

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

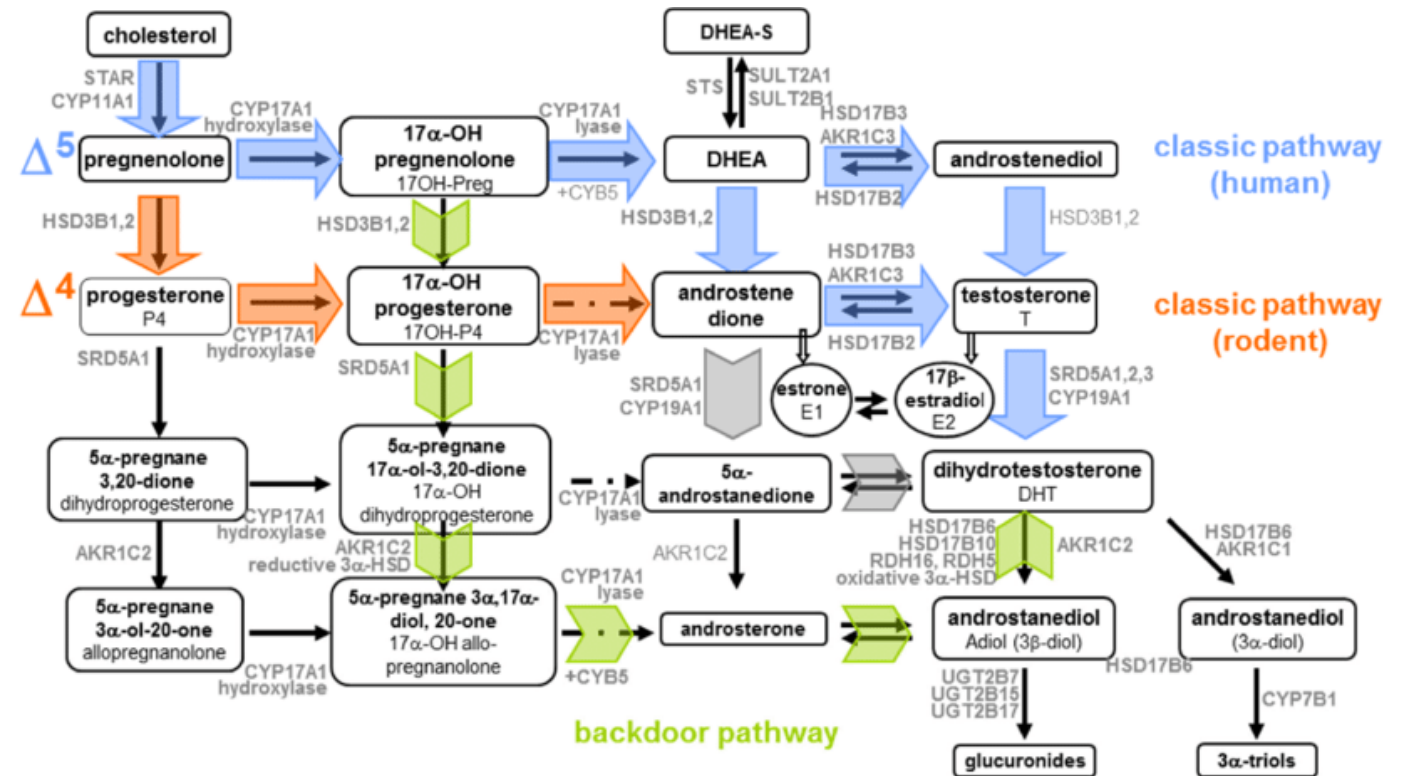
What is MENOPAUSE?

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

Stages of Menopause

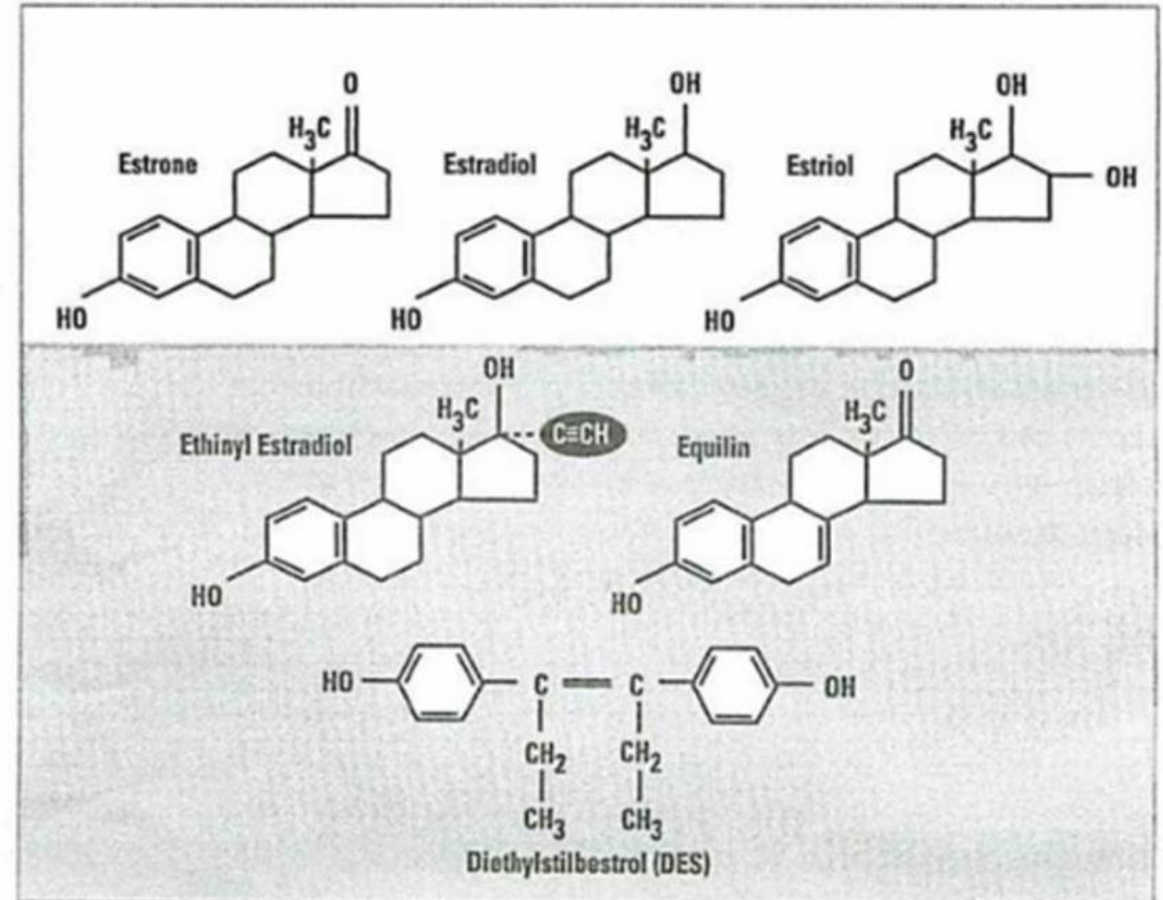
Final menstrual period (FMP)								
Stages	-5	-4	-3	-2	-1	0	+1	+2
Terminology	Reproductive			Menopausal transition		Postmenopause		
	Early	Peak	Late	Early	Late	Early	Late	
				Perimenopause				
Duration of stage	Variable			Variable		1 yr	4 years	Until demise
Menstrual cycle	Variable to regular	Regular		Variable cycle length (>7 days different from normal)	≥2 skipped cycles and an interval of amenorrhoea (≥60 days)	Amenorrhoea for 12 months	None	
Endocrine	Normal FSH		Increasing FSH	Increasing FSH		Increasing FSH		

What are hormones?



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



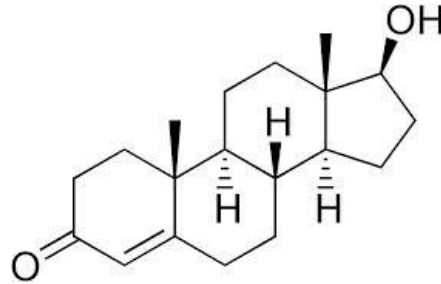
Estrogens

- 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
 - Nextstellis (drospirenone/estetrol)

Progesterone

- Bioidentical vs synthetic
- Counteract estrogen dominance
- Functions:
 - Promotion of secretory changes in the uterine endometrium
 - 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

Testosterone



- Has vasomotor effects, enhancing vaginal blood flow and lubrication
- Men and women 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 sagging, 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
- Benefits:
 - Hot flashes
 - Lethargy
 - Endogenous depression
 - Nocturia and incontinence
 - Fibrocystic disease of the breast
 - Vascular headaches (migraines)
 - Mood, sexual gratification, desire, arousal, initiation, libido, and frequency of sexual activity are affected.

DHEA

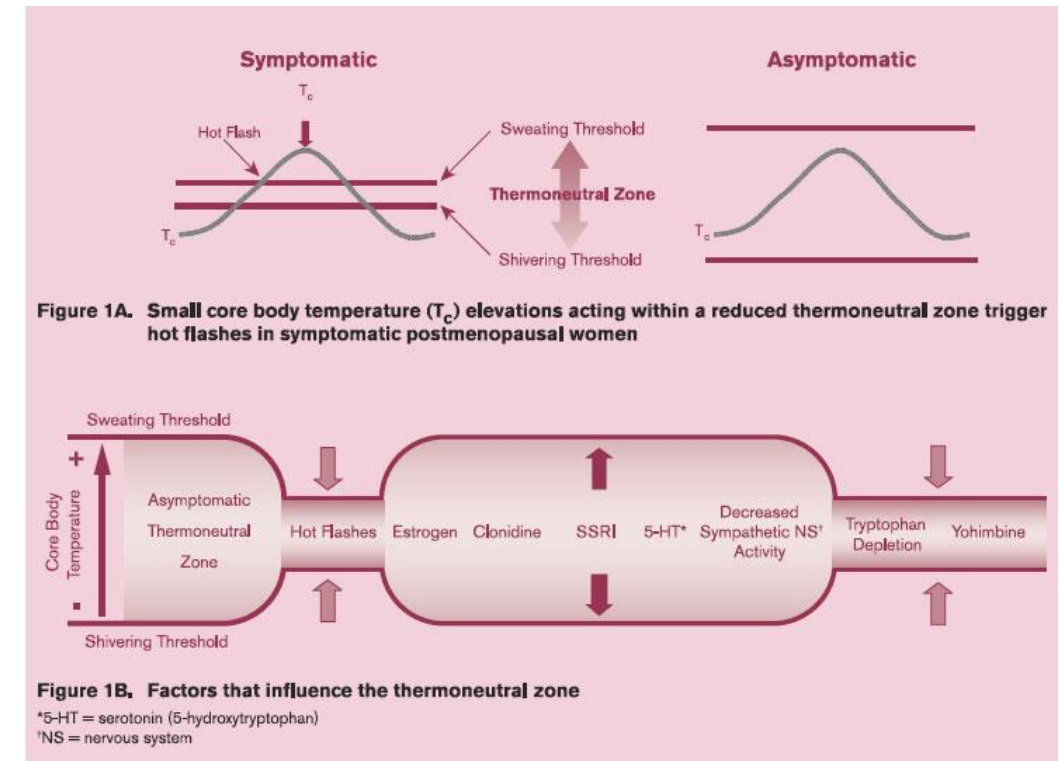
- Dehydroepiandrosterone → Androgen precursor
- Produced by the adrenal glands, brain liver, and testes
- By the time a woman reaches menopause, her DHEA secretion has decreased by an average of 60%.
- Benefits:
 - Preventing or treating osteoporosis (increase in bone mineral density) in postmenopausal women, especially those over age 70.
 - Improving sexual function in the elderly female population.
 - DHEA 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.

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 BMI
- 47% of women with moderate to severe premenstrual complaints

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



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

Vasomotor Prescriptions

- Estrogen (ET) or Estrogen-Progestosterone (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

NAMS Position Statement

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NAMS POSITION STATEMENT

The 2022 hormone 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	0.3, 0.45, 0.625, 0.9, 1.25
	Enjuvia	0.3, 0.45, 0.625, 0.9, 1.25
Esterified estrogens	Menest	0.3, 0.625, 1.25, 2.5
17 β -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)

Prescription Therapies

Transdermal Estrogen Therapy		
Composition	Product Name	Dosage, mg
17 β -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
17 β -estradiol reservoir patch	Estraderm	0.025, 0.05, 0.1 twice/wk
17 β -estradiol transdermal gel	Divigel EstroGel Elestrin	0.25, 0.5, 1.0/d 0.75/d 0.52/d
17 β -estradiol topical emulsion	Estrasorb	0.05/d (2 packets)
17 β -estradiol transdermal spray	Evamist	0.021 mg per 90 μ L spray/d

Prescription Therapies

Combination Estrogen-Progesterone Therapy		
Composition	Product Name	Dosage/d
<i>Oral Continuous-cyclic</i>		
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)
<i>Oral Continuous-combined</i>		
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
<i>Transdermal Continuous-combined</i>		
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

Progestogens		
Composition	Product Name	Dosage/d
<i>Oral tablet - Progestin</i>		
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
<i>Oral capsule - Progesterone</i>		
Micronized progesterone (peanut)	Prometrium (generics)	100 mg or 200 mg
<i>Intrauterine System - Progestin</i>		
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)
<i>Vaginal Progesterone</i>		
Gel – Progesterone	Crinone 4% or 8%	45 or 90 mg applicator
Insert – Micronized progesterone	Endometrin	100 mg insert

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

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
- Gabapentin – start with 300 mg daily QHS, increase as needed
- Clonidine – 0.05 mg BID or 0.1 mg BID (taper slowly with higher dose)



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

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

Androgens in Females

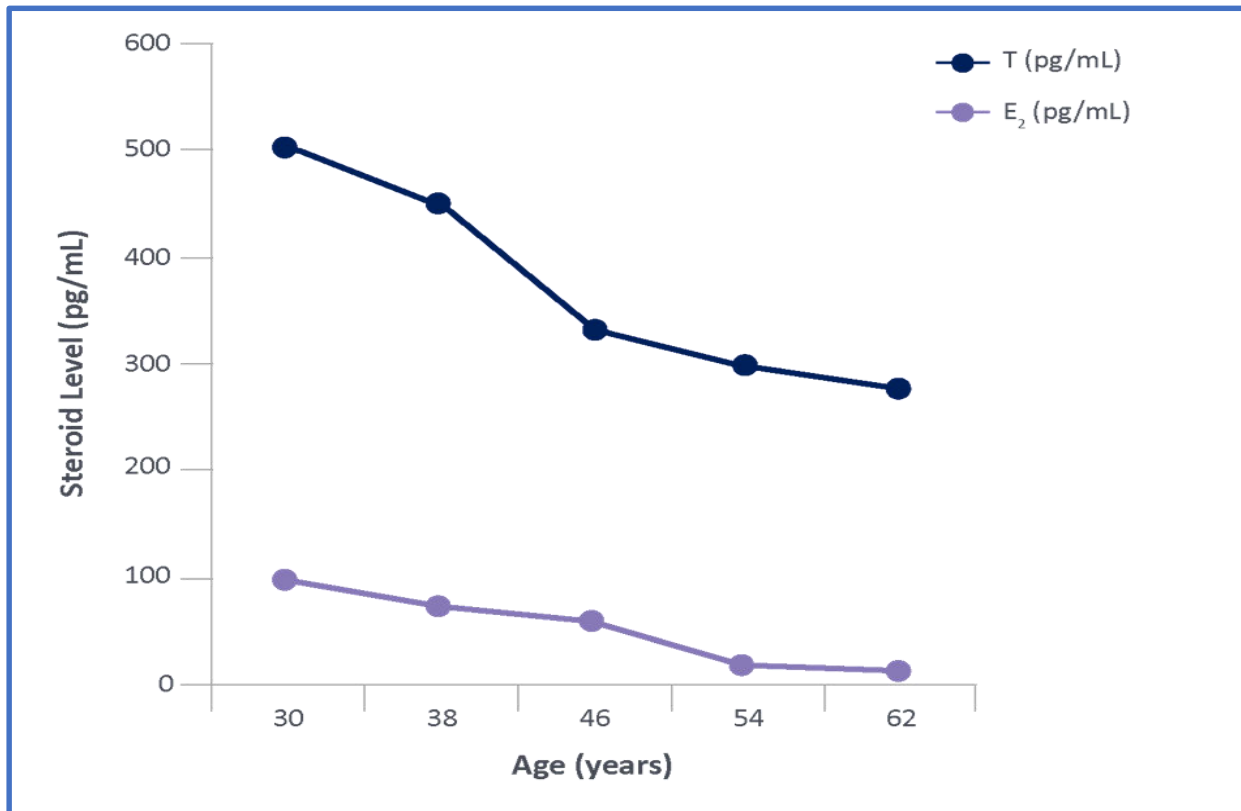


Figure adapted from: Glaser R, Dimitrakakis C. Maturitas. 2013;74(3):230-234

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 5 α -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.

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

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

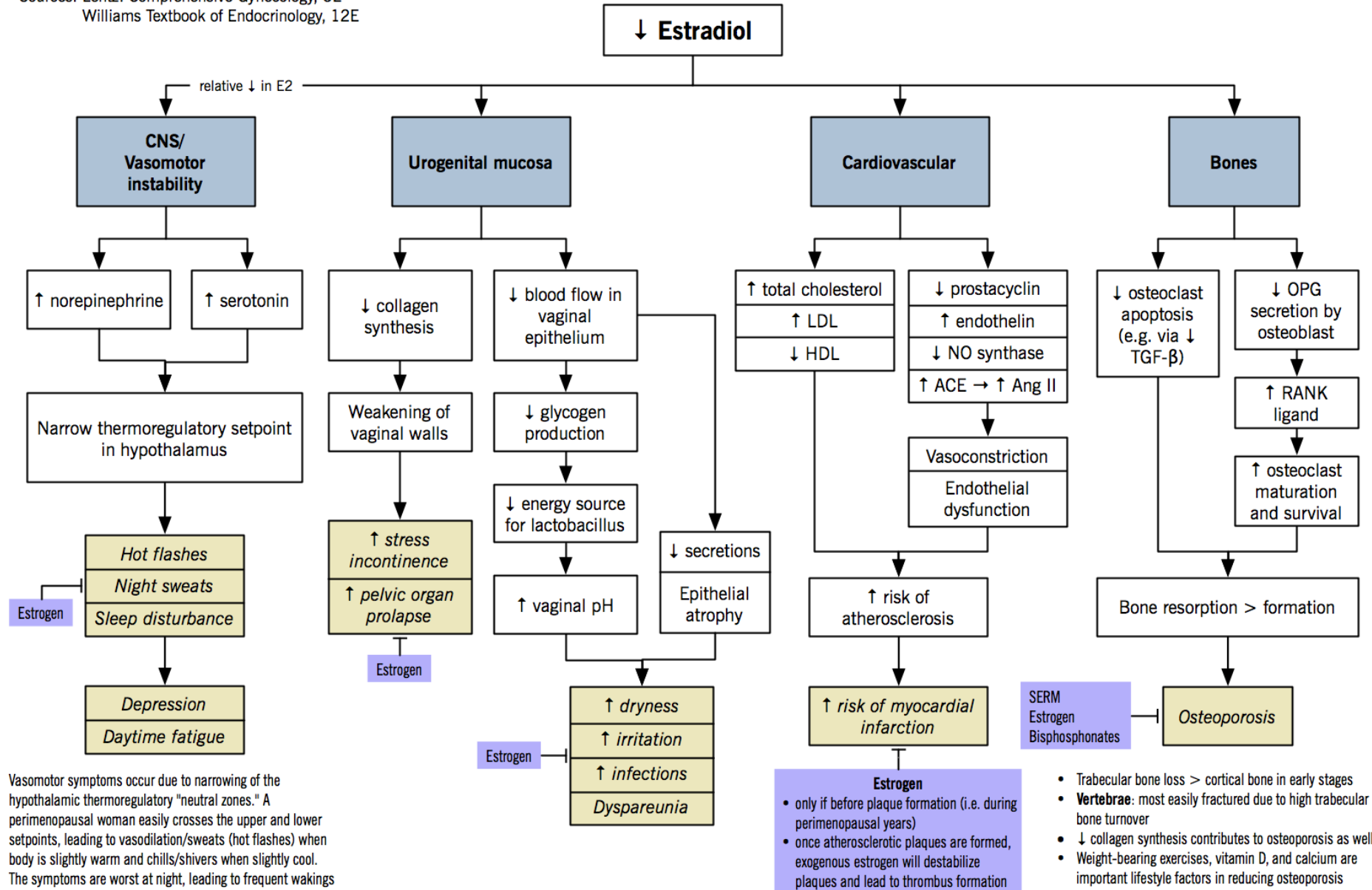
↓↑= Caused by Fluctuating Levels

**Chart obtained with permission from Innovation Compounding Pharmacy.

Pathophysiology of menopause organ changes

Eric Wong

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



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

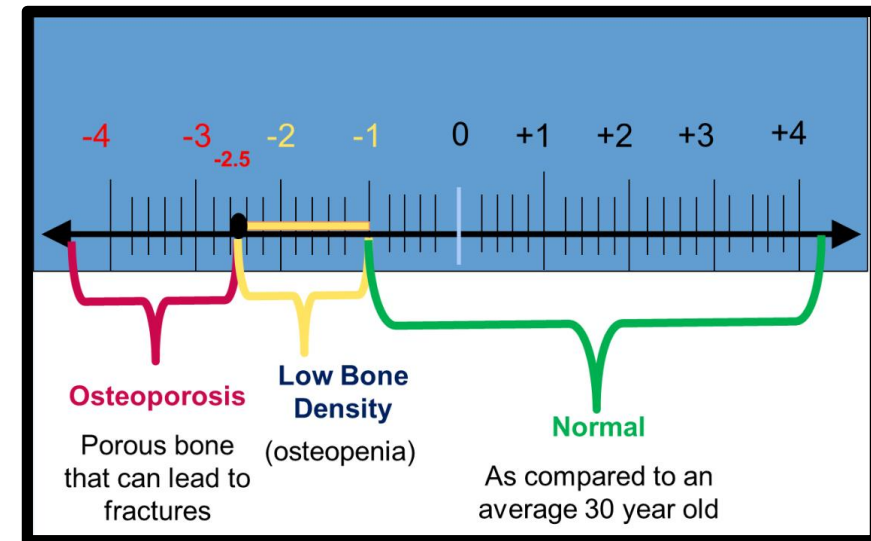
Cardiovascular Disease & Menopause

- 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
 - BMI – metabolic syndrome
- Individualized counseling and plan



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
- Z-score = secondary osteoporosis and is always used for children, young adults, women who are pre menopausal 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

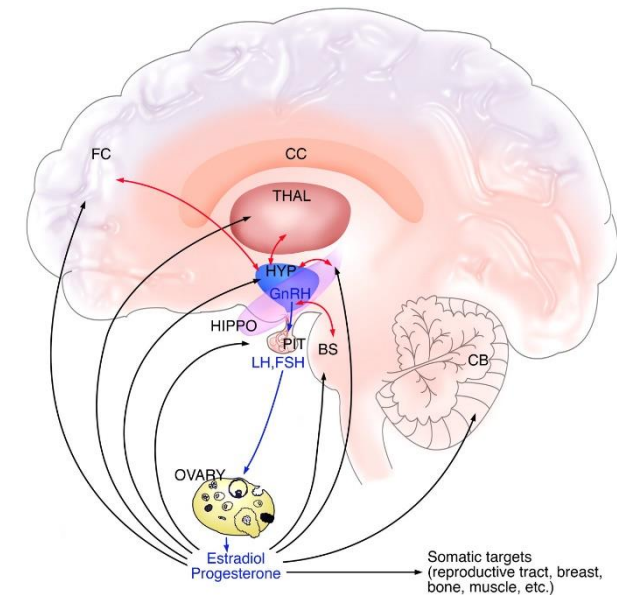
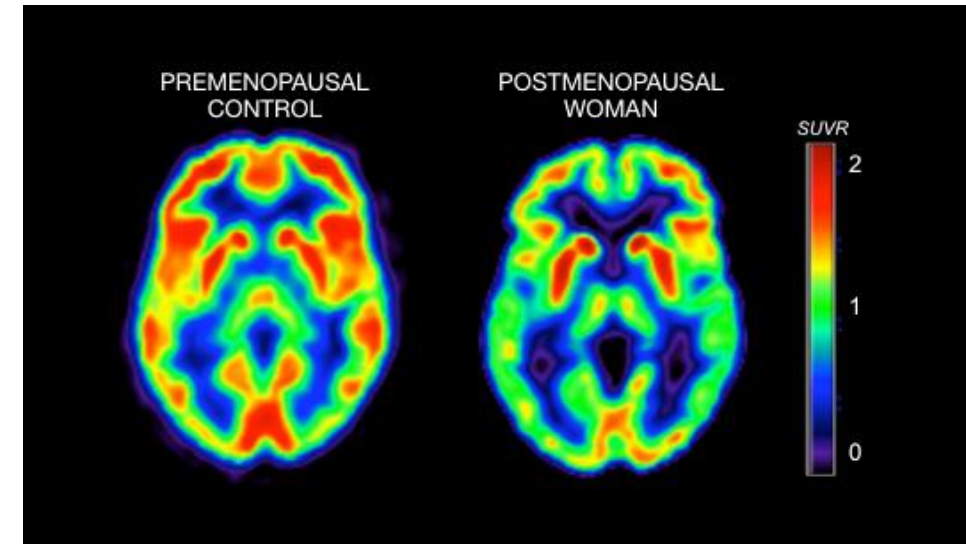


Osteoporosis – Treatment

- 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
- Medications
 - Bisphosphonates
 - 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
 - Raloxifene (SERM) 60mg PO daily
 - Miacalcin Nasal 200 IU 1 spray one nostril each day
 - Miacalcin 100 units SQ/IM qod-qd
 - Forteo 20 mcg SQ daily
 - Prolia 60 mg SQ q6months
 - Reclast 5mg IV q12months

Mental Health

- Estrogen is neuroprotective
- No support with 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
- Approx 20% of women experience depression
 - Later transition = less risk of depression
 - Consider Paroxetine for treatment
 - Mini-mental screening and suicide screening



Other considerations

- Genitourinary syndrome of menopause (GSM)
- Urinary concerns and pelvic floor muscles
- Body image
- Weight gain
- Skin changes
- Hair changes
- Mood changes and depression
- DEI concerns and impact



Special Populations and Menopause

- Polycystic Ovarian Syndrome
- Transmasculine/GNC individuals
- Chronic Pain
- Breast Cancer Patients
- History of Ovarian, Endometrial, or Cervical Cancer
- Migraines

Thank you!

Questions?

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