et al. *Mayo Clin Proc* 2018;93:467-487. doi: 10.1016/j.mayocp.2017.11.002; Davis SR, et al. *Climacteric* 2019;22:429-434. doi: 10.1080/13697137.2019.1637079; Davis SR, et al. *J Sex Med* 2019;16:1331-1337. doi: 10.1210/jc.2019-01603; Islam RM, et al. *Lancet Diabetes Endocrinol* 2019;7:754-766. doi: 10.1016/S2213-8587(19)30189-5; Parish SJ, et al. *Menopause* 2023;30:781-783. doi: 10.1097/GME.0000000000002190

Testosterone Therapy Dosing (Global Consensus Position Statement)

- Testosterone formulations targeting the normal premenopause physiologic range recommended.
- No female testosterone product is currently approved by any national regulatory authority; compounded testosterone preparations are not generally recommended.
- Male formulations can be judiciously used in female doses (1/10), with serum testosterone concentrations monitored regularly.
- Testosterone levels should be checked 6 weeks after initiating and then every 6 months.

Clayton AH, et al. *Mayo Clin Proc* 2018;93:467-487. doi: 10.1016/j.mayocp.2017.11.002; Davis SR, et al. *J Sex Med* 2019;16:1331-1337. doi: 10.1210/jc.2019-01603; Islam RM, et al. *Lancet Diabetes Endocrinol* 2019;7:754-766. doi: 10.1016/S2213-8587(19)30189-5; Parish SJ, et al. *Menopause* 2023;30:781-783. doi: 10.1097/GME.0000000000002190

SECTION 12

Management of Weight Gain at Menopause

The Menopause Society™

Body Weight in Menopause

- Obesity (BMI ≥30 kg/m^2) in the United States has increased from 30.5% between 1995 and 2000 to 42.4% between 2017 and 2018.
- Prevalence of severe obesity (BMI ≥40 kg/m^2) is highest in adults aged 40 to 59 years and higher in women.
- The connection between BMI and body fat is related to body composition and varies according to sex, age, and ethnicity.
    - So even at the same BMI, health risks vary.
- Increases in weight gain and waist circumference are seen in midlife people over time.

Gibson C, et al. *Menopause* 2023;30:709-716. doi: 10.1097/GME.0000000000002198; Hales CM, et al. NCHS Data Brief, no 360. National Center for Health Statistics; 2020.

Weight Gain in Menopause

- Weight gain at midlife is mostly because of aging and lifestyle.
- Weight changes are also influenced by estrogen-deprived state, mood, and sleep issues.
- Changes in fat distribution and body composition (decreased lean body mass and increased fat body mass) are related to menopause; however, the exact etiology is unknown.
    - Increase in central adiposity and visceral fat.
    - Decrease in lean body mass.
- Obesity in menopause is associated with MetS, type 2 DM, CVD, aortic plaque, hepatic steatosis, and breast cancer.

Hurtado MD, et al. *Curr Obes Rep* 2024;13:352-363. doi: 10.1007/s13679-024-00555-2;
Kapoor E, et al *Mayo Clin Proc* 2017;92:1552-1558. doi: 10.1016/j.mayocp.2017.08.004

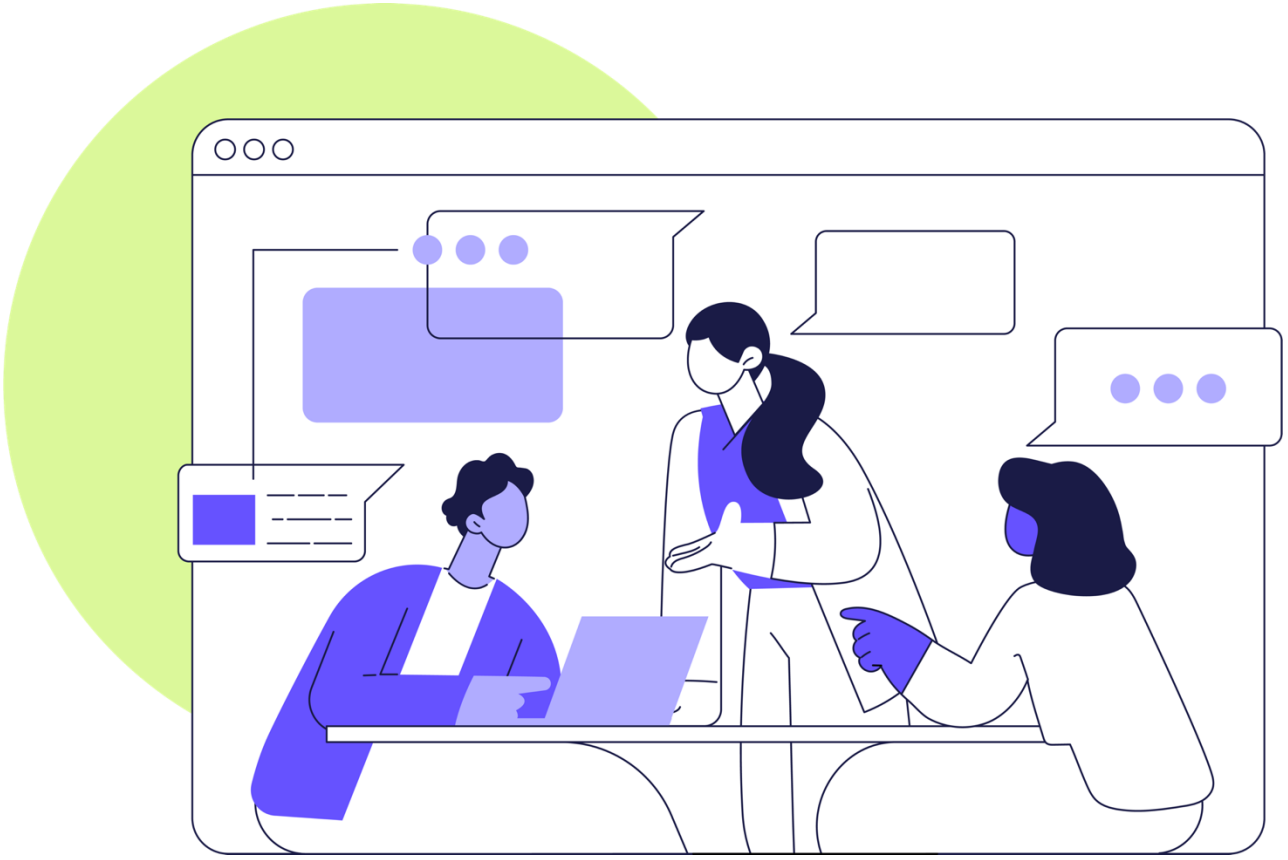
Obesity and Vasomotor Symptoms

- Increased VMS severity has been associated with greater body fat, BMI, and waist circumference.
  - The associations are likely multifactorial.
- Increases in VMS, onset of frequent VMS, and persistent VMS over time may precede weight gain in women.
- Clinicians can focus prevention to mitigate weight gain for patients with VMS, and particularly those with
  - Increased waist circumference, regardless of BMI.
  - Comorbidities.
- Further research is needed on adipokines, melatonin, and other mechanisms linked to the physiologic association between VMS and weight.

Gibson CJ, et al. *Menopause* 2023;30:709-716. doi: 10.1097/GME.0000000000002198; Hurtado MD, et al. *Curr Obes Rep* 2024;13:352-363. doi: 10.1007/s13679-024-00555-2; Kapoor E, et al. *Mayo Clin Proc* 2017;92:1552–1558. doi: 10.1016/j.mayocp.2017.08.004

Management of Weight Gain During Menopause

- Obesity management recommendations for midlife women fall under three categories:
  - Lifestyle and behavior management.
  - Pharmacology.
  - Bariatric surgery.
- Treatment is often multimodal and depends on BMI, waist circumference, and comorbidities.



Khandelwal S. *Climacteric* 2020;23:140–147. doi: 10.1080/13697137.2019.1660638

Lifestyle and Behavior Modifications

- Diet, nutrition, and physical activity have long-term success that occur on the basis of individual preferences.
- Behavior changes target caloric intake and energy expenditure.
  - Small amounts of weight loss (3% to 10% of body weight) improve metabolic parameters (blood pressure, lipids, glucose), fatty liver disease, chronic pain, and CVD risk.
  - Caloric reduction of 500 to 700 calories/d leads to 1 to 1.5 lb weight loss/wk (short term).
- Typical caloric intake goal: 1,200-1,500 calories/d.
- A very-low-calorie diet requires supervision for select cases.
- Meaningful weight loss can occur with various macronutrient compositions, with no significant long-term differences in diet approach.
  - Mediterranean diet.
  - Dietary Approaches to Stop Hypertension (DASH) diet.
  - Low-carbohydrate, high-protein, low-fat.
  - Time-restricted eating or intermittent fasting.
  - Vegan or vegetarian.

Ardisson Korat AV. *Am J Clin Nutr* 2024;119: 271-282. doi: 10.1016/j.ajcnut.2023.11.010; Khandelwal S. *Climacteric* 2020;23:140–147. doi: 10.1080/13697137.2019.1660638; US Department of Agriculture and US Department of Health and Human Services. *Dietary Guidelines for Americans, 2020-2025.* 9th ed. December 2020. US Department of Health and Human Services. *Physical Activity Guidelines for Americans*, 2nd ed. Washington, DC: U.S. Department of Health and Human Services; 2018.

General Guidelines for Diet and Nutrition for Adult Women

Protein	• 15%-20% of total calories/d	• Elevated protein intake results in greater weight, fat mass, and triglyceride reduction. • Nurses' Health Study found higher protein intake (especially plant sources) was associated with healthy aging. • Limit red meat and avoid processed meats. • Increase fish, poultry, and plant protein (nuts, beans, legumes/soy) intake.
Carbohydrates	• 50%-60% of total calories/d	• Aim for >30 g of whole-grain, whole fruits, and vegetables/d. • Limit refined carbohydrates (white pasta, bread, rice).
Fat	• 10%-20% of total calories/day	• Use olive, avocado, and corn oils for cooking and dressings when possible. • Polyunsaturated fat, up to 10% of total calories. • Monounsaturated fat, up to 20% of total calories. • Low consumption of trans fatty acids (<1% of energy).

- Avoid or limit alcohol to no more than 1 drink/d
- Limit sodium intake to <2.3 g/d
- Recommended caloric intake is 1,600-2,200/d (dependent on age, height, weight, and activity status)

Ardisson Korat AV. *Am J Clin Nutr* 2024;119: 271-282. doi: 10.1016/j.ajcnut.2023.11.010; Khandelwal S. *Climacteric* 2020;23:140–147. doi: 10.1080/13697137.2019.1660638; US Department of Agriculture and US Department of Health and Human Services. *Dietary Guidelines for Americans, 2020-2025.* 9th ed. December 2020. US Department of Health and Human Services. *Physical Activity Guidelines for Americans*, 2nd ed. Washington, DC: U.S. Department of Health and Human Services; 2018.

Physical Activity and Menopause

- Physical activity eases signs and symptoms related to hormone depletion and helps to prevent and ameliorate chronic diseases.
- 80% of US adults and adolescents are insufficiently active.
- Incorporating physical activity into day-to-day life is important.

Domains of Physical Activity	
Type	**Examples**
Recreational/Leisure	Sports participation, aerobic exercise, strength training, dancing, and gardening.
Transport	Getting from one place to another through nonmotorized means. Walking, cycling, wheeling.
Lifestyle	Walking the dog, cleaning, cooking, caring for children, laundry, vacuuming, taking the stairs.
Occupational	Any physical activity related to paid or voluntary work.

Bull FC, et al. *Br J Sports Med* 2020;54:1451-1462. doi:10.1136/bjsports-2020-102955; Chen TJ, et al. *J Phys Act Health* 2023;20:742-751. doi: 10.1123/jpah.2022-0478; Mendoza N, et al. *Maturitas* 2016;93:83–88. doi: 10.1016/j.maturitas.2016.04.017; Young J, et al. *J Family Pract* 2022;71:S17–S23. doi: 10.12788/jfp.0253

Physical Activity Recommendations

- Light to moderate-intensity exercise is safe for most people.
- Medical clearance or exercise testing is no longer recommended.
- Physician clearance is based on
  - The person's current level of structured exercise.
  - The presence of major signs and symptoms suggestive of cardiovascular, metabolic, or renal disease.
  - The desired intensity of exercise.

Guidelines on Physical Activity for Adults Aged 18 to 65 Years				
Intensity	**Duration of activity/wk**	**Rate of perceived exertion scale (0-10)**	**Metabolic equivalent tasks (METs)[a] 1 = sitting at rest mLO2/kg/min**	**Talk test**
Moderate intensity	150-300 min/wk spread throughout the wk	5-6/10	3-6 METs	You can easily talk but not sing during the activity
High intensity	75-150 min/wk spread throughout the wk	7-8/10	≥6.0 METs	You can no longer talk easily and are somewhat out of breath during the activity
Strength training of major muscle groups 2-3 times/wk. Performing 1-2 sets of 8-10 reps.				
Balance and mind-body exercises should also be added to the prescription for midlife and older adults, 2-3 times/wk.				

[a]A Metabolic Equivalent Task (MET) is a measure that approximates a person's energy expenditure during physical activity compared with a resting state by assessing the amount of oxygen used during activity to amount used at rest

2018 Physical Activity Guidelines Advisory Committee. 2018 Physical Activity Guidelines Advisory Committee Scientific Report. Washington, DC: US Department of Health and Human Services, 2018; Bull FC, et al. *Br J Sports Med* 2020;54:1451-1462. doi:10.1136/bjsports-2020-102955; Morishita S, et al. *Strength Cond J* 2018; 40:94-109. doi: 10.1519/SSC.0000000000000373; Young J, et al. *J Family Pract* 2022;71:S17–S23. doi: 10.12788/jfp.0253

Pharmacotherapy for Obesity Management

Class	Drug
Centrally acting medications	Phentermine (Adipex-P, Lomaira) Diethylpropion (Tenuate) Phendimetrazine (Bontril)
Lipase inhibitors	Orlistat
Glucagon-like peptide-1 (GLP-1) receptor agonists	Liraglutide (Saxenda) Semaglutide (Wegovy) Tirzepatide (Mounjaro, Zepbound)
Sodium-glucose cotransporter 2 (SGLT2) inhibitors	Canagliflozin (Invokana) Dapagliflozin (Farxiga) Empagliflozin (Jardiance)
Combination medications	Phentermine/Topiramate (Qsymia) Bupropion/Naltrexone (Contrave)

Indications: BMI ≥ 27 kg/m^2 and at least one weight-related comorbidity (ie, hypertension, OSA, or diabetes) or BMI ≥ 30 kg/m^2.

Grunvald E, et al. *Gastroenterology* 2022;163:1198-1225. doi: 10.1053/j.gastro.2022.08.045. Khandelwal S. *Climacteric* 2020;23:140-147. doi: 10.1080/13697137.2019.1660638

Surgical Procedures for Obesity Treatment

Bariatric surgery indications

- BMI ≥ 40 kg/m^2
- Or BMI 35 to 39.9 kg/m^2 and at least one weight-related comorbidity in those who have failed conservative treatment.

Surgical options

- Intragastric balloons.
- Endoscopic gastroplasty.
- Laparoscopic sleeve gastrectomy.
- Roux-en-Y gastric bypass.
- Biliopancreatic diversion with duodenal switch.

Long-term health risks

- Bowel obstruction.
- Dumping syndrome.
- Cholelithiasis.
- Hernias.
- Hypoglycemia.
- Nutritional deficiencies.
- Gastrointestinal reflux disease.
- Reoperation.

Khandelwal S. *Climacteric* 2020;23:140-147. doi: 10.1080/13697137.2019.1660638; Perdomo CM, et al. *Lancet* 2023;401:1116-1130. doi: 10.1016/S0140-673

SECTION 13

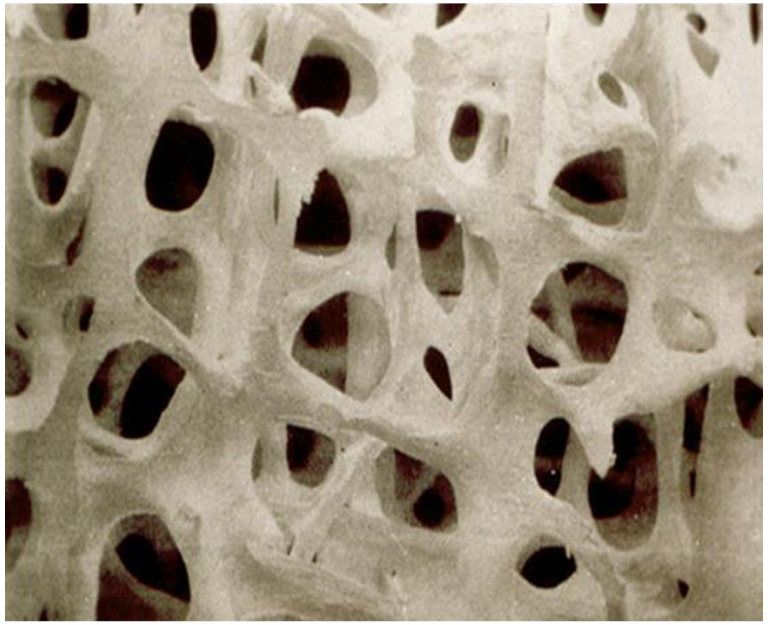
Management of Osteoporosis

The Menopause Society™

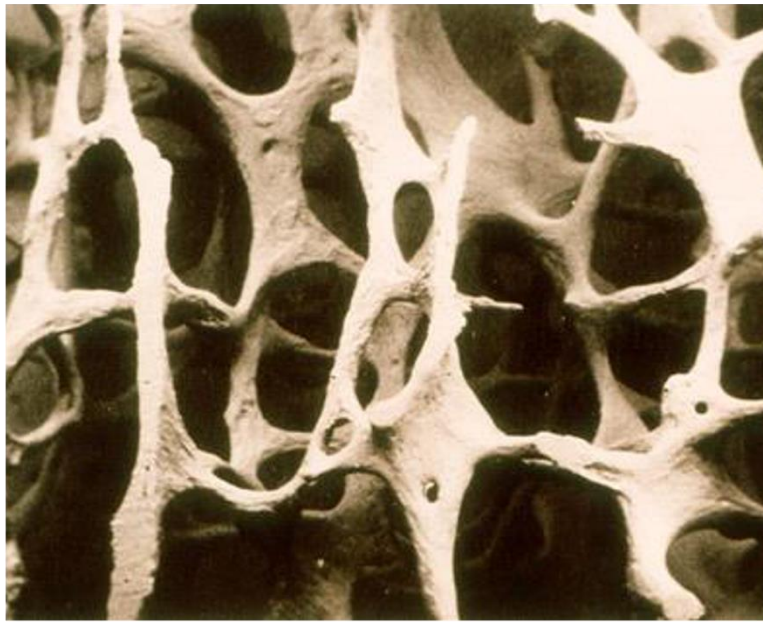
Osteoporosis

- A disease characterized by low bone mass (density) and microarchitectural deterioration leading to bone fragility and increased risk of fracture.

Normal bone



Osteoporosis



Kanis JA. *Osteoporosis Int* 1994;4:368-381. doi: 10.1007/BF01622200; Pentice A. *Public Health Nutr* 2004;7:227-243. doi: 10.1079/phn2003590

Etiology of Osteoporosis

- Peak bone mass in most women is reached by about age 20 years.
- Genetic factors account for 50% to 85% of variance in BMD; lifestyle factors such as nutrition and exercise contribute less.
- Accelerated bone loss starts in the late perimenopause stage continuing into the early menopause years and mostly affects the spine (largely comprised of trabecular bone) associated with menopause.
- By age 80 years, many women have lost about 30% of their peak bone mass.

Finkelstein JS, et al. *J Clin Endocrinol Metab* 2008;93:861-868. doi: 10.1210/jc.2007-1876 Lu J, et al. *J Clin Densitom* 2016;2:180-191. doi: 10.1016/j.jocd.2014.08.001; Ralston SH, et al. *Endocrine Rev* 2010;31:629-662. doi: 10.1210/er.2009-0044; Tannenbaum C, et al. *J Clin Endocrinol Metab* 2002;87:4431-4437. doi: 10.1210/jc.2002-020275

Prevalence of Osteoporosis

- Osteoporosis is the most common bone disorder and affects both sexes and all races.
- Risk of hip fracture doubles for every 5- to 6-year increase in age from 65 to 85 years.
- Of the 10 million Americans estimated to have osteoporosis, 8 million are women (80%).
- One in two women aged older than 50 years will sustain osteoporosis-related fracture in their lifetimes.
- A prior low-trauma fracture (fragility fracture) is also a diagnosis of osteoporosis regardless of whether DXA is available or reported.
    - Excludes fingers, toes, face, skull, or pathologic or traumatic fractures.

Kim SH, et al. *Arthritis Care Res (Hoboken)* 2012;64:751-757. doi: 10.1002/acr.21580; Sarafrazi N, et al. *NCHS Data Brief.* March 2021.

World Health Organization Definitions of Bone Density

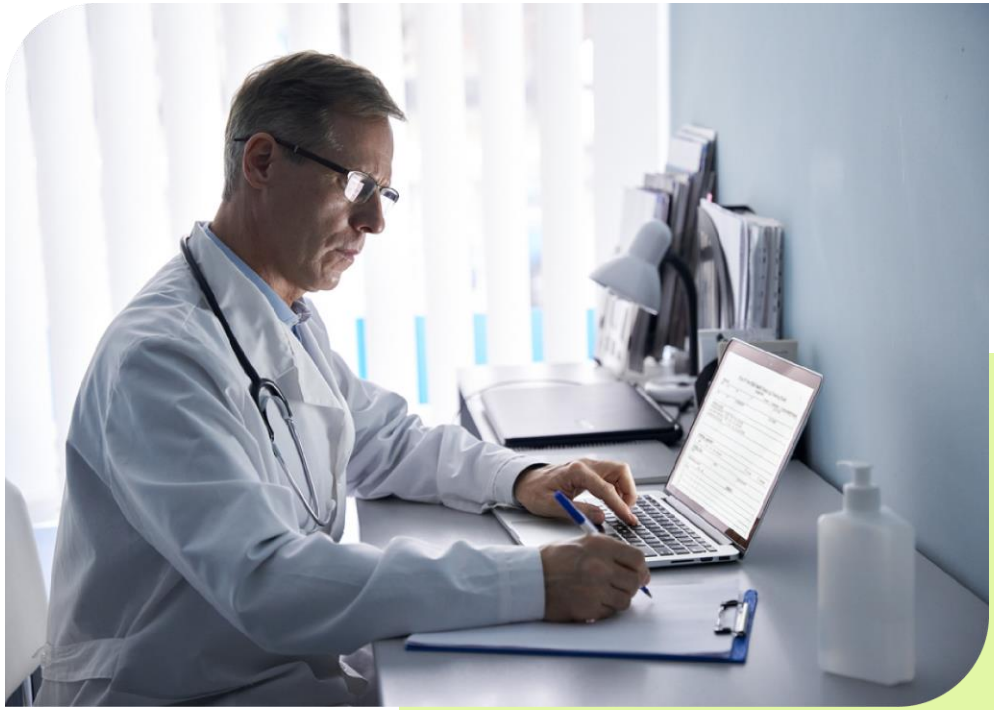
Bone Mineral Density at Any Site	
Normal	T-score ≥ −1.0
Low bone mass (osteopenia)	T-score between −1.0 and −2.5
Osteoporosis	T-score ≤ −2.5

- Based on White postmenopausal women.
- T-scores only to be used for postmenopausal women.
- Z-scores report BMD for similar age-, sex-, and race-matched premenopausal women
- BMD is useful to monitor bone loss change and assess response to therapy

Kanis JA. *Osteoporosis Int* 1994;4:368-381. doi: 10.1007/BF01622200.

Evaluation for Osteoporosis—Who Needs a DXA Scan?

- All women aged 65 and older.
- Younger postmenopausal women with risk factors: metabolic bone disorders, low body weight, prior low-trauma fracture, or high-risk medication, rheumatoid arthritis, and malabsorption.
- Anyone being considered for pharmacologic therapy for osteoporosis.
- Anyone being treated for osteoporosis, to monitor treatment effect.
- Anyone not receiving therapy in whom evidence of bone loss would lead to treatment.
- Postmenopausal women discontinuing estrogen.



National Osteoporosis Foundation. Clinician's Guide to Prevention and Treatment of Osteoporosis. 2008. www.natap.org/2008/HIV/NOF_Clinicians_Guide-1.pdf. Accessed June 7, 2024; US Preventive Services Task Force. Osteoporosis to Prevent Fractures: Screening. November 10, 2021. www.uspreventiveservicestaskforce.org/uspstf/draft-update-summary/osteoporosis-screening-prevent-fractures. Accessed June 7, 2024.

Management Approach

- Laboratory workup for secondary causes of osteoporosis (complete blood count, comprehensive metabolic panel, phosphorus, TSH, parathyroid hormone, and 24-hour urine calcium-creatinine collection).
- Lifestyle measures that reduce modifiable risk factors through dietary and activity changes (ie, smoking cessation, weight-bearing exercises, fall reduction, dietary calcium intake).
- FDA-approved pharmacologic therapy is recommended
    - For those with osteoporosis (by DXA) T-scores <−2.5 at the femoral neck, total hip, or spine.
    - For those with a history of low-trauma fracture hip or vertebral (clinical or morphometric) fractures.
    - For those at high risk for fracture based on FRAX (T-score −1 to −2.5, osteopenia) at the femoral neck, total hip, or spine and 10-year hip fracture probability ≥3% or a 10-year all major osteoporosis-related fracture probability of ≥20% based on the US-adapted WHO absolute fracture risk model.

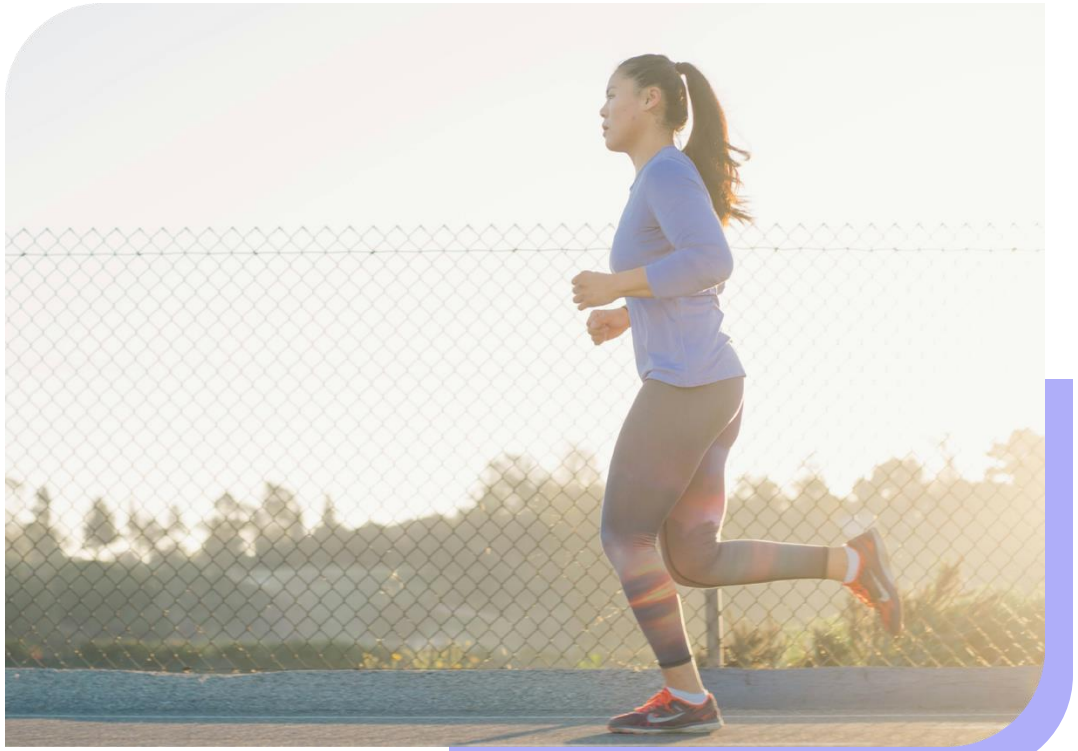
FRAX Fracture Risk Assessment Tool. https://frax.shef.ac.uk/FRAX/tool.aspx?country=9; Management of osteoporosis in postmenopausal women: 2010 position statement of The North American Menopause Society. *Menopause* 2010;17:25-54. doi: 10.1097/gme.0b013e3181c617e6

Selecting a Specific Therapy

- Decision should be individualized.
- Classify patient's risk of fracture (moderate risk [ie, no prior fracture] vs high risk [ie, prior low-trauma fracture]).
- If adherence to therapy is poor, there is better compliance with IV, subcutaneous therapies.
- Rare risks (such as osteonecrosis of jaw and atypical femoral fracture) have been reported with long-term use of antiresorptives.

Influence of Hormone Therapy on Bone Mineral Density and Fracture

- ET, EPT, help prevent and reduce fracture risks.
- Women aged older than 60 years or within 10 years of menopause and without contraindications, the benefit-risk ratio is most favorable for treatment of bothersome VMS and for those at elevated risk for bone loss or fracture.



"The 2022 Hormone Therapy Position Statement of The North American Menopause Society" Advisory Panel. *Menopause* 2022;29:767-794. doi: 10.1097/GME.0000000000002028

Treatment Categories

Antiresorptives

- Estrogen agonists/antagonists (raloxifene or tamoxifen in postmenopause).
- Bisphosphonates (oral, IV).
- Denusomab (subcutaneous).

Osteoanabolics

- Teriparatide (parathyroid hormone-34).
- Ataloparatide (parathyroid hormone-P).

Dual anabolic/antiresorptive

- Romosozumab.

SECTION 14

Menopause Support in the Workplace

The Menopause Society™

Effect of Menopause Symptoms on Work

- Roughly 20% of the workforce is in the MT.
- Women experiencing menopause symptoms were found to be eight times more likely to report difficulty meeting demands of work compared with those without symptoms.
- Severity of menopause symptoms correlates with more emotional exhaustion, less work engagement, and greater turnover intentions.
- Negative self-perceptions of work capability correlate with menopause symptoms.
- Work difficulties cited as a reason women initiate HT.

Alzueta E, et al. *Menopause* 2024;31:258-265. doi: 10.1097/GME.0000000000002333; Griffiths A, et al. *Maturitas* 2013;76:155-159. doi: 10.1016/j.maturitas.2013.07.005

Workplace Factors Affecting Menopause Symptoms

- Menopause symptoms can be exacerbated by workplace-related factors.

Workplace environment

- Poor ventilation.
- Crowded or confined workspaces.
- Higher ambient room temperatures.
- Uniforms made from synthetic materials.
- Unventilated protective equipment.

Workplace culture

- Stressful work environments (ie, high-visibility work, learning new things, detail-oriented tasks).
- Unpredictable and long work hours.
- Restrictive bathroom or break policies.
- Poor ergonomics resulting in static postures.

Workplace policy and knowledge gaps

- Inadequate awareness and training of employers and managers.
- Lack of formal menopause-accommodation policies.

Alzueta E, et al. *Menopause* 2024;31:258-265. doi:10.1097/GME.0000000000002333; Bariola E, et al. *Menopause* 2017;24:247-251. doi:10.1097/GME.0000000000000751; Griffiths A, et al. *Maturitas* 2013;76:155-159. doi:10.1016/j.maturitas.2013.07.005; Jafari M, et al. *J Menopausal Med* 2017;23:85-90. doi:10.6118/jmm.2017.23.2.85

Economic and Lost Human Capital Burden of Menopause Symptoms in the Workplace

Severe menopause symptoms associated with

- Higher rates of sick leave.
- Productivity loss.
- Less motivation at work.
- Reduction in work hours or leaving workforce.

Economic costs of menopause

- Estimated US $1.8 billion economic loss per year.
- Cost increases to $26.6 billion annually with addition of medical expenses.
- One in 10 UK women aged 45 to 54 years reportedly leave their jobs because of menopause-symptom burden.

Avandrou M, et al. *Maturitas* 2021:143:96-104. doi:10.1016/j.maturitas.2020.09.010; Faubion SS, et al. *Mayo Clin Proc* 2023;98:833-845. doi:10.1016/j.mayocp.2023.02.025; Kleinman N, et al. *J Occup Environ Med* 2013:55:465-470. doi:10.1097/JOM.0b013e3182820515

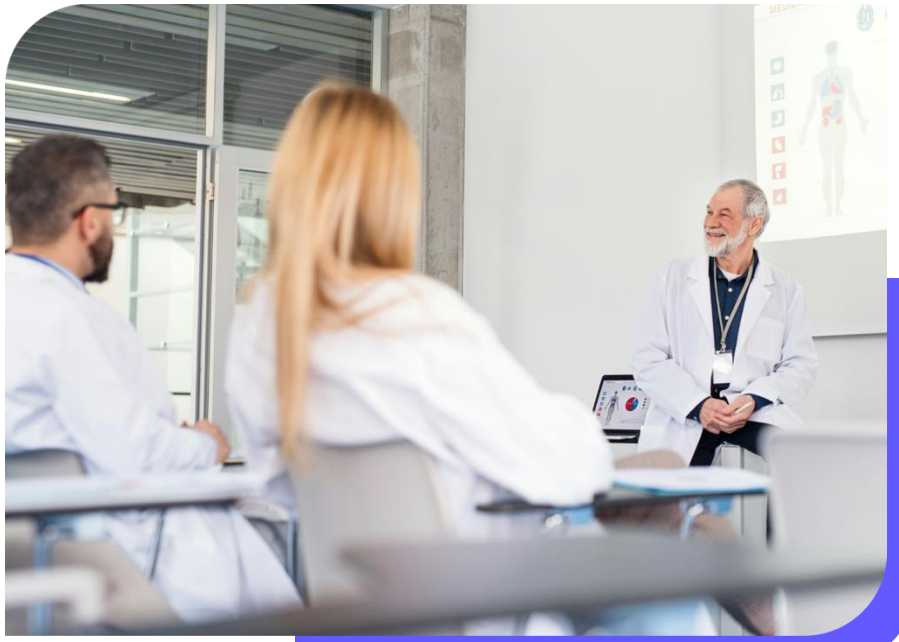
Employer Workplace Interventions

- Education and awareness programs about menopause for managers and employees.
- Higher supervisor and manager support.
- Menopause benefits.
- Menopause-specific leave.
- Workplace temperature control.
- Flexible work hours.
- Remote work option.

Bariola E, et al. *Menopause* 2017;24:247-251. doi:10.1097/GME.0000000000000751; Hickey M, et al. *J Psychosom Obstet Gynaecol* 2017;38:202-209. doi:10.1080/0167482X.2017.1327520; Mayer K, et al. Employers are turning to a new perk: menopause benefits [News]. *SHRM*. November 8, 2023.

Menopause Benefits and Offerings Found to Have a Positive Effect on Work

- Menopause benefits and offerings have been reported to have a positive effect on work, with the potential to boost retention and attraction.
    - An important consideration for employers.
- Self-help CBT is associated with improvement in mental resources for work, work presenteeism, and social adjustment.
- Systematic review of 293 menopausal women found employer-sponsored benefits to be effective strategies at work.
    - Raja Yoga.
    - Menopause consultation.
    - Work-life coaching.
    - Physical training.



Rogdrigo CH, et al. *Post Reprod Health* 2023;29:99-108. doi:10.1177/20533691231177414

SECTION 15

Case Scenarios

The Menopause Society™

Hormone Therapy Indications

A 53-year-old woman presents for consultation regarding hormone therapy (HT). Her final menstrual period was 18 months ago. Initially, she experienced episodic hot flashes and night sweats; however, she hasn't noticed any over the past 6 months. She states, "even when I did have them, they weren't terribly bothersome." Her main concerns are increased weight gain, forgetfulness and brain fog, thinning hair, and overall lack of energy. She becomes tearful discussing her 20 lb weight gain over the past couple of years. She acknowledges a more sedentary lifestyle since she started working from home and admits to poor dietary choices. She joined a Facebook group for menopause. Everyone in the group recommended HT. What do you tell her are the FDA-approved indications for HT use?

A. Vasomotor symptoms (VMS) and genitourinary syndrome of menopause (GSM)

B. VMS, genitourinary syndrome of menopause (GSM), and mood swings

C. VMS, GSM, prevention of bone loss, and premature hypoestrogenism

D. VMS, GSM, prevention of bone loss, premature hypoestrogenism, and mood swings

Hormone Therapy Indications

The answer is c: VMS, GSM, prevention of bone loss, and premature hypoestrogenism

FDA-Approved Indications for Hormone Therapy

1. Treatment of moderate to severe VMS
2. Treatment of moderate to severe GSM
3. Use in those with premature hypoestrogenism (age <45 y) resulting from hypogonadism, bilateral oophorectomy, or primary ovarian insufficiency (POI)
4. Treatment of osteopenia

"The 2022 Hormone Therapy Position Statement of The North American Menopause Society" Advisory Panel. *Menopause* 2022;29:767-794. doi: 10.1097/GME.0000000000002028

Timing Hypothesis

A 57-year-old patient presents for consultation regarding bothersome menopause symptoms, including frequent hot flashes and night sweats, sleep disturbances, and mood swings. The symptoms started 2 years ago, and their last menstrual cycle was a year ago. The patient exercises regularly and adheres to a Mediterranean diet. There is no significant past medical history; however, the patient does have a family history of dementia. Last month they were seen by another healthcare professional who told them that they were “too old” for HT. Which is true regarding the timing hypothesis?

A. HT is considered safe and effective in low-risk persons without underlying coronary artery disease or history of breast cancer.
B. HT is considered safe and effective in those aged younger than 60 years with moderate to severe VMS.
C. HT is considered safe and effective in those who are fewer than 10 years from the onset of menopause.
D. All of the above (a, b, and c)

Timing Hypothesis

The correct answer is D: All of the above (a, b, and c)

- The best candidates for starting systemic HT are those with moderate to severe VMS, are aged younger than 60 years, are within 10 years from the onset of menopause, and do not have elevated risks for CVD or breast cancer.
- Initiation of systemic HT in those aged older than 60 years or more than 10 years from the onset of menopause confers higher risks.
- New onset VMS in those remote from the onset of menopause requires workup.

Freeman EW, et al. *Obstet Gynecol* 2011:1095-1104. Doi: 10.1097/AOG.0b013e318214f0de.; "The 2022 Hormone Therapy Position Statement of The North American Menopause Society" Advisory Panel. *Menopause* 2022;29:767-794. Doi: 10.1097/GME.0000000000002028

Nonhormone Therapy Options

A 52-year-old woman with her last menstrual cycle 8 months ago presents with persistent hot flashes and night sweats. The night sweats are extremely disruptive to her sleep. She describes her job as “high stress” and notes worsening symptoms when she does formal presentations to her team, which is extremely embarrassing. She’d like to discuss treatment options but wants to avoid HT because her mother has a history of breast cancer. What nonhormone treatments do you tell her have been found to be most efficacious in the management of moderate to severe VMS?

A. Clonidine, pregabalin, selective serotonin reuptake inhibitors (SSRIs), serotonin–norepinephrine reuptake inhibitors (SNRIs), or fezolinetant
B. SSRI, SNRI, oxybutynin, gabapentin, or fezolinetant
C. Gabapentin, SSRI, SNRI, or fezolinetant
D. Herbal supplement containing black cohosh, avoidance of triggers, cooling techniques, and exercise

Nonhormone Therapy Options

The correct answer is B: SSRIs, SNRIs, oxybutynin, gabapentin, and fezolinetant have all been shown to reduce VMS.

- Level I evidence to support use: SSRIs, SNRIs, gabapentin, and fezolinetant.
- Level I-II evidence to support use: oxybutynin; however, it has been associated with cognitive decline in older adults.
- Clonidine is not recommended because of low efficacy and high adverse-event (AE) profile.
- Pregabalin is not recommended because of AEs and controlled substance prescribing restrictions.
- Herbal supplements are not recommended because they have not been shown to be better than placebo in clinical trials.
- Exercise is not associated with decreased VMS; however, weight loss has been shown to help.
- Avoidance of triggers and cooling techniques have not been found to reduce the frequency of VMS and should not be recommended as treatment.

Crandall CJ, et al. *JAMA* 2023;329:405-420. doi: 10.1001/jama.2022.24140; "The 2023 Nonhormone Therapy Position Statement of The North American Menopause Society" Advisory Panel. *Menopause* 2023; 30:573-590. doi: 10.1097/GME.0000000000002200

Bioidentical Hormone Therapy

A 54-year-old-patient was referred to you for consultation regarding worsening VMS. The final menstrual period was more than a year ago. They've tried several over-the-counter treatments without success. Past medical history is significant for well-controlled hypertension. The patient denies any significant family history. A few of their friends have started bioidentical "pellet" HT they obtained through a compounding pharmacy. Your patient would like to know your thoughts. How do you counsel your patient?

A. Bioidentical HT is safer than other forms of HT.
B. Compounded bioidentical hormones are approved by FDA.
C. Marketing claims about the safety and effectiveness of compounded preparations are supported by properly controlled clinical trials.
D. Bioidentical hormones consisting of estradiol preparations and micronized progesterone (MP) are approved by FDA and are available by prescription.

Bioidentical Hormone Therapy

The correct answer is D: Bioidentical hormones consisting of estradiol preparations and MP are approved by FDA and are available by prescription.

- Bioidentical HT refers to both US government-approved and compounded bioidentical HT.
- US government-approved options are regulated and monitored for purity and efficacy.
- Drugs prepared by compounding pharmacies have not undergone stringent testing for efficacy and safety. In addition, nonstandard, untested routes of administration often result in supratherapeutic serum hormone concentrations (ie, pellets, implants, or trouches), resulting in higher AEs.
- Salivary and urine hormone testing is unreliable and not recommended.
- Compounded formulations can be considered for persons with allergies to ingredients in US government-approved products

Stuenkel CA. *Menopause* 2021:576-578. doi: 10.1097/GME.0000000000001735; "The 2022 Hormone Therapy Position Statement of The North American Menopause Society" Advisory Panel. *Menopause* 2022;29:767-794. doi: 10.1097/GME.0000000000002028

Long-Term Use of Hormone Therapy

A 69-year-old woman recently transferred care because her primary healthcare professional retired. She presents for an annual exam and refill on HT. She has no complaints. Her past medical history is unremarkable. Family history is positive for osteoporosis in her mother and her father's death at age 55 of a myocardial infarction. Her only medication is 2 mg oral estradiol that she started on after her hysterectomy 15 years ago. Vital signs are stable. Her body mass index (BMI) is 21. Physical examination is unremarkable. You counsel the patient on the risks associated with HT use in someone aged older than 65 years and more than 10 years from the onset of menopause. Despite the risks, she would still like to stay on. What is the next best step?

A. Discontinue systemic HT.

B. Refill current HT formulation.

C. Switch to an equivalent dose transdermal preparation of HT.

D. Switch to a lower-dose transdermal preparation of HT.

Long-Term Use of Hormone Therapy

The correct answer is D: Switch to a lower-dose transdermal preparation of HT.

By expert opinion it is reasonable to suggest that the patient switch to a lower-dose systemic route of administration. Based on data from SWAN, VMS tend to subside for most women about 4.5 years after the FMP; however, for some women symptoms persist for a much longer duration of time. For those with persistent VMS or those with bone loss concerns, extending the use of HT can be considered if they are counseled on the increased associated risks of breast cancer, CVD, and VTE. Additionally, some studies have shown an increased risk of cognitive decline or dementia. The conversation should be documented in the medical record. In this setting, transdermal routes of administration should be considered at a lower dose.

Continuation of systemic HT use is not the same as initiating systemic HT in someone aged older than 65 years and more than 10 years from the onset of menopause, which is associated with an elevated risk of CVD. In this instance, a workup evaluating other causes of VMS should be initiated. They should be counseled on nonhormone treatment strategies.

Cho L, et al. *Circulation* 2023;147: 597-610. doi:10.1161/CIRCULATIONAHA.122.061559

Primary Ovarian Insufficiency

A 20-year-old presents with irregular menstrual cycles. Menarche began at age 11. Menstrual cycles initially came every 28 to 30 days up until 2 years ago when she started college. At that time, cycles started to space out. The longest she went without a menses was 3 months. She started on oral contraceptives (OCPs) to regulate her cycle; however, no workup was done. After 6 months, she stopped the OCP because she'd heard cycles can sometimes self-regulate over time. Since stopping OCPs about a year and a half ago, she's only noted light spotting for a few days some months. You order labs with the following results: follicle-stimulating hormone (FSH), 40 IU/L and estradiol, 20 pg/mL, with normal karyotype. She denies hot flashes or night sweats, mood swings, or vaginal dryness. She is sexually active and does not desire pregnancy. How do you counsel this patient?

A. Tell her she most likely has primary ovarian insufficiency (POI); however, to confirm she will need to return in a few months for repeat blood work. You instruct patient to keep a log of menstrual cycles and use a backup form of birth control because she doesn't desire fertility.

B. Tell her she most likely has POI, based on labs and clinical picture, and should resume combined OCP or have a levonorgestrel releasing intrauterine device placed with the addition of transdermal estradiol to reduce the risks of fracture, CVD, heart failure, diabetes, dementia, and overall mortality.

C. Tell her she most likely has POI, based on labs and clinical picture, and should be placed on HT to protect against facture, CVD, heart failure, diabetes, dementia, and overall mortality.

D. Tell her she most likely has POI, which affects fertility. Recommend she not initiate HT because it may reduce her chances of fertility and refer her to a reproductive endocrinologist.

Primary Ovarian Insufficiency

The correct answer is B: Tell her she most likely has POI, based on labs and clinical picture, and should resume combined OCP or have a levonorgestrel releasing intrauterine device placed with the addition of transdermal estradiol to reduce the risks of fracture, CVD, heart failure, diabetes, dementia, and overall mortality.

- POI results from the early loss of ovarian follicular function in persons aged younger than 40 years that can be transient for some. The early loss of ovarian function is associated with increased risk of fracture, CVD, heart failure, diabetes, dementia, and overall mortality. To minimize risks, HT is recommended until the person reaches the average age of menopause, approximately 52 years.
- Spontaneous pregnancy may occur in approximately 5% of women, and for this reason, hormone contraception may be the best option for this patient because she does not desire fertility at this time.
- Reasonable to refer her to a reproductive endocrinologist to discuss future fertility options.
- The diagnosis is made after having two elevated FSH levels a month apart; however, this patient likely had POI 2 years ago when her cycles first became irregular.

"The 2022 Hormone Therapy Position Statement of The North American Menopause Society" Advisory Panel. *Menopause* 2022;29:767-794. doi: 10.1097/GME.0000000000002028

Genitourinary Syndrome of Menopause

A 65-year-old woman presents with pain and bleeding with intercourse and decreased libido. She recently became sexually active after having been abstinent for more than 20 years. Her FMP was around age 48. She relayed that she had a relatively "easy" menopause transition and never needed to be on HT. She and her partner have tried over-the-counter lubricants, and she recently started a vaginal moisturizer that she applies twice weekly when she remembers. Although she notes some relief, vaginal penetration is still painful. Her past medical history is positive for deep vein thrombosis after she had a knee replacement 3 years ago. Physical examination and pelvic ultrasound are unremarkable. She'd like to discuss treatment options for her sexual dysfunction. You recommend

A. CO^2 laser therapy.
B. Increase the use of the vaginal moisturizer and start PFPT.
C. Prescribe intravaginal dehydroepiandrosterone (DHEA) or ospemifene because estrogen therapy (ET) is contraindicated because of history of DVT.
D. Start patient on local, low-dose vaginal ET or intravaginal DHEA and have her follow up in 8-12 weeks.

Genitourinary Syndrome of Menopause

The correct answer is D: Start patient on local, low-dose vaginal ET or intravaginal DHEA and have her follow up in 8 to 12 weeks.

- Low-dose, local vaginal ET is the most effective treatment for management of GSM and because there is minimal systemic absorption can be used in those with a history of VTE, stroke, CVD, or estrogen-responsive cancers. Unlike VMS, genitourinary symptoms do not improve without treatment.
- Nonestrogen alternatives, ospemifene, and intravaginal DHEA are FDA approved for treatment of postmenopause dyspareunia; however, ospemifene is associated with a slight increased risk of blood clots.
- Laser and radiofrequency procedures are not recommended because of lack of data showing efficacy and long-term safety.
- PFPT can be helpful; however, the underlying vaginal atrophy needs to be addressed first.

Cho L, et al. *Circulation* 2023;147: 597-610. doi:10.1161/CIRCULATIONAHA.122.061559; Phillips NA, et al. *Menopause* 2021;28:579-588. doi: 10.1097/GME.0000000000001728; "The 2022 Hormone Therapy Position Statement of The North American Menopause Society" Advisory Panel. *Menopause* 2022;29:767-794. doi: 10.1097/GME.0000000000002028

Sleep Disturbances in Midlife

A 49-year-old woman started having problems falling asleep, awakening 3-4 times per night and staying up for 45-60 minutes each time. She reported she has been feeling very hot and that her mind will not shut off. Her husband noticed she has been tossing and turning throughout the night and has been irritable during the day.

Her primary healthcare professional suggested that she take sedative-hypnotics, but she stated that she does not trust taking medications. After she declined to take the sleep aide, she was not offered treatment options. She has a visit with you in 1 week.

What is the first step you would take to help this patient?

A. Suggest melatonin.
B. Suggest HT.
C. Provide education about treatment options. Then ask: What do you think you need to better manage your problems with sleep?
D. Suggest psychiatry.
E. Suggest psychology.

Sleep Disturbances in Midlife

The correct answer is C: Provide education about treatment options. Then ask: What do you think you need to better manage your problems with sleep?

- Patients may not be aware of their options. A conversation can provide insight about their distrust of medications. They may be more likely to engage in treatment if they feel listened to and respected. This approach can help empower, encourage shared decision-making, and reduce the potential for inequitable treatment.
- HT is the gold standard treatment for VMS and may improve sleep. Improving sleep quality can improve mood.
- Melatonin may help with sleep and may be used when HT is contraindicated or not preferred.
- Consult with a psychiatrist if their main concerns are racing thoughts and if they are open to psychiatric medications.
- Referral to a psychologist who can help with cognitive and behavioral skills to manage racing thoughts, insomnia, and night sweats for those that want to avoid pharmacotherapy.

European Patient Forum. *EPF Background Brief: Patient Empowerment.* May 15, 2015. www.eu-patient.eu/policy/campaign/patientsprescribe/. Accessed June 6, 2024; Perzynski A, et al, eds. *Health Disparities: Weaving a New Understanding Through Case Narratives*. Springer; 2019.

Mood Disorders and Cognitive Decline in Midlife

A 48-year-old woman has been referred to you for some new symptoms: irritability, mood swings, and hot flashes. She has a history of major depressive disorder and is afraid that she is relapsing after being stable for 3 years. For the past year, her menstrual cycles have been irregular. Her psychiatrist referred her to you because of her having hot flashes and mood swings. She is confused as to why her psychiatrist included mood swings in their referral.

During your evaluation, the patient reported feeling more depressed than usual and feeling as though she is losing her mind. In addition, she has been forgetful, such as forgetting where she places her keys and phone. She is concerned that she has early stage Alzheimer disease. She is feeling helpless and has asked you what to do.

What suggestions would you give this patient?

A. I am also confused why your psychiatrist referred you to me for mood swings. I will let them know that you are just depressed, and this is not my area of expertise.

B. You are describing perimenopause depression. This means that changes in your hormones are causing menopause symptoms and likely exacerbating your depressive symptoms. Hormone therapy is the gold-standard treatment for hot flashes. Hormone therapy also has antidepressant effects but are not FDA approved to treat depression.

C. I think you should see our psychologist. She uses CBT to help women cope with menopause-related symptoms.

D. Suggest B and C.

Mood Disorders and Cognitive Decline in Midlife

The correct answer is D: Suggest B and C

This patient is describing perimenopause depression, which is a combination of psychosocial stress, menopause, and depressive symptoms.

- Hormone therapy is the gold-standard treatment for VMS. Although HT may help mitigate depression, it is not FDA approved to treat this condition.
- A psychologist trained in menopause can provide education to help the patient understand their symptoms; use CBT to help them cope with their depression and hot flashes; perform memory testing to rule out cognitive impairment; and provide education about cognitive changes during the MT.

Conklin DY, et al. *J Psychosom Res* 2020;128:109882. doi: 10.1016/j.jpsychores.2019.109882; Green SM, et al. Menopause 2019;26:972-980. doi: 10.1097/GME.0000000000001363; Maki PM, et al. *J Womens Health (Larchmt)* 2019;28:117-134. doi: 10.1089/jwh.2018.27099.mensocrec; Panay N, et al, eds. *Managing the Menopause*. 2nd ed. Cambridge University Press; 2020.

Management of Midlife Weight Gain

A 55-year-old woman, who has been your patient for several years, complains of problems with weight gain, especially in her midsection. She is not taking medications that would cause weight gain, and she does not have problems sleeping through the night. She disclosed that her mother moved in with the family from Puerto Rico and has been making her favorite foods. She has gained 20 lb in the past 2 years. Her BMI is 31. She stated even though she has been eating her favorite cultural dishes, she has been eating in moderation and going for 20- to 30-minute walks three times per week. However, she is frustrated because she cannot lose the “muffin top.”

What suggestions would you give this patient?

A. Don’t worry about it. It is normal to gain weight around your waistline at your age. It’s not a big deal.
B. Add weight training in addition to walking.
C. Would you be willing to meet with a registered dietician who can help you balance your cultural food preferences along with healthier options? Research has shown that a Mediterranean diet is recommended for menopausal women.
D. A healthy waist circumference is less than 35 inches for women.
E. B and C
F. B, C, and D.

Management of Midlife Weight Gain

The correct answer is F: B, C, and D.

- This patient's BMI falls into the Class 1 obesity range. Excess weight and a waist circumference over 35 inches are associated with an increased risk in medical conditions, such as type 2 diabetes and CVD.
- Though not fully understood, central and visceral fat increases and lean muscle mass decreases for menopausal women, partly because of multiple changes in hormones. Conversely, weight gain is mostly because of age, with 0.8 lb per year, on average.
- The Mediterranean diet is recommended for menopausal women to help maintain a healthy weight range.
- Exercise of moderate intensity for 60 to 90 minutes most days of the week is recommended for this population. Exercise should consist of cardio and weight training.

Conklin D, et al. Cardiovascular risks and menopause. CARDI-OH Project ECHO. Virtual Presentation. March 14, 2024; Crandall CJ, et al, eds. *Menopause Practice: A Clinician's Guide*, 6th ed. The North American Menopause Society; 2019; Gunter J. *The Menopause Manifesto. Own Your Health With Facts and Feminism*. Citadel Press; 2021; Tonstad S. et al. *Nutr Metab Cardiovasc Dis* 2013;292-299. doi: 10.1016/j.numecd.2011.07.004; Vetrani C, et al. *Front Endocrinol* 2022;13:1-8. doi: 10.3389/fendo.2022.886824

Osteoporosis in Midlife

A 53-year-old White woman whose last menstrual period was 11 years ago presented to the office with complaints of abnormal weight loss of 10-15 lb, dry skin, and racing heart for the past 6 months. She has not changed her lifestyle or added any supplements. She has a balanced diet with three meals a day, walks daily, and lifts weights three times weekly. She denies any other symptoms but has been told that “her neck looks bigger” and that she has a hoarse voice. She has no other medical issues. Her family history is significant for thyroid disease in her mother. Vital signs are normal except for a pulse of 100, and the examination is remarkable for a goiter only. Lab work reveals a normal complete blood count and comprehensive metabolic panel, but her thyroid-stimulating hormone is <0.01 and free thyroxine is 5.5. A thyroid ultrasound shows multiple nodules. Her mammogram is normal, but a DXA scan shows osteoporosis of both her spine and hips. She was started on methimazole for her hyperthyroidism, but how do you counsel her on her low bone density? Should she be started on medication to treat the osteoporosis?

A. No, wait until her thyroid disorder is under control and recheck the DXA.
B. No, send her to an endocrine surgeon to remove thyroid nodules, then recheck the thyroid function tests and DXA.
C. Yes, make sure she is taking adequate calcium and vitamin D and start a bisphosphonate.

Osteoporosis in Midlife

The correct answer is C: Yes, make sure she is taking adequate calcium and vitamin D and start a bisphosphonate.

- This patient probably had subclinical hyperthyroidism until 6 months ago when the symptoms became apparent.
- Thyroid hormones play a critical role in the maintenance of adult bone structure and strength.
- Women are more likely to have thyroid disease, and the prevalence increases with age. Between the ages of 40 and 60 years, the prevalence of hyperthyroidism has been estimated to be as high as 45%, and it increases 1% to 4% after age 60 years.
- Both subclinical and overt hyperthyroidism have long been recognized as a cause of high bone turnover and high risk for osteoporosis and fragility fractures. This patient should be counseled about adequate calcium intake and vitamin D supplementation and exercise. She should start on a treatment for osteoporosis, such as a bisphosphonate. It is essential to treat her hyperthyroidism to reduce bone turnover and improve BMD. Although studies have shown that bone turnover markers will normalize within 1 month of any treatment of hyperthyroidism, BMD may not return to the normal range for up to 3 to 5 years.

Ale AO, et al. *Int J Endocrino*.2018;2018:3540256. doi: 10.1155/2018/3540256; Delitala AP, et al. *J Clin Med* 2020;9:1034. doi: 10,3390/ jcm9041034; Nicholls JJ, et al. *J Endocrinol* 2012;213:209-221. doi: 10.1530/JOE-12-0059

Hormone Therapy and Breast Cancer

A 56-year-old woman was diagnosed with left breast ductal carcinoma in situ at age 45 and treated with lumpectomy, local radiation, and 5 years of tamoxifen. She has no family history of the disease. Since her last menstrual period at age 50, she has experienced nightly VMS that disrupt her sleep, as well as dyspareunia and urge incontinence.

Various botanicals and SSRIs have been ineffective. The patient desires ET for her symptoms. Shared decision-making should include which of the following statements?

A. TSEC oral tablet (SERM + CEE) has been shown in preclinical trials to have antitumor effects.
B. Safety for the use of intravaginal DHEA and oral ospemifene to treat GSM in patients with breast cancer has been well established.
C. The patient does not meet the National Comprehensive Cancer Network (NCCN) criteria for germline genetic testing.

Hormone Therapy and Breast Cancer

The correct answer is A: The TSEC oral tablet (SERM plus CEE) has been shown in preclinical trials to have antitumor effects.

- Lack of randomized, placebo-controlled trials of exogenous hormones (local and systemic) in survivors of breast cancer limits data-driven clinical decision-making.
    - Twenty-five studies of HT use after a breast cancer diagnosis, published between 1980 and 2013, were recently reviewed.
    - Hormonal Replacement Therapy After Breast Cancer—Is It Safe? (HABITS) trial, demonstrated an increased risk of recurrence, which was limited to local or contralateral and not distant recurrence.
    - None of the studies reported increased breast cancer mortality associated with HT.
- Pairing a SERM with estrogen to create a TSEC has been shown to have antitumor effects in preclinical studies.
- GSM in survivors is underrecognized and undertreated, often affecting intimacy, necessitating open discussion.
    - Nonhormone options are first-line treatment.
    - Intravaginal DHEA and oral ospemifene (an estrogen agonist/antagonist) FDA approved for the treatment of dyspareunia, but safety in survivors was not established.
- Risk assessment in patients with breast cancer is crucial. This patient meets NCCN criteria for germline genetic testing, a test that may inform her choices and those of family members, given her age at diagnosis.
- Use of systemic HT at the lowest effective dose may be considered with input from oncology if non-hormone therapies fail to alleviate symptoms.
    - Consider combining estrogen with MP, shown to pose less risk than synthetic progestogen in a case-control study and animal models.

Crean-Tate KK, et al. *Am J Obstet Gynecol* 2020;222:103-113. doi: 10.1016/j.ajog.2019.08.043; National Comprehensive Cancer Network. Genetic/Familial High-Risk Assessment: Breast, Ovarian, and Pancreatic. Version 3.2024. February 12, 2024.

Hormone Therapy and *BRCA* Genetic Mutations

A 39-year-old woman who was found to have a *BRCA 1* genetic mutation presents to you before RRBSO for a menopause consultation. She is concerned about the symptoms she may experience and risks associated with treatment options. Because of an extensive family history of cancer and CVD, she prefers a more "natural" approach to treatment. How would you counsel this patient?

A. Reiterate that HT would increase the risk of breast cancer and CVD especially with her family history and genetic mutation.
    1. Provide her with information on foods rich in calcium and recommended daily allowances, along with information on the benefits of weight-bearing exercises and supplements to help minimize menopause symptoms and risk of osteoporosis and CVD.
B. Discourage surgical menopause at a young age and recommend waiting to have surgery closer to the natural age of menopause.
C. Share that current research shows removal of the fallopian tubes with retention of the ovaries confers the same risk reduction of breast and ovarian cancer as RRBSO.
D. Discuss ideal timing of RRBSO based on family history of age at onset of cancer diagnosis and completion of childbearing.
    1. Relay risks associated with early menopause and recommended treatment of systemic HT until the natural age of menopause to minimize risks of osteoporosis, CVD, and cognitive decline.

Hormone Therapy and *BRCA* Genetic Mutations

The correct answer is D: Discuss ideal timing of RRBSO based on family history of age at onset of cancer diagnosis and completion of childbearing. Relay risks associated with early menopause and recommended treatment of systemic HT until the natural age of menopause to minimize risks of osteoporosis, CVD, and cognitive decline.

- The standard of care is to offer RRBSO (with or without hysterectomy) as soon as possible after childbearing is complete, ideally by age mid-40s; however, it depends on whether *BRCA 1* or *2* and age of index case(s).
    - *BRCA 1*: Recommended RRBSO between the ages of 35 and 40 y
    - *BRCA 2*: Recommended RRBSO between the ages of 40 and 45 y
- Early menopause is associated with more severe menopause-related symptoms (eg, VMS, GSM, mood and cognitive changes, sleep disturbances) and reduced QOL, along with other health consequences (eg, CVD, stroke, osteoporosis) and all-cause mortality.
- Use of systemic HT in those with *BRCA 1* or *2* genetic variants after RRBSO has not been found to increase the risk of developing breast cancer and should be initiated and continued until the average age of natural menopause.
- BS (Bilateral Salpingectomy) with retention of ovaries is associated with decreased ovarian cancer risk in patients with gene mutations and the general population; however, it may not afford the same risk reduction for breast cancer.

Kingsberg SA, et al. *Obstet Gynecol* 2020;135:853-868. doi:10.1097/AOG.0000000000003729; "The 2022 Hormone Therapy Position Statement of The North American Menopause Society" Advisory Panel. *Menopause* 2022;29:767-794. doi: 10.1097/GME.0000000000002028

The Menopause Society appreciates the contributions of these members of The Menopause Society Education Committee

Monica M. Christmas, MD, FACOG, MSCP, *Project Leader*
Associate Professor and Director of the Menopause Program
and Center for Women's Integrated Health
Section of Minimally Invasive Gynecologic Surgery
UChicago Medicine and Biological Sciences
Chicago, Illinois
Consultant/Advisory Board for the FDA Bone, Reproductive, and Urologic Products Committee; Speaker Honoraria for Fertility IQ.

Mercedes Castiel, MD, FRCSC, FACOG, MSCP, GCRA
The Cancer Care Concierge
Oncology Navigation, Advocacy, Support
Pelham, New York
No relevant financial relationships with ineligible companies.

Danette Conklin, PhD
Clinical and Health Psychologist
Director, Behavioral Health Services, Bariatric Surgery and Weight Management
University Hospitals Cleveland Medical Center
Assistant Professor of Psychiatry and Reproductive Biology
Case Western Reserve University
Cleveland, Ohio
Consultant for the American Heart Association.

Cheryl Cox Kinney, MD, FACOG, MSCP
Director, Center for Female Health and Hormone Disorders
Dallas, Texas
No relevant financial relationships with ineligible companies.

Catherine Hansen, MD, FRCSC, FACOG, MPH, MSCP
Head of Menopause at Pandia Health
Founder Empowered Women's Circle
Houston, Texas
Consultant/Speaker for Exeltis; Consultant/Advisory Board for Pandia Health.

Jennifer Lanoff, WHNP-BC, MSCP, JD
Reiter, Hill, and Johnson of Advantia
Washington, DC
No relevant financial relationships with ineligible companies.

Diedra R. Manns, DPT, MSPT, COMT, NCPT
CEO/Founder of Monarch Wellness Group Inc
Los Angeles, California
No relevant financial relationships with ineligible companies.

Sally E. MacPhedran, MD, MS, FACOG, IF, MSCP
Associate Professor Reproductive Biology
Medical Director, Physician Assistant Program
Case Western Reserve University School of Medicine
Director, Comprehensive Sexual Health Center
MetroHealth Medical Center
Cleveland, Ohio
No relevant financial relationships with ineligible companies.

Holly J. Pederson, MD, MSCP
Medical Breast Services, Integrated Surgical Institute
Cleveland Clinic
Professor of Medicine, Cleveland Clinic Lerner College of Medicine
Cleveland, Ohio
Consultant for Myriad Genetics, Vira Health, and Era Institute.

Mary E. Peterson, MD, FACOG, MSCP
Clinical Associate Professor
University of Pittsburgh Medical Center
Pittsburgh, Pennsylvania
No relevant financial relationships with ineligible companies.

Katherine Scruggs, MD, FACOG, MSCP
Physician, Midlife Women's Associates
Allegheny Health Network
Cranberry Township, Pennsylvania
No relevant financial relationships with ineligible companies.

Barbara A. Soltes, MD, FACOG, MSCP
Professor, Dept of Ob/Gyn
Rush University Medical Center
Chicago, Illinois
Director, Center for Women's Care and Research
Palos Heights, Illinois
No relevant financial relationships with ineligible companies.

Richa Sood, MD, MS, FACP, MSCP
Associate Professor of Medicine
Menopause and Women's Sexual Health Clinic
General Internal Medicine
Mayo Clinic
Rochester, Minnesota
No relevant financial relationships with ineligible companies.

La'Nasha Tanner-Sanders, MD, FACOG
Assistant Clinical Professor
Associate Program Director
Department of OBGYN
Louisiana State University School of Medicine
New Orleans, Louisiana
No relevant financial relationships with ineligible companies.

Suneela Vegunta, MD, FACP, MSCP
Associate Professor of Medicine
Program Director, Womens Health Fellowship, AZ
Assistant Director, Mayo Clinic School of Medicine
Mayo Clinic
Scottsdale, Arizona
No relevant financial relationships with ineligible companies.

We would like to acknowledge the contributions of Kathy Method, MA, Editor for The Menopause Society, to this project.