THE MENOPAUSE PLAYBOOK

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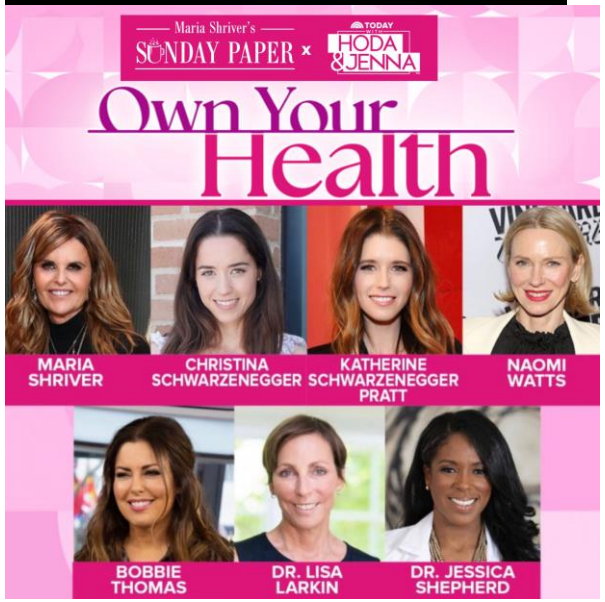
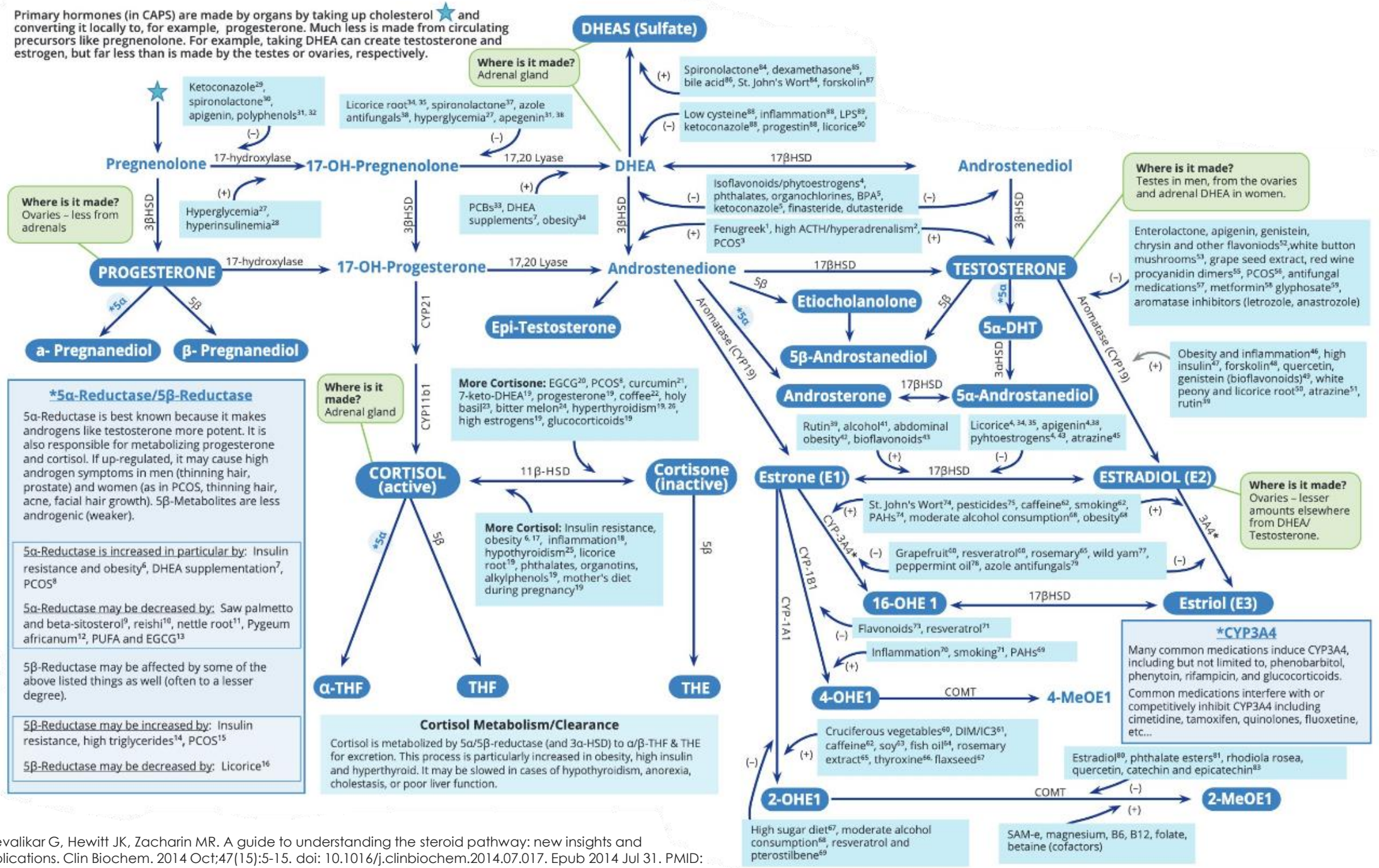
Urology, Women's Health, Sexual Medicine
Skin, Bones, Hearts, and Private Parts 2024

OBJECTIVES

- Discuss the stages of menopause and pathophysiology of organ changes
- Apply hormone therapy options for women seeking menopause symptom relief
- Identify risk factors associated with the menopause transition

BEFORE WE BEGIN…

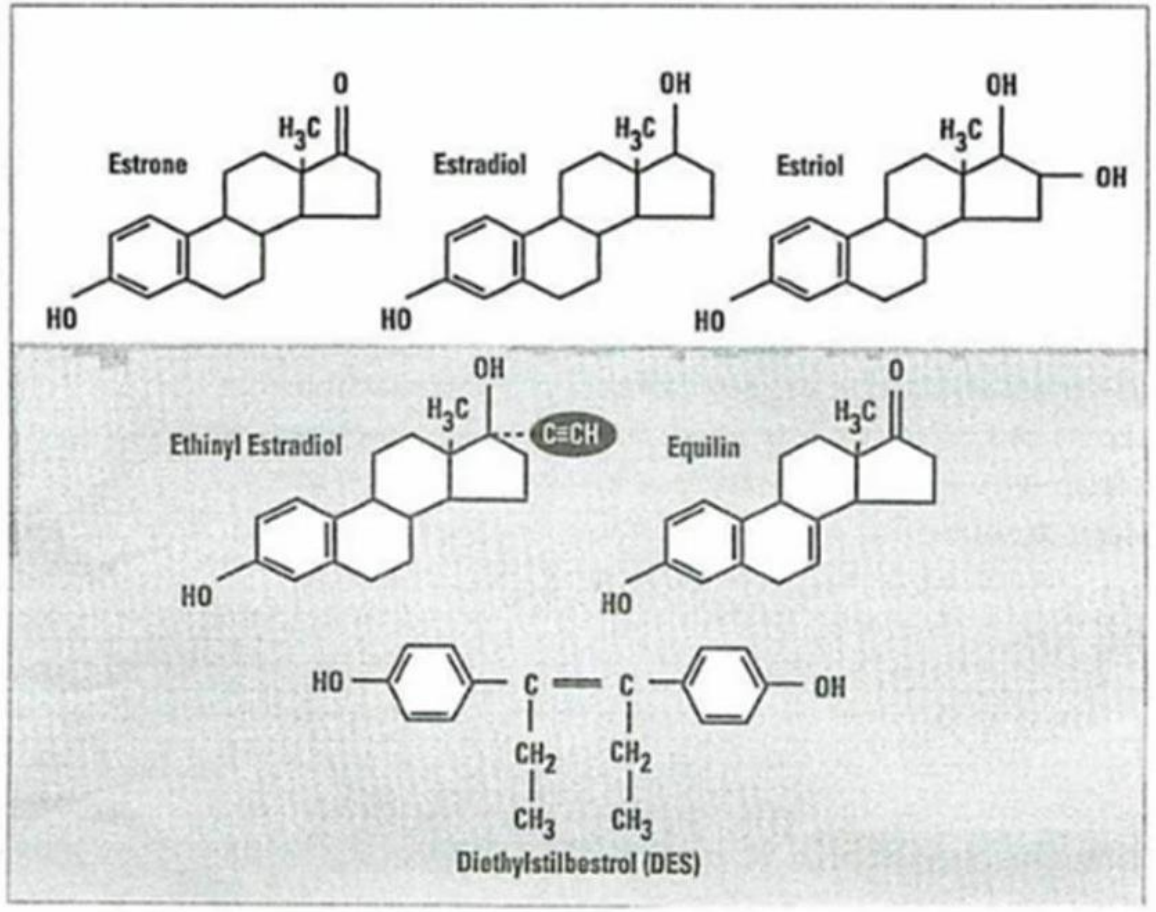




Greaves RF, Jevalikar G, Hewitt JK, Zacharin MR. A guide to understanding the steroid pathway: new insights and diagnostic implications. Clin Biochem. 2014 Oct;47(15):5-15. doi: 10.1016/j.clinbiochem.2014.07.017. Epub 2014 Jul 31. PMID: 25086367.

BIOIDENTICAL HORMONES

- Bioidentical = Replacement
  - Identical to the hormone in the body
  - Derived from wild yams
- Synthetic = Substitution
  - Conjugated equine estrogens → Premarin
  - Progestins → Medroxyprogesterone
  - Prempro (combo – conjugated equine estrogens + medroxyprogesterone)
- Goals of bHRT
  - Alleviate the symptoms caused by the natural decrease in production of hormones by the body
  - Restore the protective benefits which were originally provided by naturally occurring hormones
  - Re-establish hormone balance



Rocky Mountain Analytical Pharmacy

ESTROGENS

- **E1 = Estrone**
  - 10-20% circulating estrogen
  - Primary estrogen produced after menopause
- **E2 = Estradiol**
  - 10-30% of circulating estrogen
  - Most potent
  - Primary estrogen during reproductive years
  - Improves hot flashes, increase HDL, lowers LDL/TG
  - Increases serotonin levels
  - Helps with absorption of Calcium, Magnesium, and Zinc
- **E3 = Estriol**
  - 60-80% circulating estrogen
  - Questionable breast cancer protection
  - Minimal to no endometrial build-up
  - Blocks estrone receptor sites in breast tissue
  - Helps in maintaining pregnancy
  - Can benefit vaginal lining - pH
- **E4 = Estetrol**
  - Found in the fetus
  - Contraception and menopause use

Fuentes N, Silveyra, P. Advances in Protein Chemistry and Structural Biology. Chapter Three - Estrogen receptor signaling mechanisms. Academic Press, 116, 2019: 135-170. https://doi.org/10.1016/bs.apcsb.2019.01.001.
Gérard C, Foidart JM. Estetrol: From Preclinical to Clinical Pharmacology and Advances in the Understanding of the Molecular Mechanism of Action. Drugs R D. 2023 Jun;23(2):77-92. doi: 10.1007/s40268-023-00419-5. Epub 2023 May 3. PMID: 37133685; PMCID: PMC10293541.

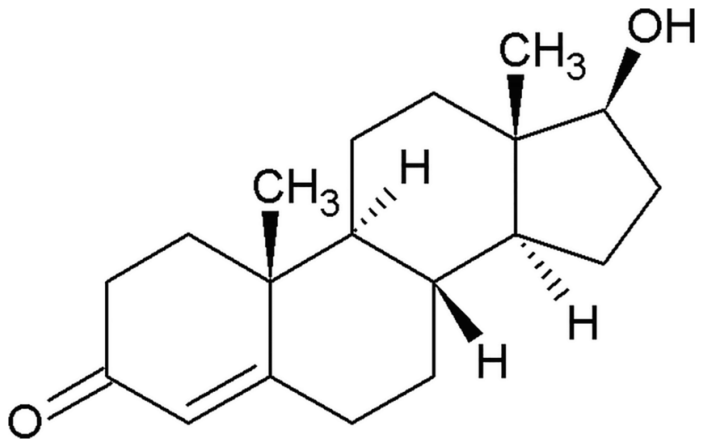
PROGESTERONE

- Bioidentical (micronized) vs synthetic(progestin)
- Made from pregnenolone
- Counteract estrogen dominance
- Functions:
  - Promotion of secretory changes in the uterine endometrium
  - Has anti-inflammatory properties
  - Preparing the breasts to initiate lactation
  - Counteracting the proliferative actions of estrogen
  - Having a helpful effect on sleeping patterns
  - Aiding in the production of bone tissue
  - Preventing possible anxiety, irritability, and mood swings
  - Helping the bladder function properly
  - Assisting the gut to break down and absorb essential nutrients in the body

Cable JK, Grider MH. Physiology, Progesterone. In: StatPearls. StatPearls Publishing, Treasure Island (FL); 2022. PMID: 32644386.

TESTOSTERONE

- Has vasomotor effects, enhancing vaginal blood flow and lubrication
- Everyone can benefit from testosterone therapy, yet in different doses
- Increases sexual interest (libido), increases sense of emotional well-being, increases muscle mass and strength, maintains memory, decreases skin sagginess, decreases excess body fat, maintain bone strength. Has vasomotor effects, enhancing vaginal blood flow and lubrication
- 50% of women in natural menopause lose testosterone
- 80-90% of women with surgical menopause lose testosterone
- Majority is bound to sex hormone binding globulin (SHBG)
- Benefits:
  - Vasomotor symptoms
  - Lethargy and fatigue
  - Muscle – mass, strength and endurance
  - Osteoporosis
  - Endogenous depression
  - Nocturia and incontinence
  - Fibrocystic disease of the breast
  - Vascular headaches (migraines)
  - Mood and irritability
  - Sexual gratification



Rawda Naamneh Elzenaty, Therina du Toit, Christa E. Flück. Best Practice & Research Clinical Endocrinology & Metabolism. Basics of androgen synthesis and action. 36, 4, 2022: 101665. https://doi.org/10.1016/j.beem.2022.101665.

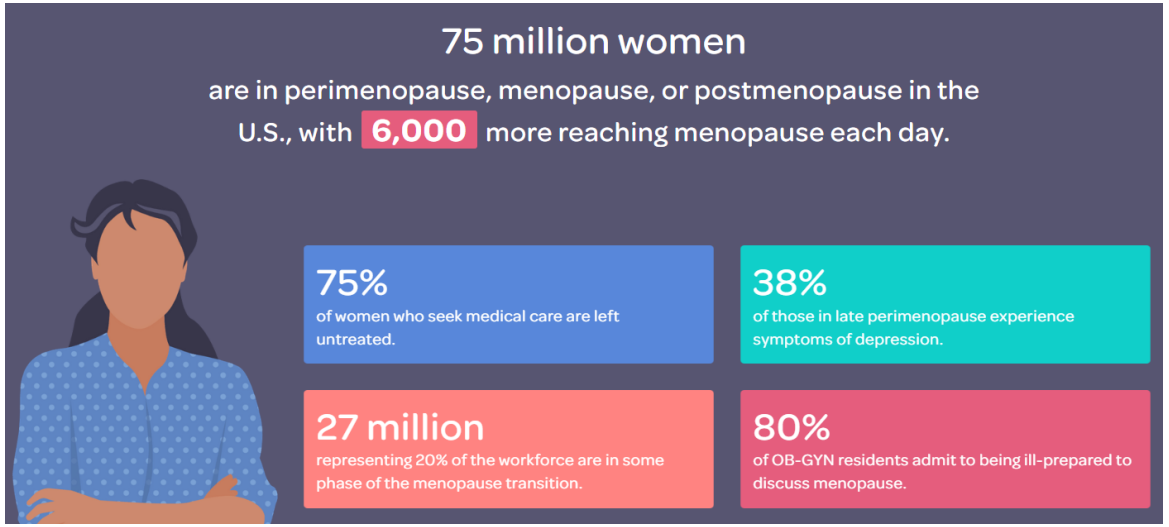
DHEA

- Dehydroepiandrosterone → Androgen precursor → testosterone → estradiol
- Produced by the adrenal glands, brain, skin, liver, and testes
- By the time a woman reaches menopause, her DHEA secretion has decreased by an average of 60%.
- Benefits:
  - Preventing or treating osteoporosis (increase in bone mineral density) in postmenopausal women, especially those >age 70.
  - Improving sexual function in the elderly female population.
  - May also help reduce symptoms in women with lupus, but it probably does not alter the long-term course of the disease.
  - Stimulate vaginal maturation without affecting the endometrium.
  - Activates immune system function
  - Decreases joint stiffness
  - Elevates growth hormone levels
  - Improves sleep
  - Increases feeling of well-being and libido, without significant side effects.
  - Increases muscle strength and lean body mass
  - Increases quality of life
  - Increases sensitivity of insulin
  - Favorably associated with executive function, concentration, and working memory.

Rawda Naamneh Elzenaty, Therina du Toit, Christa E. Flück. Best Practice & Research Clinical Endocrinology & Metabolism. Basics of androgen synthesis and action. 36, 4, 2022: 101665. https://doi.org/10.1016/j.beem.2022.101665.

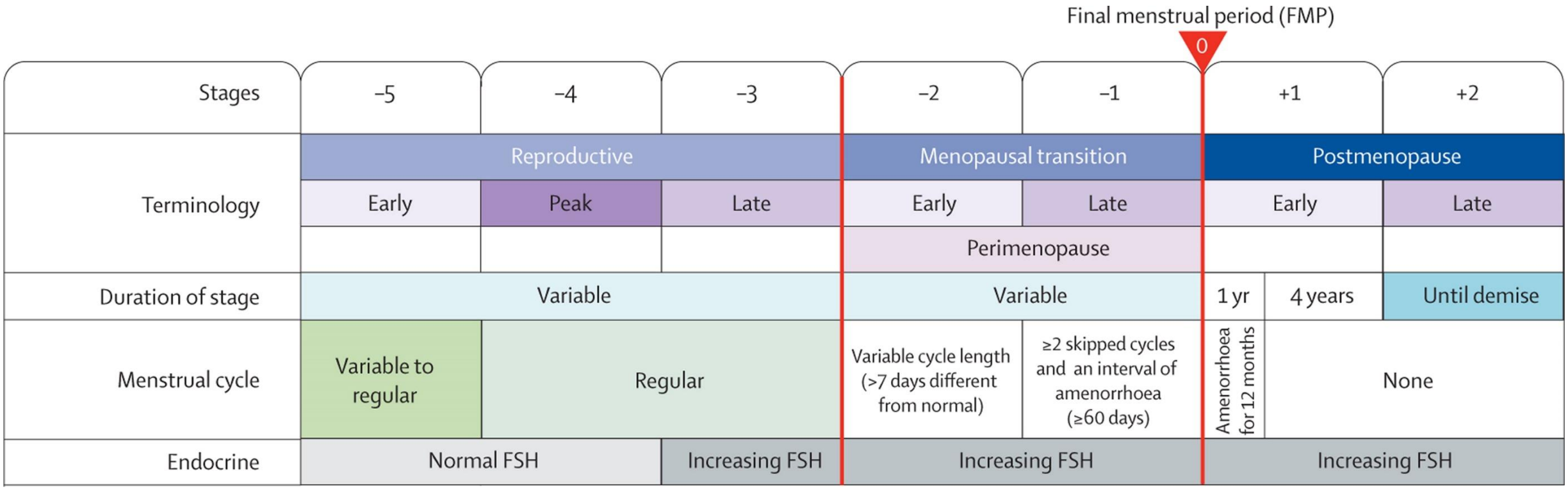
WHAT IS MENOPAUSE?

- Definitions of menopause:
  - Menopausal transition
  - Premenopause
  - Early menopause
  - Late menopause
  - Perimenopause
  - Natural menopause
  - Postmenopause
- Additional definitions
  - Primary ovarian insufficiency
  - Induced (surgical vs cancer treatments) menopause



The North American Menopause Society, Menopause Practice: A Clinician's Guide, 6th Edition. 2019.

STAGES OF MENOPAUSE



The North American Menopause Society, Menopause Practice: A Clinician's Guide, 6th Edition. 2019.

Low Libido	Period Changes	Anxiety Depression	Brain Fog
Urinary Symptoms	Vasomotor Symptoms	Weight Changes	Sleep Issues
Sexual Changes	Heart Palpitations	Joint Pain	Irritability
Fatigue	Skin Changes	Genitourinary Syndrome	Headaches Migraines
Irritability	Menstrual Changes	Dry Eyes	Cognitive Concerns

let's talk menopause!

Symptoms Checklist

Over the past 3 months have you experienced any of the symptoms below?

Symptoms	Never	Sometimes	Often
Anxiety: Overly worried or tense, feeling stressed out, panicky, overwhelmed	○	○	○
Brain Fog: Difficulty focusing, forgetful, poor word retrieval, easily distracted, feeling out of it	○	○	○
Depression: Feeling low or hopeless; loss of interest in things once enjoyed; easily fatigued; increased mood swings; small tasks take great energy; feeling overwhelmed	○	○	○
Fatigue: Low energy, tire easily	○	○	○
Headaches and/or Migraines: Head pain, often intense or throbbing, sometimes to the point of debilitation; nausea; light and/or noise sensitivity	○	○	○
Heart Palpitations: Racing, skipping, or fluttering heartbeat	○	○	○
Hot Flashes / Night Sweats: Intense spreading heat, usually across the chest, neck, or face; excessive sweating; racing heart	○	○	○
Incontinence: Urinary leaks when laughing or coughing, loss of bladder control	○	○	○
Irritability: Unusually impatient, quick to anger—even rage, easily frustrated	○	○	○
Joint Pain: Soreness, heat, or swelling, especially in the neck, back, knees, ankles, fingers, elbows or jaw; feeling unusually stiff and creaky	○	○	○
Low Libido: Diminished sex drive, difficulty feeling aroused	○	○	○
Painful Sex: Vaginal dryness or tightness; burning in the vagina or vulva before, during, or after intercourse	○	○	○
Period Changes: Lighter or heavier blood flow, shorter or longer cycles, entirely skipped cycles	○	○	○
Skin and/or Hair Changes: Dry, itchy, skin; thinning or coursening hair; new facial hair; appearance of dark spots	○	○	○
Sleep Issues: Difficulty falling or remaining asleep; tossing, turning, or fitful sleep	○	○	○
Urinary Tract Infections (UTIs): Bacterial infection with symptoms that include frequent urination, burning, change in the color or odor or urine, pain in the pelvic region, fever, and/or nausea	○	○	○
Weight Gain: Increased weight, especially around abdomen and thighs; feeling bloated	○	○	○

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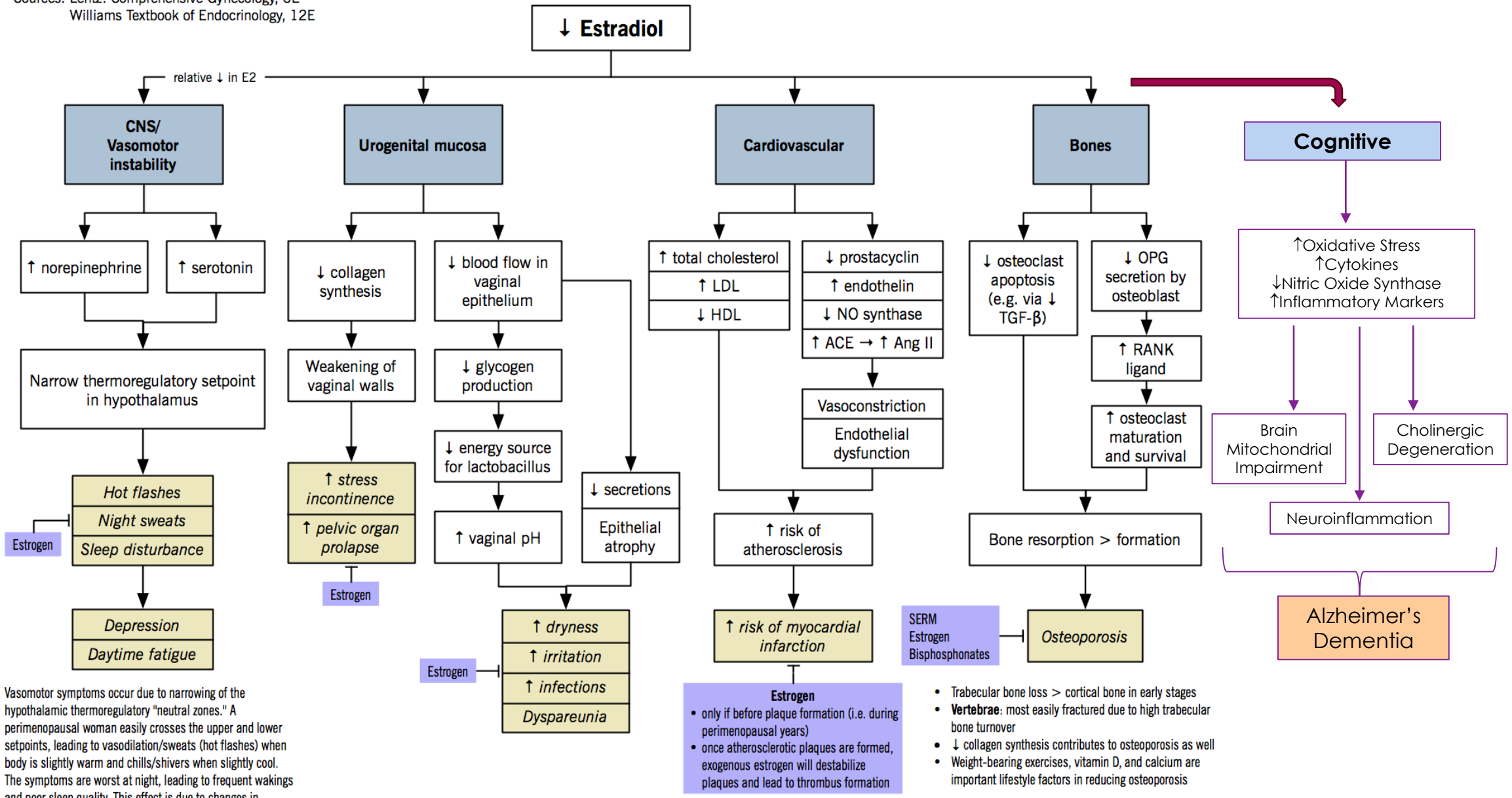
The North American Menopause Society, Menopause Practice: A Clinician's Guide, 6th Edition. 2019.

Pathophysiology of menopause organ changes

Eric Wong

Sources: Lentz: Comprehensive Gynecology, 6E
Williams Textbook of Endocrinology, 12E



Vasomotor symptoms occur due to narrowing of the hypothalamic thermoregulatory "neutral zones." A perimenopausal woman easily crosses the upper and lower setpoints, leading to vasodilation/sweats (hot flashes) when body is slightly warm and chills/shivers when slightly cool. The symptoms are worst at night, leading to frequent wakings and poor sleep quality. This effect is due to changes in estrogen level rather than absolute deficiency. Unlike other menopause changes, this will improve over time.

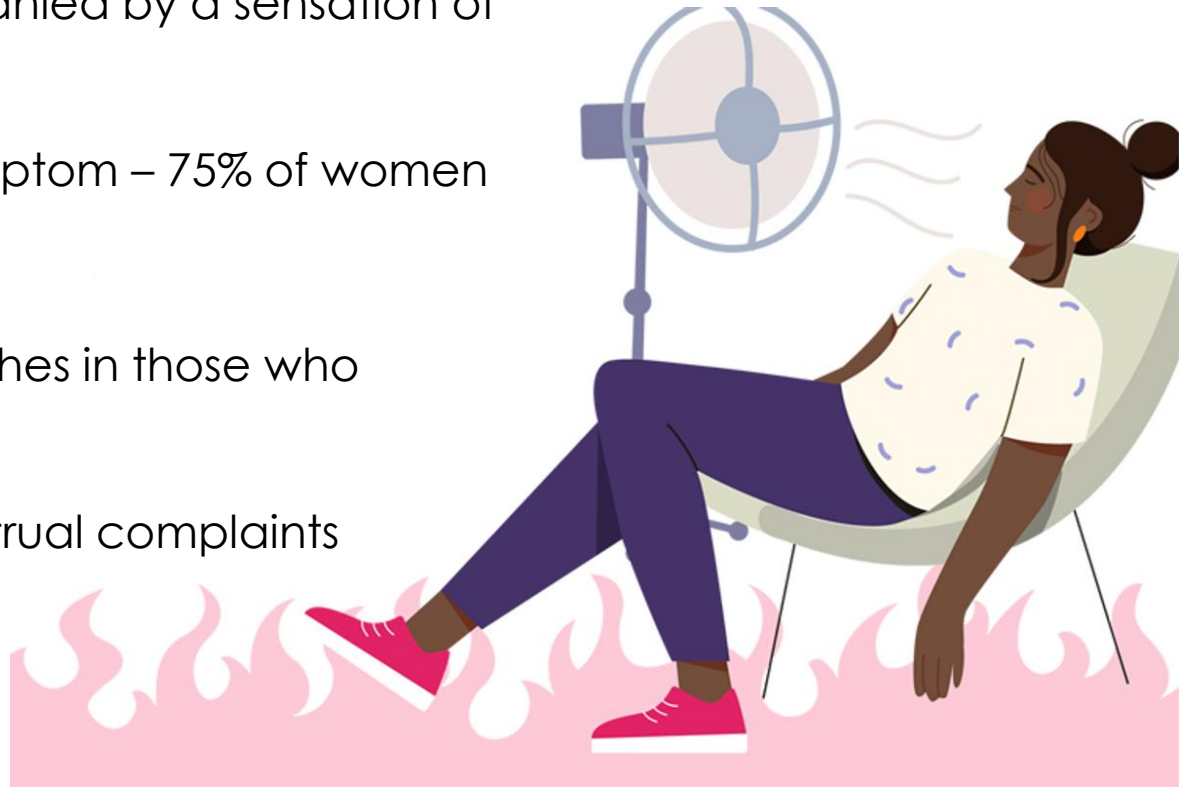
Estrogen
- only if before plaque formation (i.e. during perimenopausal years)
- once atherosclerotic plaques are formed, exogenous estrogen will destabilize plaques and lead to thrombus formation

- Trabecular bone loss > cortical bone in early stages
- **Vertebrae**: most easily fractured due to high trabecular bone turnover
- ↓ collagen synthesis contributes to osteoporosis as well
- Weight-bearing exercises, vitamin D, and calcium are important lifestyle factors in reducing osteoporosis

Ali N, Sohail R, Jaffer SR, Siddique S, Kaya B, Atowoju I, Imran A, Wright W, Pamulapati S, Choudhry F, Akbar A, Khawaja UA. The Role of Estrogen Therapy as a Protective Factor for Alzheimer's Disease and Dementia in Postmenopausal Women: A Comprehensive Review of the Literature. Cureus. 2023 Aug 6;15(8):e43053. doi: 10.7759/cureus.43053. PMID: 37680393; PMCID: PMC10480684.

VASOMOTOR SYMPTOMS

- AKA – hot flashes, hot flushes, night sweats
- Recurrent, transient episodes of flushing accompanied by a sensation of warmth to intense heat on upper body and face
- Adversely affect QOL
- 2nd most frequently reported perimenopausal symptom – 75% of women
- Start in late perimenopause and last 6-24 months
- Associated with circadian rhythm
- Penn Ovarian Aging Study → 6-20x severe hot flashes in those who smoked
- SWAN study – ethnic groups and larger bodies
- 47% of women with moderate to severe premenstrual complaints



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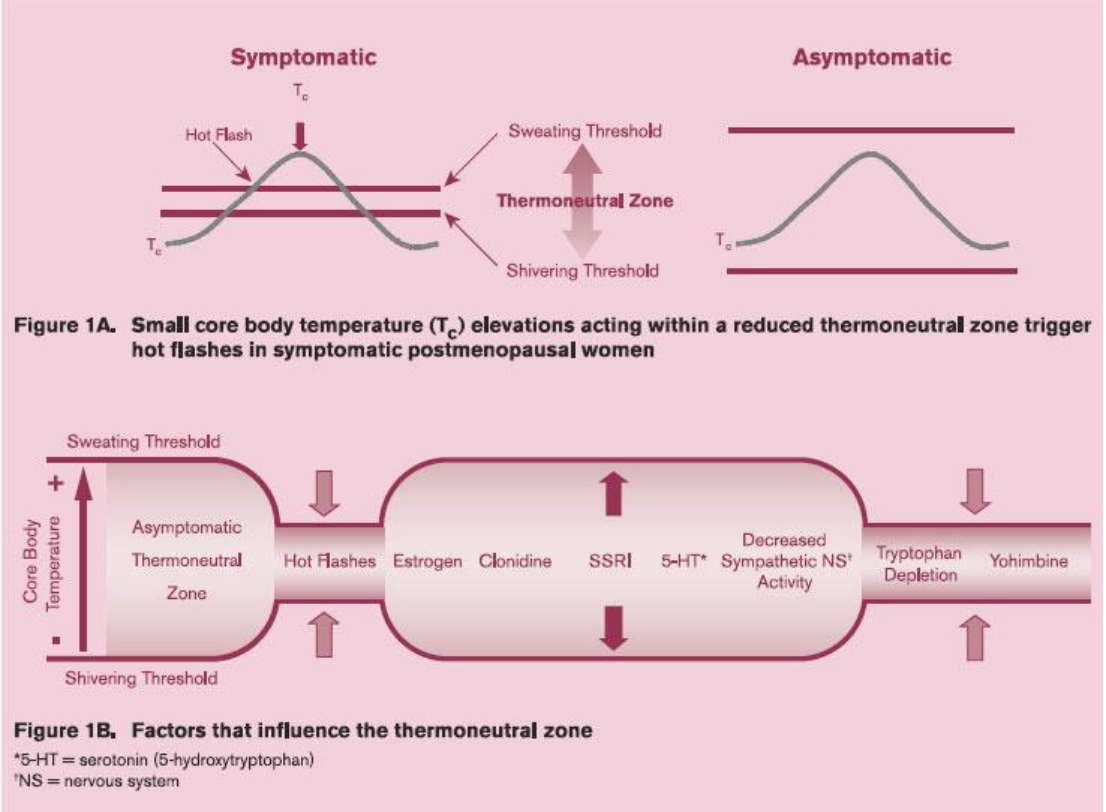
VASOMOTOR SYMPTOMS – WHY?

- Normal thermoregulation
  - Upper limit – sweating
  - Lower limit – shivering
- Decreases in estrogen
  - Reduced or absent thermoneutral zone
  - Small elevations in core body temperatures → heat dissipation response
- Theory support
  - Triggered by peripheral heating (warm room)
  - Core body heating (hot drink)
  - Ameliorated by ambient and internal cooling
- Other causes = thyroid, epilepsy, infection, insulinoma, pheochromocytoma, carcinoid syndromes, leukemia, pancreatic tumors, autoimmune, new-onset hypertension, mast-cell disorders
- Drugs that block estrogen/inhibit estrogen biosynthesis, SSRIs/SNRIs
- Night sweats – tuberculosis and lymphoma



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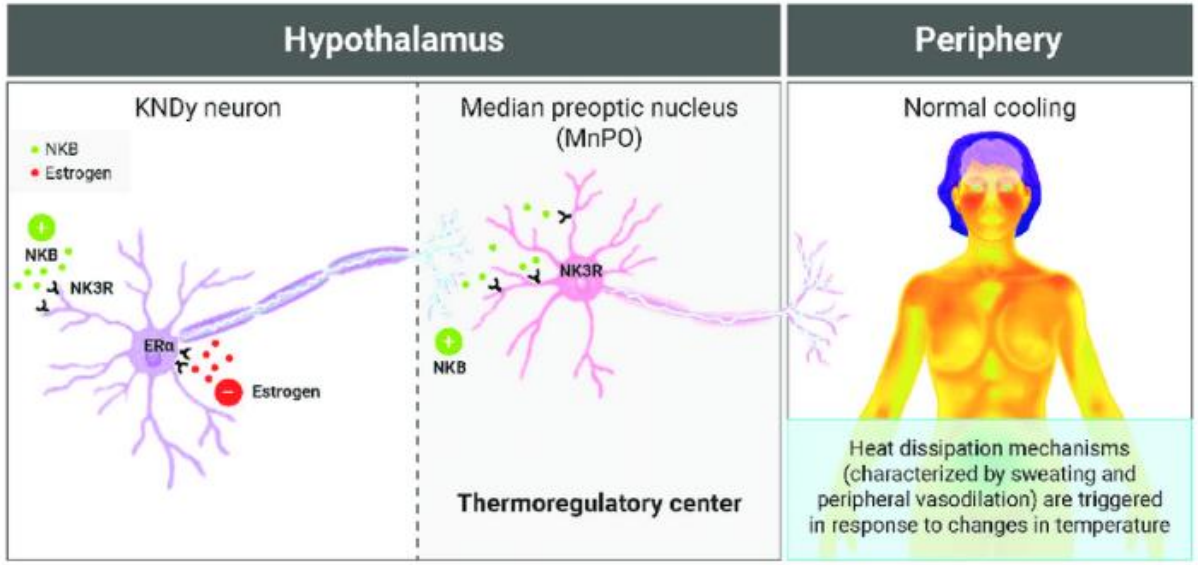
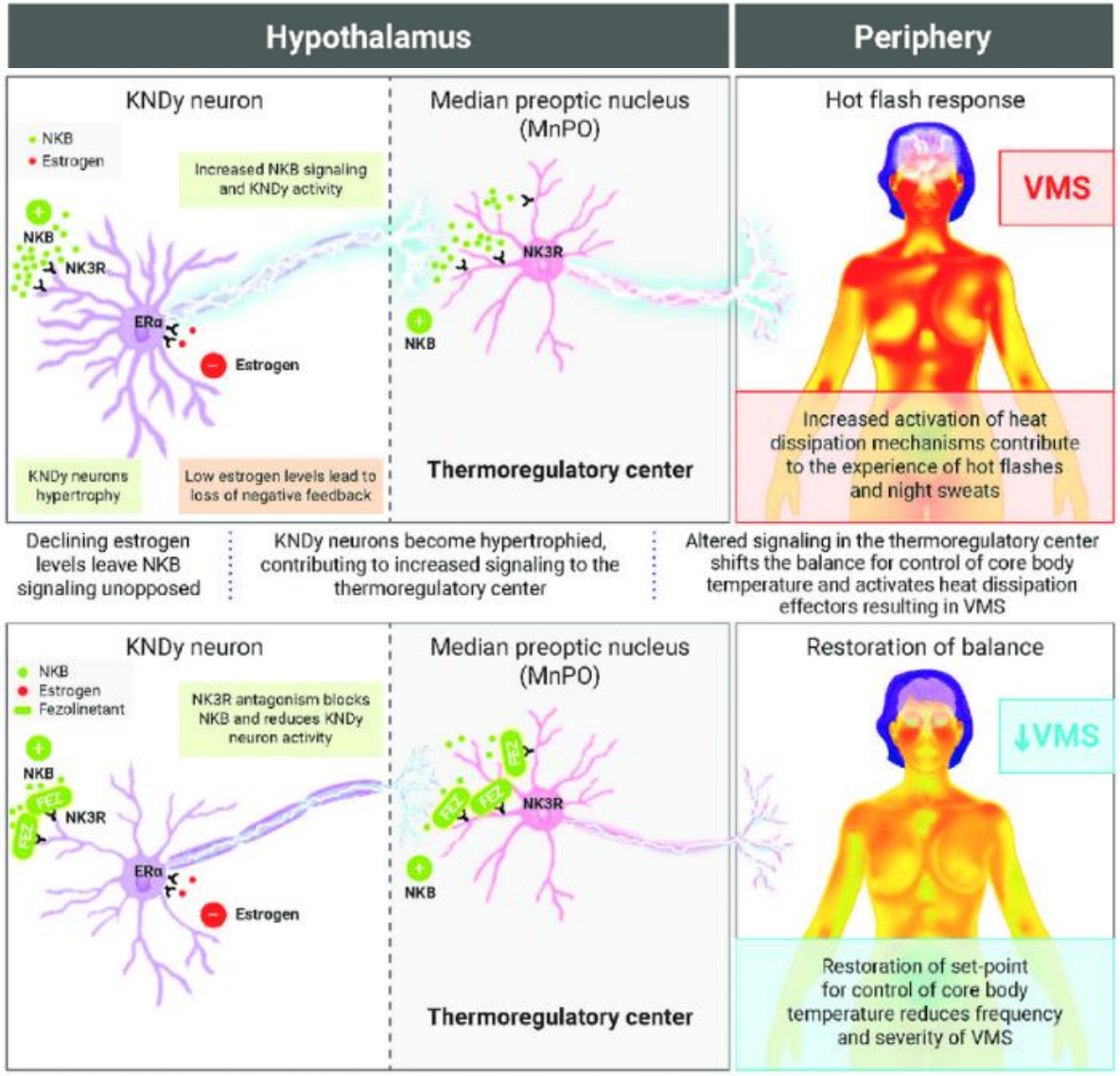


The thermoregulatory center of the hypothalamus is innervated by KNDy neurons that are stimulated (+) by NKB via NK3R and inhibited (−) by estrogen



Fezolinetant, an oral NK3R antagonist, moderates NKB signaling and KNDy neuron activity, helping to restore thermoregulatory balance

Depypere, Herman & Lademacher, Christopher & Siddiqui, Emad & Fraser, Graeme. (2021). Fezolinetant in the treatment of vasomotor symptoms associated with menopause. Expert Opinion on Investigational Drugs. 30. 10.1080/13543784.2021.1893305.

VMS MANAGEMENT

- 25% of women seek help
- Symptomatic relief only – there is no "cure"
- Treatment should be tailored to each individual
- Cancer survivors more likely to have severe VMS
- Nonpharmacological treatments
  - Lifestyle
    - Enhanced relaxation techniques – meditation, yoga, massage, lukewarm bath
    - Regular exercise and maintain a healthy body weight
    - No smoking
    - Paced respirations
    - Dress in layers, ice packs, avoid hot/spicy foods and caffeine/alcohol
- Nonprescriptive remedies
  - Soy foods/phytoestrogens or isoflavone supplements
  - Black cohosh
  - Vitamin E and Omega-3 fatty acids
  - Ginseng root
- Complimentary/Alternative Treatments
  - Cognitive Behavioral Therapy (CBT)
  - Acupuncture

The North American Menopause Society, Menopause Practice: A Clinician's Guide, 6th Edition. 2019.

VASOMOTOR PRESCRIPTIONS

- Estrogen (ET) or Estrogen-Progesterone (EPT) Combo
  - Hysterectomy – ET only
  - Retains uterus – EPT
  - Start early, lowest dose, shortest duration
  - Examples
    - Oral: Conjugated estrogens or human estrogens with/without progestins
    - Transdermal: Patches and creams/gels
    - First pass effects – oral vs. transdermal
      - Less effect on clotting factors, triglycerides, c-reactive protein, SHBG

The North American Menopause Society, Menopause Practice: A Clinician's Guide, 6th Edition. 2019.

NAMS POSITION STATEMENT

Menopause: The Journal of The North American Menopause Society
Vol. 30, No. 6, pp. 573–590
DOI: 10.1097/GME.0000000000002200

NAMS Position Statement

The 2023 nonhormone therapy position statement of The North American Menopause Society

PRESCRIPTION THERAPIES

Oral Estrogen Therapy		
Composition	**Product Name**	**Dosage, mg/d**
Conjugated estrogens	Premarin	0.3, 0.45, 0.625, 0.9, 1.25
Synthetic conjugated estrogens	Cenestin Enjuvia	0.3, 0.45, 0.625, 0.9, 1.25 0.3, 0.45, 0.625, 0.9, 1.25
Esterified estrogens	Menest	0.3, 0.625, 1.25, 2.5
17β-estradiol	Estrace (varying generics)	0.5, 1.0, 2.0
Estropipate	Ogen (varying generics)	0.625 (0.75), 1.25 (1.5), 2.5 (3.0)

The North American Menopause Society, Menopause Practice: A Clinician's Guide, 6th Edition. 2019.

PRESCRIPTION THERAPIES

Transdermal Estrogen Therapy		
Composition	**Product Name**	**Dosage, mg**
17β-estradiol matrix patch	Alora Climara Menostar Minivelle Vivelle Vivelle-Dot	0.025, 0.05, 0.075, 0.1 twice/wk 0.025, 0.0375, 0.05, 0.075, 0.1 once/wk 0.014 once/wk (osteoporosis) 0.0375, 0.05, 0.075, 0.1 twice/wk 0.025, 0.0375, 0.05, 0.075, 0.1 twice/wk 0.025, 0.0375, 0.05, 0.075, 0.1 once or twice/wk
17β-estradiol reservoir patch	Estraderm	0.025, 0.05, 0.1 twice/wk
17β-estradiol transdermal gel	Divigel EstroGel Elestrin	0.25, 0.5, 1.0/d 0.75/d 0.52/d
17β-estradiol topical emulsion	Estrasorb	0.05/d (2 packets)
17β-estradiol transdermal spray	Evamist	0.021 mg per 90 µL spray/d

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PRESCRIPTION THERAPIES

Combination Estrogen-Progesterone Therapy		
Composition	**Product Name**	**Dosage/d**
Oral Continuous-cyclic		
Conjugated estrogens (E) + medroxyprogesterone acetate (P)	Premphase	0.625 mg E + 5.0 mg P (E 1-14 days then E+P 15-28 days)
Oral Continuous-combined		
Conjugated estrogens (E) + medroxyprogesterone acetate (P)	Prempro	0.3 or 0.45 mg E + 1.5 mg P
Ethinyl estradiol (E) + norethindrone acetate (P)	Femhrt	2.5 µg E + 0.5 mg P or 5.0 µg E + 1.0 mg P
17β-estradiol (E) + norethindrone acetate (P)	Activella	0.5 mg E + 0.1 mg P 1.0 mg E + 0.5 mg P
17β-estradiol (E) + drospirenone (P)	Angeliq	0.5 mg E + 0.25 mg P 1 mg E + 0.5 mg P
Transdermal Continuous-combined		
17β-estradiol + norethindrone acetate (P)	CombiPatch	0.05mg E + 0.14 mg P twice/wk 0.05 mg E + 0.25 mg P twice/wk
17β-estradiol (E) + levonorgestrel (P)	Climara Pro	0.045 mg E + 0.015 mg P once/wk

The North American Menopause Society, Menopause Practice: A Clinician's Guide, 6th Edition. 2019.

Progestogens		
Composition	**Product Name**	**Dosage/d**
Oral tablet - Progestin		
Medroxyprogesterone acetate	Provera (generics)	2.5 mg, 5 mg, 10 mg
Norethindrone	Micronor (generics)	0.35 mg
Norethindrone acetate	Aygestin (generics)	5 mg
Megestrol acetate	Megace (generics)	20 mg or 40 mg tab 40 mg suspension
Oral capsule - Progesterone		
Micronized progesterone (peanut)	Prometrium (generics)	100 mg or 200 mg
Intrauterine System - Progestin		
Levonorgestrel	Mirena Liletta Kyleena Skyla	20 µg/d release (52 mg for 5y) 19.5 µg/d release (52 mg for 5y) 17.5 µg/d release (19.5 mg for 5y) 6 µg/d release (13.5 mg for 3y)
Vaginal Progesterone		
Gel – Progesterone	Crinone 4% or 8%	45 or 90 mg applicator
Insert – Micronized progesterone	Endometrin	100 mg insert

The North American Menopause Society, Menopause Practice: A Clinician's Guide, 6th Edition. 2019.

COUNSELING FOR HRT

- Contraindications
  - Undiagnosed abnormal genital bleeding
  - Known, suspected, or history of breast cancer
  - Known, suspected, or history of estrogen-dependent neoplasia
  - Active or history of DVT and/or PE
  - Active or history of arterial thromboembolic disease (CVA or MI)
  - Liver dysfunction or disease
  - Known or suspected pregnancy
  - Known hypersensitivity to ET or EPT
  - Smoking/tobacco use and >35 years

- Potential Adverse Effects
  - Uterine bleeding (starting or recurrence)
  - Breast tenderness and sometimes enlargement
  - Nausea
  - Abdominal bloating
  - Fluid retention in extremities
  - Changes in shape of cornea (possible contact lens intolerance)
  - Headache (including migraine)
  - Dizziness
  - Mood changes

NAMS Position Statement. The 2022 hormone therapy position statement of The North American Menopause Society. *Menopause*. 29(7); 767-794.

OTHER THERAPIES

- Paroxetine 7.5mg – first nonhormonal medication approved for VMS
- Bazedoxifene (BZA) 20 mg + Conjugated Estrogen (CE) 0.45 mg and 0.625 mg – first SERM for menopausal symptoms and osteoporosis
- SSRIs
  - Escitalopram 10 mg or 20 mg per day
- SNRIs
  - Venlafaxine 37.5 mg to 75 mg per day
  - Desvenlafaxine 100 mg to 150 mg per day
- Eszopiclone – nighttime hot flashes
- Gapabentin – start with 300 mg daily QHS, increase as needed
- Clonidine – 0.05 mg BID or 0.1 mg BID (taper slowly with higher dose)
- Fezolinetant 45mg – first-in-class selective NK3R antagonist

Adverse effects – nausea and sexual problems, caution after breast cancer

The North American Menopause Society, Menopause Practice: A Clinician's Guide, 6th Edition. 2019.

WHAT ABOUT TESTOSTERONE?

- Did you know that women need testosterone too?
- Produced by the ovaries and adrenal glands
- Reasons for female low T
  - Declining sex steroid hormones secondary to menopause and aging
  - Problems with ovaries, pituitary gland, adrenal glands, thyroid gland
- Diagnostic testing – labs (total testosterone and SHBG)
  - http://www.issam.ch/freetesto.htm
  - Normal = 0.6 to 1.0 ng/dL
- Treatment options?
  - No FDA approved formulations
  - 1/10 of male dose, compounded, DHEA
  - Caution in supraphysiological levels
  - Side effects – acne, mood changes, hirsutism,

Symptoms
Sluggishness
Muscle weakness
Fatigue
Depressed mood
Hot flashes
Weight gain
Fertility issues
Irregular menstrual cycles
Sleep disturbances
Low libido
Orgasm concerns
Vaginal dryness
Loss of bone density

Rawda Naamneh Elzenaty, Therina du Toit, Christa E. Flück. Best Practice & Research Clinical Endocrinology & Metabolism. Basics of androgen synthesis and action. 36, 4, 2022: 101665. https://doi.org/10.1016/j.beem.2022.101665.

ANDROGENS IN FEMALES

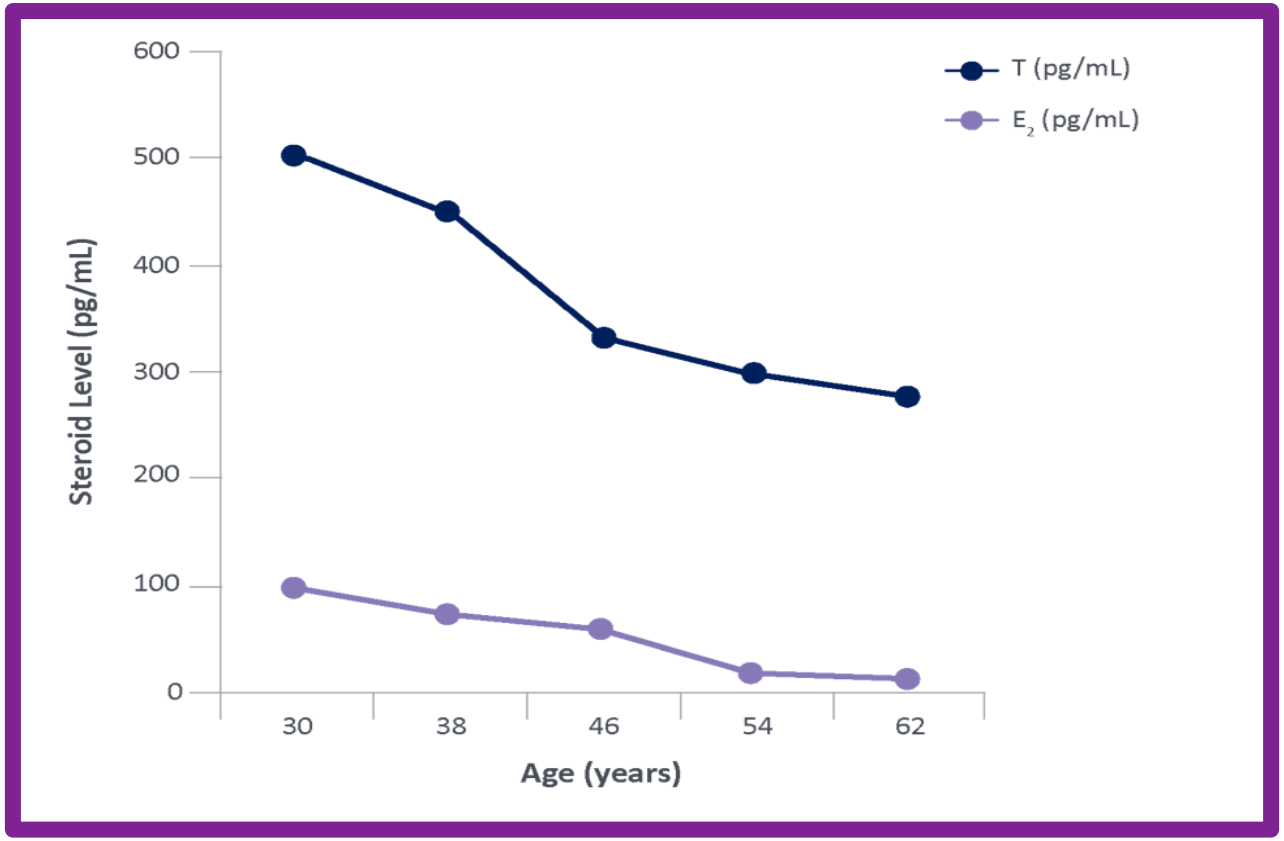

Figure adapted from: Glaser R, Dimitrakakis C. Maturitas. 2013;74(3):230-234

Table 1. Key take-away messages

- Androgens, including testosterone, are essential hormones for development and maintenance of female sexual anatomy and physiology and modulation of sexual behavior.
- Testosterone has many physiological actions in women, directly through its cell-specific receptor, by non–receptor-mediated actions, and by conversion to 5α-DHT and estrogens.
- There is no testosterone level for diagnosis of HSDD or for use as a treatment target.
- Total testosterone concentration is the best practical assay.
- Total testosterone and SHBG should be measured before initiating therapy.
- Proper dosing should attain and maintain total testosterone levels in the premenopausal physiological range.
- If an approved female formulation is not available, one-tenth of a standard male dose of 1% transdermal testosterone or about 300 mcg/day can usually achieve the normal premenopausal physiological range.
- Compounded testosterone, pellets, IM injections, and oral formulations are not recommended.
- Additional testing and alternative strategies may be required to assess failure to respond to typical testosterone treatment, particularly when testosterone or SHBG levels are high.

5α-DHT = 5α-dihydrotestosterone; HSDD = hypoactive sexual desire disorder.

ISSWSH Clinical Guidelines for Systemic Testosterone Use for Female HSDD, J Sex Med. 2021; 1-19.

HORMONE SYMPTOM EVALUATION CHART

Fibrocystic Breast	↑	E	↓	P						
Weight Gain	↑	E	↓	P	↓	TH				
Heavy/Irregular menses	↑	E	↓	P						
Hot Flashes	↓	E	↓↑	E	↓	P				
Dry Skin/Hair	↓	E								
Anxiety	↑	E	↓	P	↓	E				
Depression	↓	E	↑	P	↓	T	↑	C	↓	TH
Night Sweats	↓	E	↓↑	C						
Vaginal Dryness	↓	E	↓	T						
Headaches	↓↑	E	↓↑	P	↓	T	↓	TH		
Irritability	↑	E	↓↑	P						
Mood Swings	↑	E	↓	P						
Breast Tenderness	↑	E	↓	P	↑	P				
Sleep	↓	P	↓	E	↑	T				
Cramps	↓	P								
Fluid Retention	↓	P	↑	E						
Breakthrough Bleeding	↓	P								
Fatigue	↓	T	↓	TH	↑	P	↓	C		
Loss of Memory	↓	T	↓	E						
Bladder Symptoms	↓	E	↓	T						
Arthritis	↓	T	↓	P						
Harder to Reach Climax	↓	T	↓	E	↓	P				
Decreased Sex Drive	↓	T	↑	E	↓	C	↓	TH		
Hair Loss	↑	T	↓↑	TH	↓↑	E	↓↑	P		

E=Estrogen
P= Progesterone
T= Testosterone
C= Cortisol
TH= Thyroid
↓= Caused by Low Level
↑= Caused by High Level
↓↑= Caused by Fluctuating Levels

**Chart obtained with permission from Innovation Compounding Pharmacy.

WHAT ABOUT HORMONE TESTING?

The Menopause Society and ACOG

- There is a lack of high-quality data on the safety and efficacy of custom-compounded bioidentical hormone therapy for the management of menopausal symptoms. Compounded bioidentical menopausal hormone therapy should not be prescribed routinely when FDA-approved formulations exist.
- Currently, there are no FDA-approved salivary or urinary tests for steroid hormone measurement and are not endorsed.
- There is no FDA-approved testosterone formulation for the management of menopausal symptoms. Clinicians and patients should use a shared decision-making framework when considering the use of compounded testosterone for this indication. Based on the lack of safety data and inability to remove the pellet, ACOG recommends preparations other than pellet therapy for the delivery of testosterone.

POSTMENOPAUSAL BLEEDING

- Abnormal uterine bleeding
  - PALM-COEIN Classification
- Causes of bleeding in postmenopausal patient
  - Vulvar, urethral, cervix, vagina, uterine, anal/rectal, hormone therapy
- Evaluation
  - Begin with TVUS to measure endometrial thickness and detect structural concerns
  - If endometrial thickness is >4mm, proceed with an endometrial biopsy
  - If other structural causes found, proceed with appropriate treatment modality

ACOG Committee Opinion No. 734. *Obstet Gynecol.* 2018;131(5):e124-e129.

GENITOURINARY SYNDROME OF MENOPAUSE (GSM)

- GSM vs vaginal atrophy
- Describes the symptoms and signs resulting from hormone deficiency in the female genitourinary tract – vulva, vagina, clitoris, urethra, bladder, pelvic floor musculature
- Lack of testosterone AND estradiol in the vulvovaginal tissues.
- GSM is a chronic, progressive, and symptoms do not improve without treatment

27-84% of Peri/Middle/Post menopause
84% of women identified on exam
50% have never been treated

Vaginal Health: Insights, Views, & Attitudes (VIVA)
45% reported vaginal symptoms
75% felt negative impact of their life

NAMS Position Statement - The 2020 genitourinary syndrome of menopause position statement of The North American Menopause Society. Menopause. Vol. 27, No. 9, pp. 976-992.
Edwards D, Panay N. Treating vulvovaginal atrophy/genitourinary syndrome of menopause: how important is vaginal lubricant and moisturizer composition? *Climacteric*. 2015;19(2):151-161.

GENITOURINARY SYNDROME OF MENOPAUSE (GSM)

How do you diagnose?

Symptoms + Physical Exam = GSM		
Labial atrophy	Friable tissues	Caruncles
Vulvovaginal dryness	Hypopigmentation	Telescoping
Introital stenosis	Petechiae	Prolapse
Clitoral atrophy	Ulcerations	Polyps
Prepuce phimosis	bleeding	Weak pelvic floor

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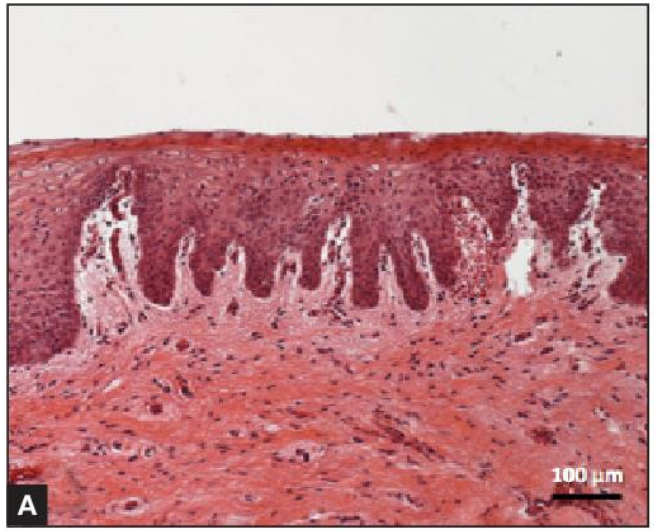
Edwards D, Panay N. Treating vulvovaginal atrophy/genitourinary syndrome of menopause: how important is vaginal lubricant and moisturizer composition? *Climacteric*. 2015;19(2):151-161.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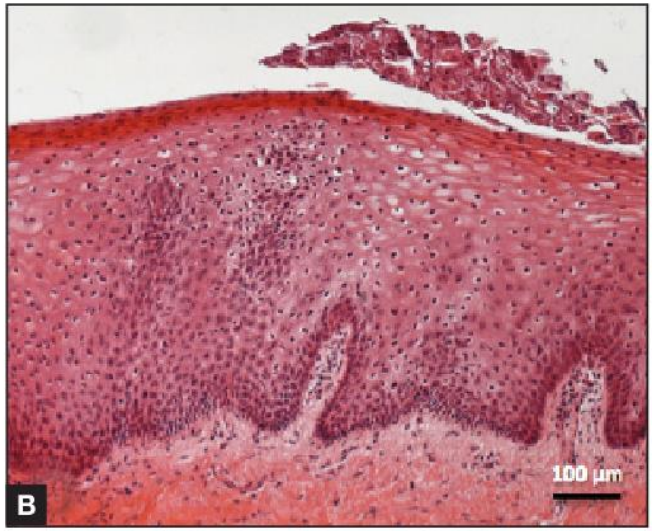
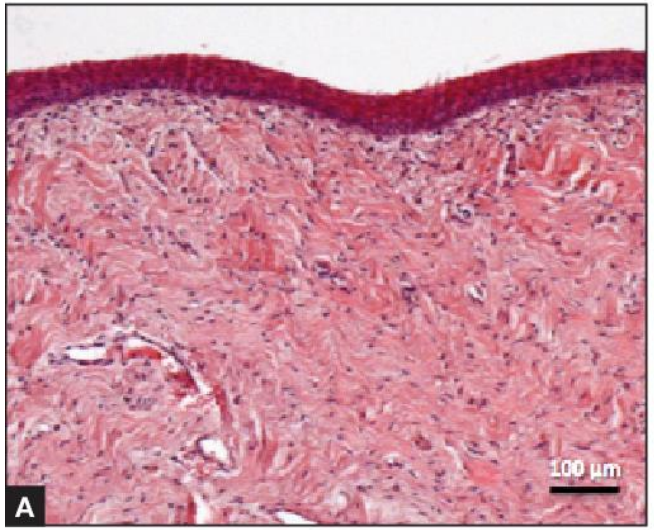

100 µm
B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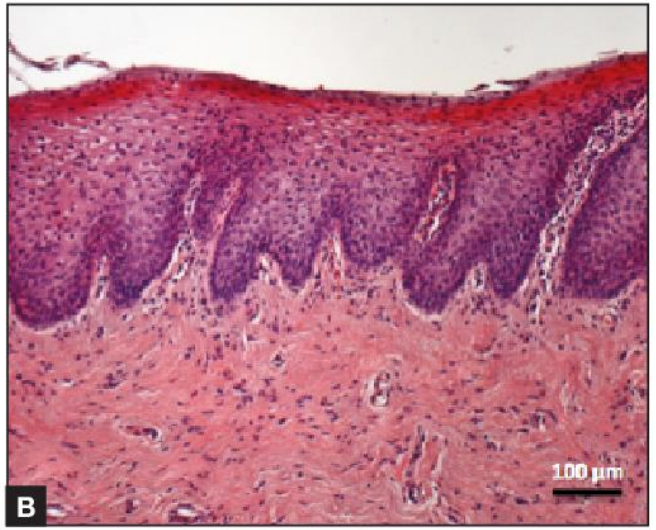
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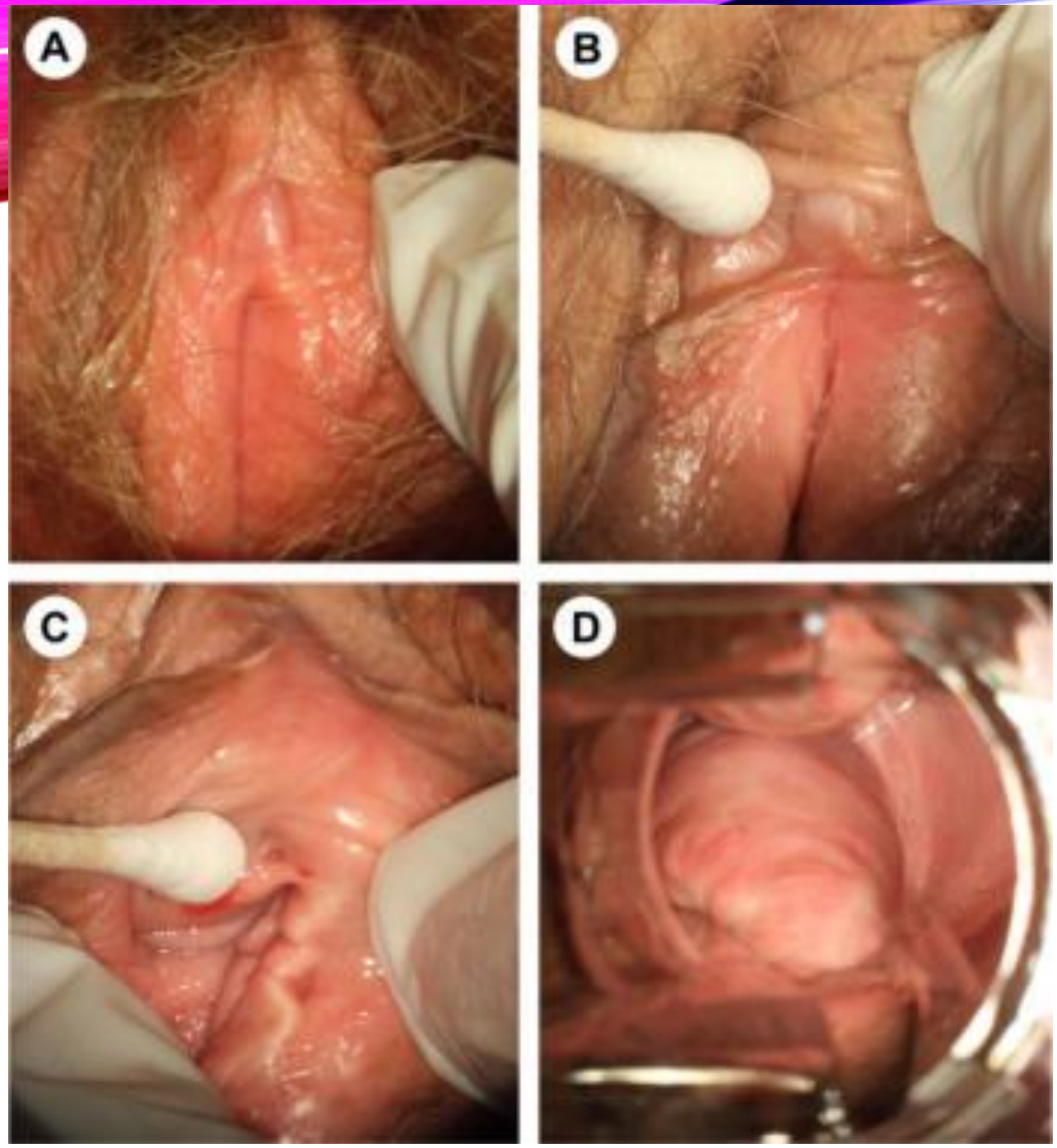
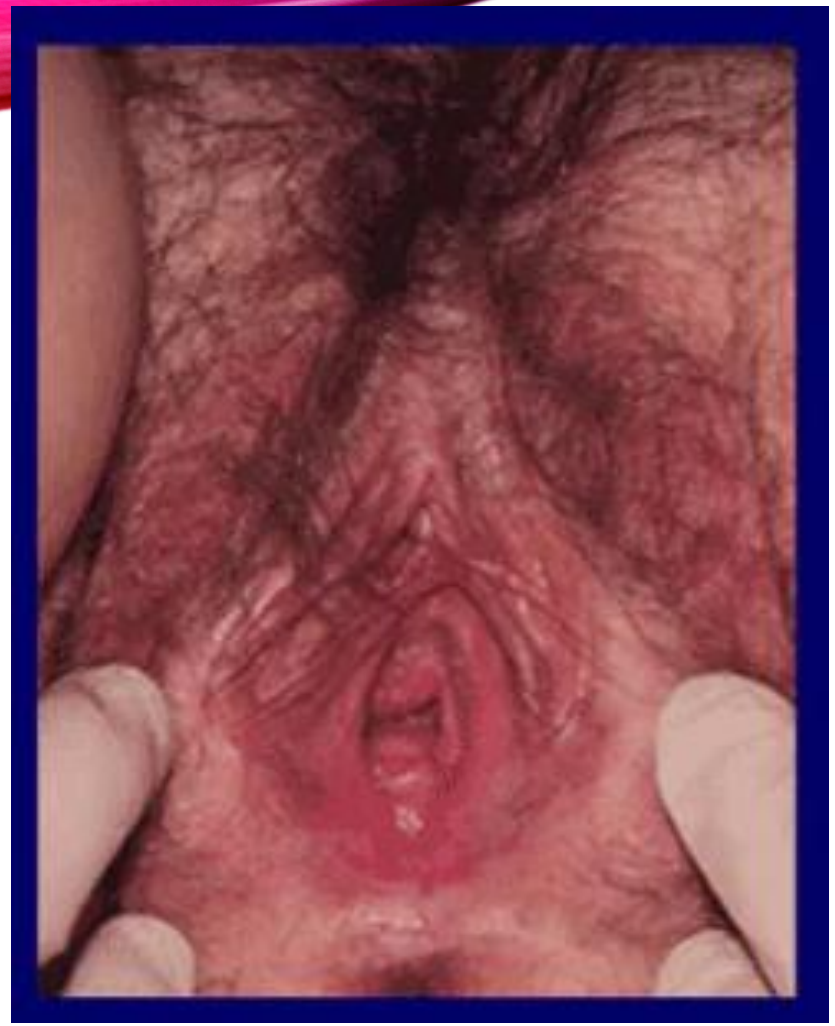
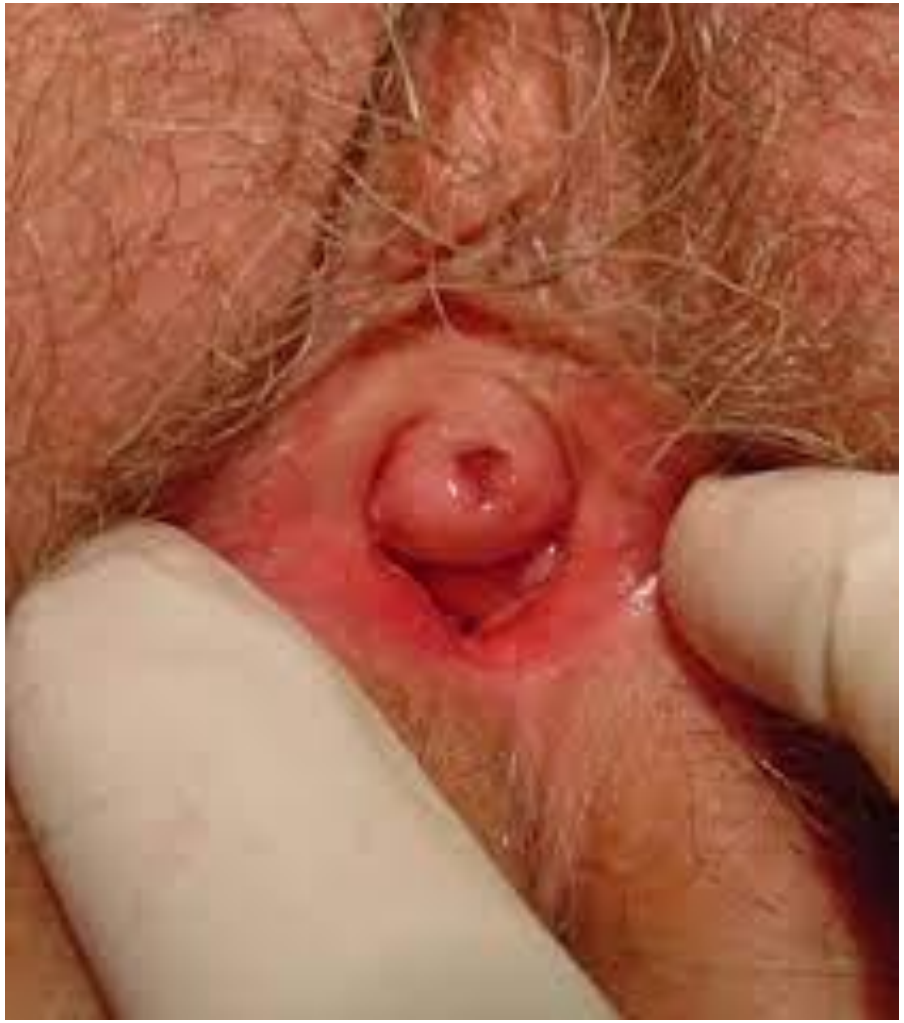


Figure 1. Atrophy of the vulva, clitoris, and vagina.
(A) Vaginal atrophy is associated with pale, dry, shiny vulvar tissue and loss of adipose tissue in the labia majora and labia minora.
(B) The prepuce and clitoris are often pale and reduced in size, while examination shows that
(C) the introitus may be narrowed and friable.
(D) In vaginal atrophy, the vaginal walls lack rugae and may be pale and/or erythematous.

Irwin Goldstein, Brian Dicks, Noel N. Kim, Rose Hartzell, Multidisciplinary Overview of Vaginal Atrophy and Associated Genitourinary Symptoms in Postmenopausal Women, Sexual Medicine, Volume 1, Issue 2, 2013, Pages 44-53, ISSN 2050-1161, https://doi.org/10.1002/sm2.17.



Bachmann GA, Nevadunsky NS.
http://www.aafp.org/20000515/3090.html



Vulvovaginal Atrophy
Omnia Education

GENITOURINARY SYNDROME OF MENOPAUSE (GSM)

Nonhormonal Medications

- Moisturizers vs lubricants
- Lubricants have been shown to aid in vaginal dryness and increase sexual satisfaction
- Most women use a lubricant during self pleasure vs partnered pleasure
- Apply the lubricant to the entire genital area – not just the vagina
- Others → Hyaluronic acid and Aloe Vera

Pelvic Floor Therapy

- Strengthen PFMs
- Vaginal dilators
- Manual stretching

Lubricant safety

Avoid glycerin, parabens, fragrances, menthol.

Options silicone, water-based, hybrid

No silicone lubes with silicone toys

Brands: Uberlube, Good Clean Love, Sliquid, Aloe Cadobora

Avoid KY Jelly, Astroglide, Durex

NAMS Position Statement - The 2020 genitourinary syndrome of menopause position statement of The North American Menopause Society. Menopause. Vol. 27, No. 9, pp. 976-992.
Edwards D, Panay N. Treating vulvovaginal atrophy/genitourinary syndrome of menopause: how important is vaginal lubricant and moisturizer composition? *Climacteric*. 2015;19(2):151-161.

GENITOURINARY SYNDROME OF MENOPAUSE (GSM)

FDA Approved Therapies	
Vaginal Creams	17ß-estradiol 0.01% cream Conjugated estrogens 6.25mg cream
Vaginal Inserts	17ß-estradiol 4mcg or 10mcg ovules Estradiol 10mcg tablet Prasterone (DHEA) 6.5mg suppository 17ß-estradiol ring 7.5mcg/d
Oral	Ospemifene 60mg tablet
OFF Label Not FDA Approved	
Testosterone Locally	Compounded 1mg/mL
Energy-based Therapies	CO2 Fractional Laser Radiofrequency Electrohydraulic

NAMS Position Statement - The 2020 genitourinary syndrome of menopause position statement of The North American Menopause Society. Menopause. Vol. 27, No. 9, pp. 976-992.
Edwards D, Panay N. Treating vulvovaginal atrophy/genitourinary syndrome of menopause: how important is vaginal lubricant and moisturizer composition? *Climacteric*. 2015;19(2):151-161.

Menopause: The Journal of The North American Menopause Society
Vol. 27, No. 3, pp. 361-370
DOI: 10.1097/GME.0000000000001463

OPEN

Review Article

Systemic estradiol levels with low-dose vaginal estrogens

Richard J. Santen, MD,[1] Sebastian Mirkin, MD,[2] Brian Bernick, MD,[2] and Ginger D. Constantine, MD[3]

Menopause: The Journal of The North American Menopause Society
Vol. 25, No. 6, pp. 596-608
DOI: 10.1097/GME.0000000000001121

Consensus Recommendations

Management of genitourinary syndrome of menopause in women with or at high risk for breast cancer: consensus recommendations from The North American Menopause Society and The International Society for the Study of Women's Sexual Health

Stephanie S. Faubion, MD, FACP, NCMP, IF,[1] Lisa C. Larkin, MD, FACP, NCMP, IF,[2] Cynthia A. Stuenkel, MD, NCMP,[3] Gloria A. Bachmann, MD,[4] Lisa A. Chism, DNP, APRN, BC, NCMP, CSC, FAANP,[5] Risa Kagan, MD, FACOG, CCD, NCMP,[6] Andrew M. Kaunitz, MD, FACOG, NCMP,[7] Michael L. Krychman, MD, FACOG, MPH, IF,[8] Sharon J. Parish, MD, IF, NCMP,[9] Ann H. Partridge, MD, MPH,[10] JoAnn V. Pinkerton, MD, FACOG, NCMP,[11] Tami S. Rowen, MD, MS,[12] Marla Shapiro, CM, MDCM, CCFP, MHSC, FRCPC, FCFP, NCMP,[13] James A. Simon, MD, CCD, NCMP, IF, FACOG,[14] Shari B. Goldfarb, MD,[15] and Sheryl A. Kingsberg, PhD[16]

CLIMACTERIC
2023, VOL. 26, NO. 4, 296–301
https://doi.org/10.1080/13697137.2023.2184253

Taylor & Francis Group

Check for updates

REVIEW

Treating genitourinary syndrome of menopause in breast cancer survivors: main challenges and promising strategies

C. Castelo-Branco*, E. Mension*, I. Torras, I. Cebrecos and S. Anglès-Acedo

Clinic Institute of Gynecology, Obstetrics and Neonatology, Faculty of Medicine, University of Barcelona, Hospital Clinic – Institut d'Investigacions Biomèdiques August Pi i Sunyer (IDIBAPS), Barcelona, Spain

November 2, 2023

Vaginal Estrogen Therapy Use and Survival in Females With Breast Cancer

Lauren McVicker, PhD[1]; Alexander M. Labeit, PhD[1]; Carol A. C. Coupland, PhD[2,3]; et al

» Author Affiliations

JAMA Oncol. 2024;10(1):103-108. doi:10.1001/jamaoncol.2023.4508

Original Investigation | Obstetrics and Gynecology

November 14, 2022

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

Secondary Analysis of a Randomized Clinical Trial

Caroline M. Mitchell, MD, MPH[1]; Joseph C. Larson, MS[2]; Carolyn J. Crandall, MD[3]; et al

» Author Affiliations | Article Information

JAMA Netw Open. 2022;5(11):e2241743. doi:10.1001/jamanetworkopen.2022.41743

CARDIOVASCULAR DISEASE & MENOPAUSE

- 1 in 3 women will die of heart disease regardless of race or ethnicity
- Does estrogen play a role? Controversial and Confusing
- Early menopause (especially due to oophorectomy) are at increased risk of coronary heart disease than compared to age-matched premenopausal women
- Increase in total cholesterol and low-density lipoprotein cholesterol (LDL-C)
- SWAN Study
  - Association between earlier changes in lipids and the menopause transition
- Despite abundance of evidence for cardiovascular benefit, it is the opinion that estrogen therapy NOT be prescribed for the purpose of heart disease prevention
  - No randomized trials of HRT and primary prevention of heart disease
  - No benefit of hormone therapy for secondary prevention of recurrent clinical events or atherosclerosis progression among women diagnosed with heart disease
- Remember…initiation of hormone therapy for women between 50-59 years of age or within 10 years of menopause has not been shown to increase risk of CVD events
- Oral hormone therapy increases VTE

D'Agostino RB Sr, Vasan RS, Pencina MJ, et. al. General Cardiovascular Risk Profile for Use in Primary Care. The Framingham Heart Study. *Circulation*. 2008 Jan 22.
Iorga A, Cunningham CM, Moazeni S, Ruffenach G, Umar S, Eghbali M. The protective role of estrogen and estrogen receptors in cardiovascular disease and the controversial use of estrogen therapy. Biol Sex Differ. 2017 Oct 24;8(1):33. doi: 10.1186/s13293-017-0152-8. PMID: 29065927; PMCID: PMC5655818.

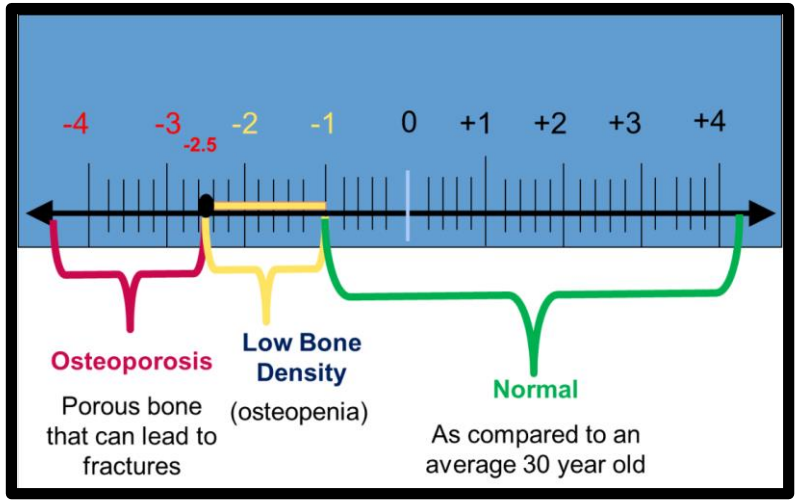
CARDIOVASCULAR DISEASE & MENOPAUSE

- So what can you do?
  - Identify risk factors:
    - Pericardial fat accumulation and elevated coronary calcium
    - Age, smoking, hypertension, DM, abnormal plasma lipids, FHx of premature CVD, poor exercise capacity on stress test, metabolic syndrome
  - Monitoring lipids should be primary prevention of CVD
  - No support is performing ECG
  - Calculated risk-assessment tools
    - Framingham Heart Study, www.uptodate.com
    - ASCVD Risk Estimator Plus, https://tools.acc.org/ASCVD-Risk-Estimator-Plus/#!/calculate/estimate/
- ACOG guidelines for women with history of preeclampsia
  - Annual blood pressure
  - Fasting glucose
  - Fasting lipids
  - Metabolic syndrome
- Individualized counseling and plan

D'Agostino RB Sr, Vasan RS, Pencina MJ, et. al. General Cardiovascular Risk Profile for Use in Primary Care. The Framingham Heart Study. *Circulation*. 2008 Jan 22.

OSTEOPOROSIS

- AKA: "porous bone"
- Significant health threat for aging postmenopausal women with increased risk of fracture
- Bone strength = bone quantity and bone quality → bone mineral density (BMD)
- Peak bone mass is peaked at a women's third decade of life
- ACOG recommendation for DEXA or BMD test annually starting at age 65 → sooner for risk factors
- Z-score = secondary osteoporosis and is always used for children, young adults, women who are premenopausal and men under age 50
- T-score = bone mass differs from a healthy 30-year-old
  - Total hip, femoral neck, lumbar spine
- Categorized
  - Primary = age-related
  - Secondary = disease or medication related
  - Idiopathic = no known cause (young)
- Primary goal of management is to reduce fracture risk
- Prevalence
  - 19% of women 65 to 74 years
  - >50% of women 85 years and older



Camacho PM, Petak SM, Binkley N, et al. American Association of Clinical Endocrinologists and American College of Endocrinology clinical practice guidelines for the diagnosis and treatment of postmenopausal osteoporosis 2016. Endocr Pract 2016; 22(Suppl 4):1-42. https://www.aace.com/files/postmenopausal-guidelines.pdf.

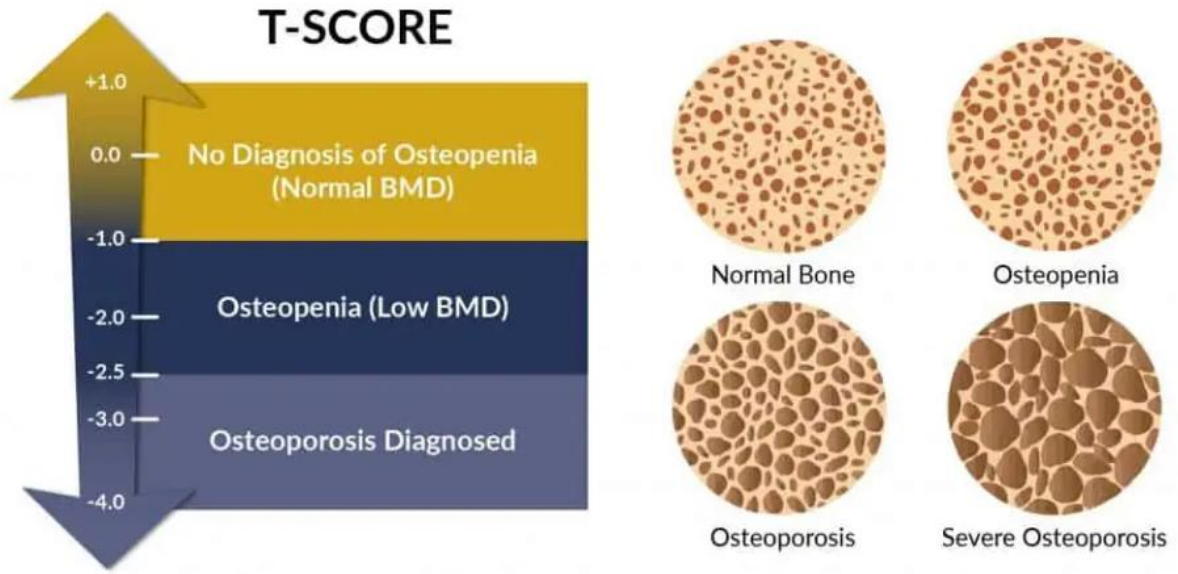
OSTEOPOROSIS – TREATMENT

- 1 in 2 women >50-year-old will sustain osteoporosis-related fracture in their lifetime.
- World Health Organization's Fracture Risk Assessment Tool
  - http://www.shef.ac.uk/FRAX/index.aspx
- Conservative
  - Weight-bearing, balance, and resistance exercises
- Serum vitamin D3 levels >30 ng/mL
- 1200 mg calcium daily
- ACOG recommends postmenopausal women take 600 IU of vitamin D3 daily
- NOF recommends women >50 years 800-1000 IU of vitamin D3
- Counsel on smoking cessation and limit alcohol intake
- When to initiate therapy?
  - History of vertebral, hip, fragility, or low-trauma fracture
  - Aromatase inhibitors or chronic glucocorticoids

Camacho PM, Petak SM, Binkley N, et al. American Association of Clinical Endocrinologists and American College of Endocrinology clinical practice guidelines for the diagnosis and treatment of postmenopausal osteoporosis 2016. Endocr Pract 2016; 22(Suppl 4):1-42. https://www.aace.com/files/postmenopausal-guidelines.pdf.

OSTEOPOROSIS – TREATMENT

- Medications
  - Antiresorptives
    - Menopause hormone therapy
    - CE and Bazedoxifene
    - Raloxifene (SERM) 60mg PO daily
    - Tamoxifen (SERM) 20mg PO daily
    - Bisphosphonates – oral/IV
      - Fosamax 70mg qweekly 30 min prior to food/drink taken with full glass of water
      - Actonel 35mg qweekly 30 min prior to food/drink taken with full glass of water
      - Reclast 5mg IV q12months
    - Prolia 60 mg SQ q6months
  - Osteoanabolics
    - Forteo 20 mcg SQ daily
  - Dual anabolic/antiresorptive
    - Romosozumab
  - Other Class
    - Miacalcin 100 units SQ/IM qod-qd



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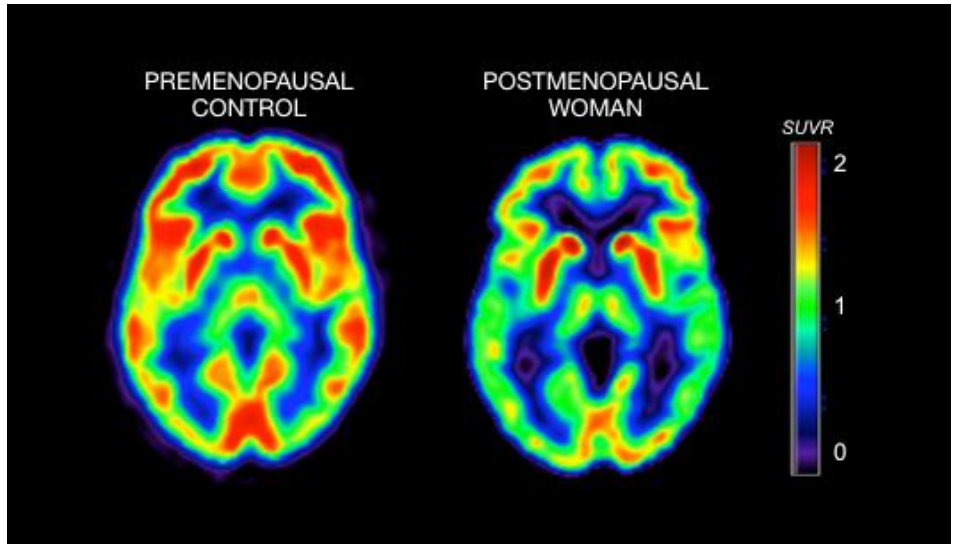
MENTAL HEALTH

- Estrogen is neuroprotective
- Limited data to support use of estrogen solely for cognitive benefits
  - Some supportive evidence in younger women undergoing surgical menopause
- Mind-body therapies – mindfulness, yoga
- Combo conjugated equine estrogen and medroxyprogesterone acetate in >65 years increases risk for dementia
  - Without medroxyprogesterone DID NOT increase risk
- Early intervention of estrogen in women <65 or within 10 years of LMP can decrease risk of Alzheimer/dementia
- Objective decline in verbal recall, verbal fluency, and regional brain activation
- Critical Window Hypothesis in neuroplasticity and estrogen
- Anxiety – worsening or onset
- Depression – 60% to 70% of women experience menopausal symptoms including mood and cognitive disturbances, including depression.
  - Later transition = less risk of depression
  - Consider Paroxetine for treatment
  - Australian Menopause Society – consider hormone therapy
  - Mini-mental screening and suicide screening



Berent-Spillson A, Persad CC, Love T, et al. Hormonal environment affects cognition independent of age during the menopause transition. J Clin Endocrinol Metab 2012; 97(9) E1686-94.

Cureus
Publishing Beyond Open Access

Cureus. 2023 Aug; 15(8): e43053.
Published online 2023 Aug 6. doi: 10.7759/cureus.43053

PMCID: PMC10480684
PMID: 37680393

The Role of Estrogen Therapy as a Protective Factor for Alzheimer's Disease and Dementia in Postmenopausal Women: A Comprehensive Review of the Literature

Monitoring Editor: Alexander Muacevic and John R Adler

Noor Ali,[1,2] Rohab Sohail,[3] Syeda Rabab Jaffer,[4] Sadia Siddique,[5] Berfin Kaya,[6,7] Inioluwa Atowoju,[8] Alizay Imran,[9] Whitney Wright,[10] Spandana Pamulapati,[11] Faiza Choudhry,[12] Anum Akbar,[13] and Uzzam Ahmed Khawaja[14,15]

Original Investigation | Psychiatry

November 1, 2022

Association of Hormone Therapy With Depression During Menopause in a Cohort of Danish Women

Marie K. Wium-Andersen, MD, PhD, DMSc[1]; Terese S. H. Jørgensen, MSc, PhD[1,2]; Anniken H. Halvorsen, BSc[1]; et al

» Author Affiliations | Article Information

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Neurotherapeutics (2019) 16:649–665
https://doi.org/10.1007/s13311-019-00766-9

REVIEW

The Role of Estrogen in Brain and Cognitive Aging

Jason K. Russell[1,2] · Carrie K. Jones[1,2] · Paul A. Newhouse[3,4]

Published online: 30 July 2019

HOW FAR SHOULD WE GO?

Menopause
The Journal of The Menopause Society

ORIGINAL STUDIES

Use of menopausal hormone therapy beyond age 65 years and its effects on women's health outcomes by types, routes, and doses

Baik, Seo H. PhD; Baye, Fitsum MS; McDonald, Clement J. MD

Author Information

Menopause 31(5):p 363-371, May 2024. | *DOI:* 10.1097/GME.0000000000002335

OPEN SDC Editorial

Metrics

SPECIAL POPULATIONS AND MENOPAUSE

- Polycystic ovarian syndrome
- Gender diverse individuals
- Chronic pain
- Breast cancer patients
- History of ovarian, endometrial, or cervical cancer
- Migraines

Treatment of menopausal symptoms with hormone therapy. Special Populations. UpToDate. January 2023. Accessed February 2, 2023.

THANK YOU!

Questions?

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