To MENOPAUSE and BEYOND

ALEECE FOSNIGHT, MSPAS, PA-C, CSC-S, CSE, NCMP, IF

UROLOGY, WOMEN'S HEALTH, SEXUAL MEDICINE

SKIN, BONES, HEARTS, AND PRIVATE PARTS 2021

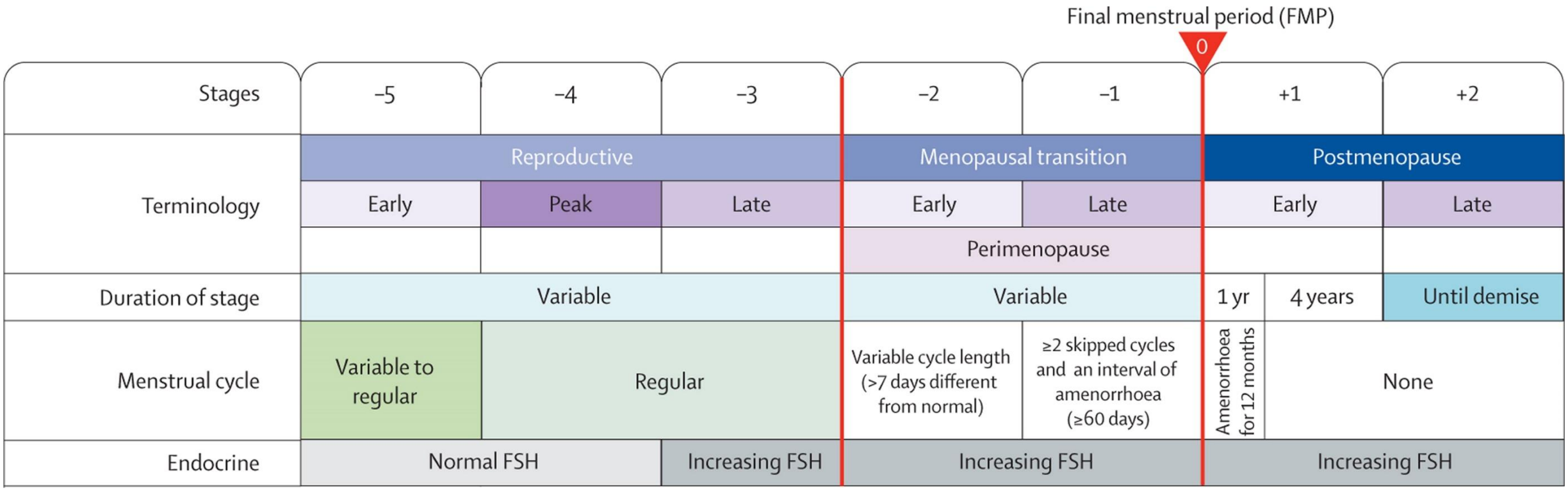
Objectives

- 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

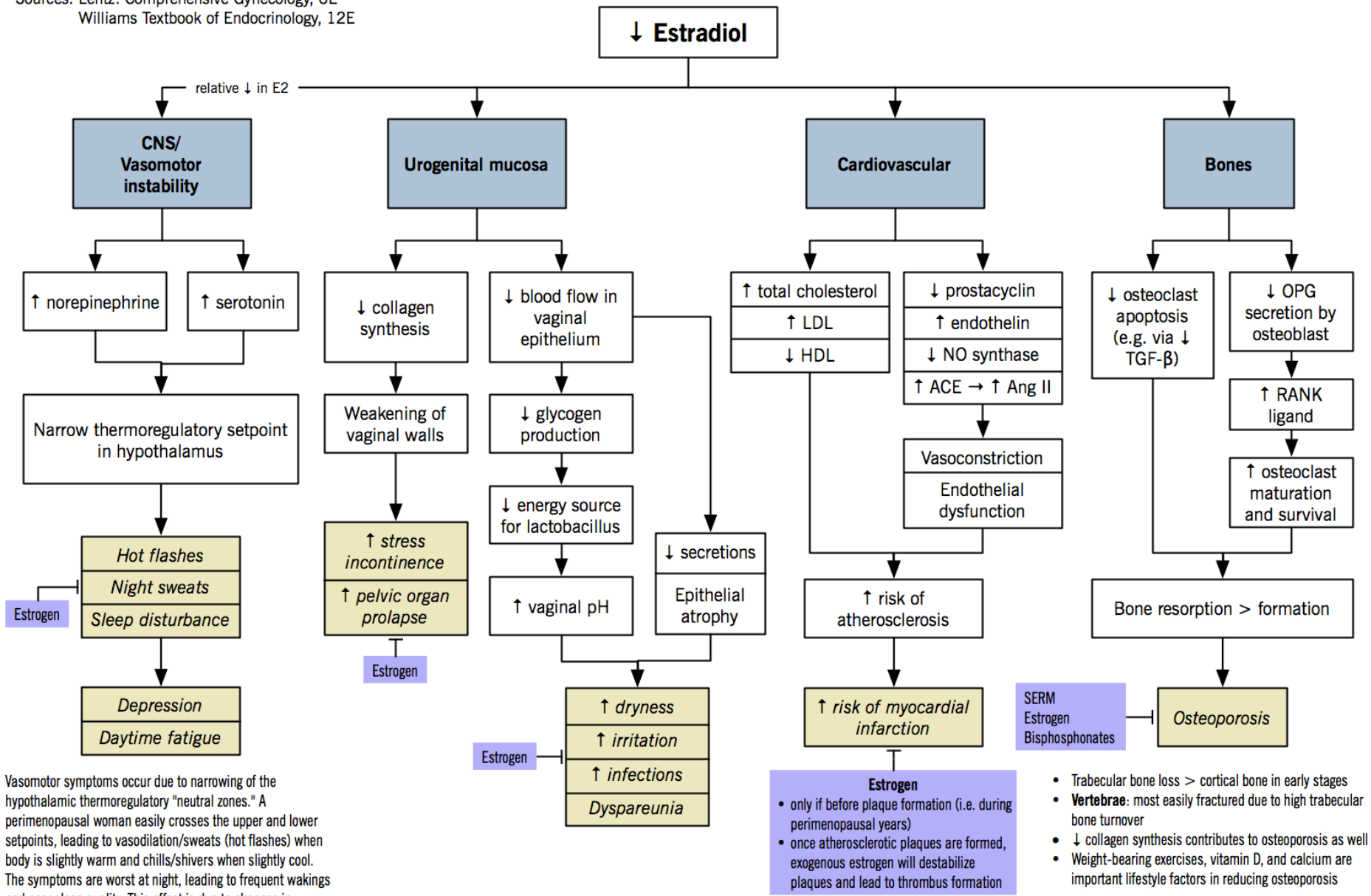
Stages of Menopause



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

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

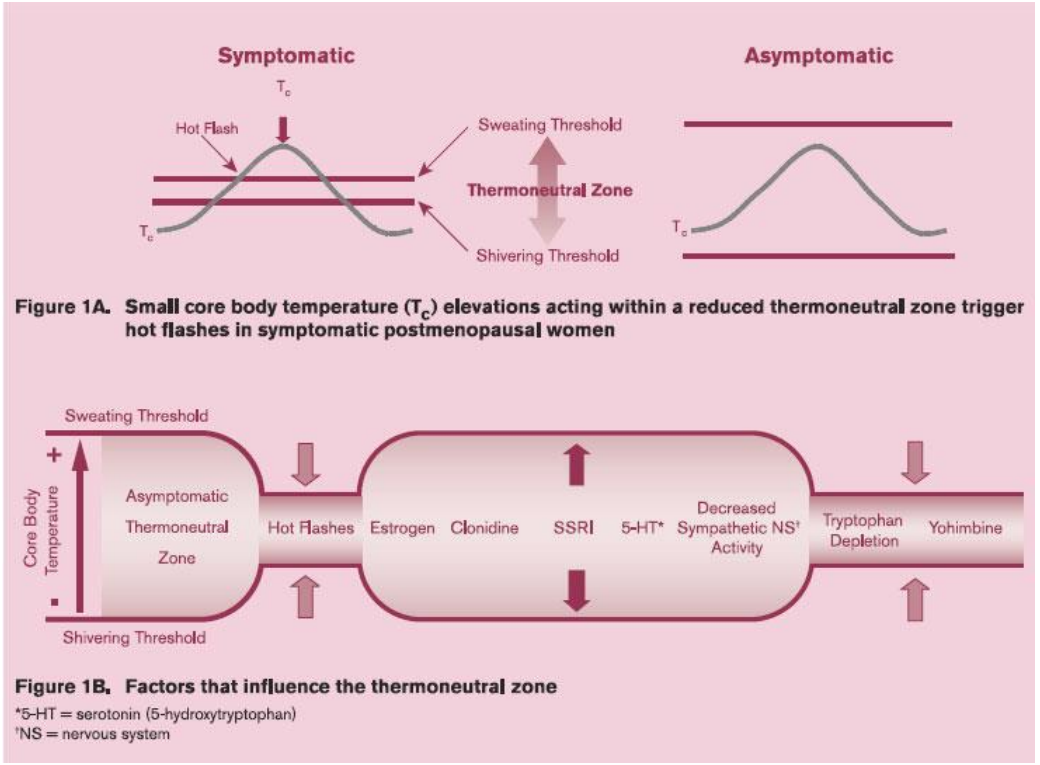


Figure 1A. Small core body temperature (T_c) elevations acting within a reduced thermoneutral zone trigger hot flashes in symptomatic postmenopausal women

Figure 1B. Factors that influence the thermoneutral zone

*5-HT = serotonin (5-hydroxytryptophan)
†NS = nervous system

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

VMS 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

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)

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

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

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

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
- 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)

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

Sexual Function

- PRESIDE Study
  - At least 40% of women and 12% have personal distress
  - A third to half perimenopauseal/postmenopausal women experience one or more concerns with sexual functioning
- Decrease in ovarian function
  - Loss of testosterone – key player!
  - Sex drive → motivation, desire, and sexual sensation
- Non-hormonal causes at midlife and beyond
  - Psychological, sociocultural, and interpersonal

Sexual Function

- North American Menopause Society Questionnaire
  - Are you currently sexually active?
    - If yes, are you currently have sex with men, women, both? History of partners?
    - If no, why not?
  - How long have you been with your current partner?
    - Is the relationship committed, monogamous?
    - Safe sex practices
    - Any sexually transmitted infections?
  - Do you have any concerns about your sex life?
    - Loss of interest in sexual activities? Libido? Desire?
    - Loss of arousal? Loss or diminished orgasm?
    - Any pain with sexual activity? Intercourse? Outercourse?
      - If yes, when did the pain start? Does it happen every time?

Sexual Function

- PLISSIT Model
  - Permission
    - Gives the patient permission to discuss their concern
    - Example: "Most women going through menopause have a sexual health concern, is this a concern for you?" Expand with – Tell me more.
  - Limited Information
    - The provider can provide a small amount of information of the concern and normalize the situation.
    - Example: Pathophysiology of disease.
  - Specific Suggestions
    - Provide specific suggestions to improve the patient's concern.
    - Example: Communication skills, literature, OTC, Rx's, PFPT, sensate focus, masturbation, position modification, lubricants, dilators, etc.
  - Intensive Therapy
    - Referral to sex therapy or sex counseling.
    - Example: Long standing conflict within the relationship, unresolved trauma/abuse, infidelity/affairs

Cardiovascular Disease & Menopause

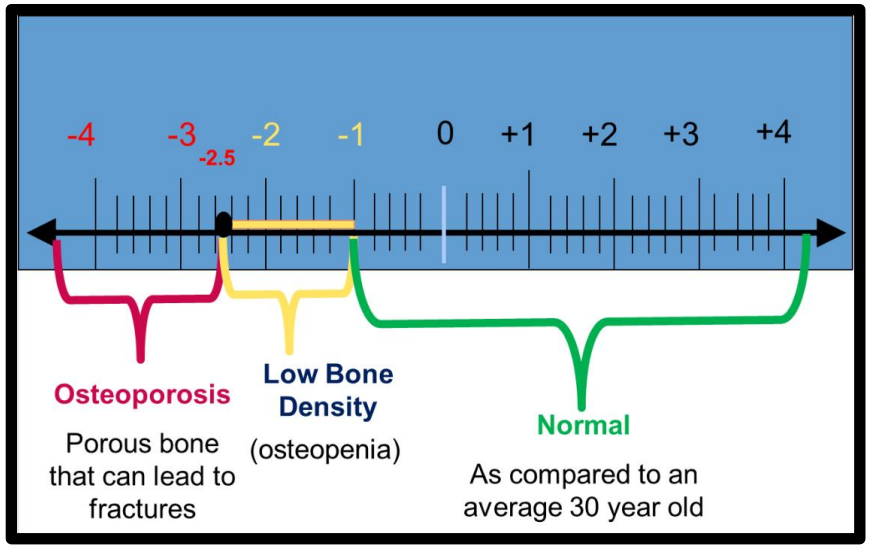
- 1 in 3 women will die of hear disease regardless of race or ethnicity
- Does estrogen play a role? Controversial and Confusing
- Early menopause (especially due to oophorectomy) are at increased risk of coronary heart disease than compared to age-matched premenopausal women
- Increase in total cholesterol 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

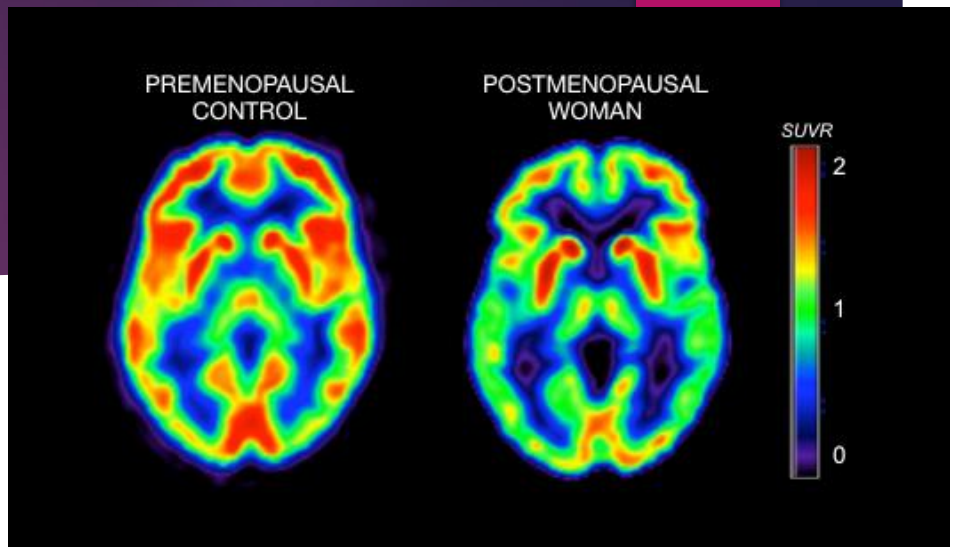
- AKA: "porous bone"
- Significant health treat for aging postmenopausal women with increased risk of fracture
- Bone strength = bone quantity and bone quality → bone mineral density (BMD)
- Peak bone mass is peaked at a women's third decade of life
- ACOG recommendation for DEXA or BMD test annually 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



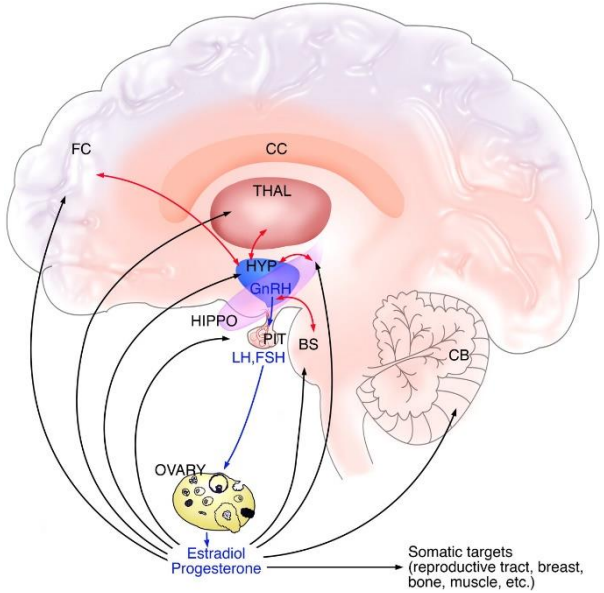
Osteoporosis – Treatment

- 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

References

- Stormo AR, Saraiya M, Hing E, Henderson JT, Sawaya GF. Women's clinical preventive services in the United States: who is doing what? JAMA Intern Med 2014;174:1512–4.
- Ley SH, Li Y, Tobias DK, et al. Duration of reproductive life span, age at menarche, and age at menopause area associated with risk of cardiovascular disease in women. J Am Heart Assoc 2017; 6:e006713.
- Goodman NF, Cobin RH, Ginzberg SB, et al. American Association of Clinical Endocrinologists medical guidelines for clinical practice for the diagnosis and treatment of menopause. Endocr Pract 2011; 17(6):1-25. https://www.aace.com/files/menopause.pdf. Accessed December 10, 2018.
- The NAMS 2017 Hormone Therapy Position Statement Advisory Panel. The 2017 hormone therapy position statement of the North American Menopause Society. Menopause 2017; 24(7):728-53.
- 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.
- 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.
- 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. Accessed December 14, 2018.
- American College of Obstetricians and Gynecologists, Practice bulletin no. 141: management of menopausal symptoms. Obstet Gynecol 2014; 123(1):202-16.
- The North American Menopause Society, Menopause Practice: A Clinician's Guide, 6th Edition. 2019.
- Parish S, et al. International Society for the Study of women's Sexual Health Clinical Practice Guideline for the Use of Systemic Testosterone for Hypoactive Sexual Desire Disorder in Women. Journal of Sexual Medicine. 2021; 1-19.

Thank you!

Questions?

Aleece Fosnight, MSPAS, PA-C, CSC-S, CSE, NCMP, IF
Urology, Women's Health, Sexual Medicine
Skin, Bones, Hearts, and Private Parts 2021
aleece@fosnightcenter.com
www.fosnightcenter.com