**Clinical Cases Applicability:** menopausal symptoms (hot flashes, atrophy), osteopenia/osteoporosis, menopausal hormone, premature ovarian insufficiency

**Learning Objectives:**
1. Understand the physiologic changes in estrogen levels and the hypothalamic-pituitary-ovarian axis in menopause
2. Describe the pathophysiology of the various symptoms of peri-menopause menopause
3. Discuss treatment options for the symptoms of menopause

**What hormonal changes occur in perimenopause and menopause (defined as 1 year of cessation of menstruation)? How does this affect the HPO axis?**

**Perimenopause:** Reduced ability of aging follicles to secrete inhibin (produced in granulosa cells of developing follicles) → lack of negative feedback from ↓ inhibin → ↑ FSH → ↑ ovarian follicular response → maintain overall estrogen levels

**Menopause:** Ovarian follicles undergo accelerated loss until depletion of follicles → ↓ ovarian steroid hormone (estrogen, progesterone) release → lack of negative feedback → ↑ GnRH release → ↑ circulating FSH and LH

**What are common symptoms of menopause? What is the pathophysiology?**

**Abnormal uterine bleeding**: increased anovulatory cycles; With ↑ unopposed estrogen levels → increasing risk for developing hyperplasia/carcinoma

**Vasomotor symptoms (hot flashes):** occur in up to 80% of women; lasts 1-5 minutes, sudden wave of heat that spreads over the body, particularly the upper body & face; associated with sweating, palpitations, anxiety, sleep disturbance
- Dysfunction of the thermoregulatory nucleus of the hypothalamus (regulates perspiration & vasodilatation – nucleus activates heat dissipation mechanisms to maintain core body temperature in a regulated range, “the thermoregulatory zone”)
- women with severe vasomotor symptoms → narrower thermoregulatory zone – minimal changes in core body temperature induce hot flush (Figure 1)
- ↓ estrogen → ↑ norepinephrine & serotonin levels → Norepinephrine & serotonin lower the thermoregulatory set point and triggers the heat loss mechanisms (Figure 1)

**Bone loss:** Normal bone remodeling – constant resorption of bone carried out by osteoclasts & bone formation by osteoblasts; Osteoblasts produce proteins RANKL and OPG (osteoprotegerin) (Figure 2)
- RANKL binds to RANK – a receptor on the surface of the osteoclast progenitor cells → promotes development of osteoclasts → leads to bone resorption
- OPG binds to RANKL preventing it from binding with RANK → decreased osteoclast development
- ↓ estrogen → ↑ RANKL production outnumbers OPG → osteoclast development & bone resorption favored → ongoing bone loss over time

**Cardiovascular disease:** ↓ estrogen affects lipid profile, with slightly ↑ LDL → ↑ risk for CVD

**Skin changes:** dryness, wrinkles, thinning; ↓ collagen content, ↓ sebaceous gland secretion, ↓ elasticity, ↓ blood supply

**Vulvovaginal atrophy:** dryness, itching, dyspareunia; ↓ estrogen results in thinning of the vaginal epithelium; Loss of vaginal collagen, adipose tissue, rugae flatten; pH >4.5 (alkaline); for the vulva, ↓ sebaceous glands, subcutaneous fat loss → shrinkage & retraction of clitoral prepuce & urethra, introital narrowing

**Urinary symptoms:** incontinence, urgency, recurrent UTIs; ↓ estrogen → thinning of urethral and bladder mucosa, ↑ risk of incontinence from decreased urethral mucosa coating or “seal”

**Depression:** ↑ risk of new-onset depression in the menopausal transition; unclear if secondary to ↓ estrogen or symptoms related to menopause (hot flashes, sleep disturbances, etc)

**What are treatment options?**

Menopausal hormone therapy: goal is to relieve symptoms, especially vasomotor symptoms; minimal dose for shortest amount of time possible
- For healthy symptomatic women in their 50s, overall risk for complications is low
- For women with an intact uterus, progestin therapy must be added to estrogen to prevent endometrial hyperplasia & carcinoma
- Risks with estrogen + progestin: ↑ risk of breast cancer, stroke, coronary heart events, venous thromboembolism
- Risks with estrogen only: ↑ risk of stroke & venous thromboembolism

Vaginal estrogen: low dose estrogen, minimal systemic absorption, improves urogenital symptoms

SSRIS/SNRIs, Clonidine, Gabapentin – alternatives for hot flashes

Herbal medications: black cohosh, phyto-estrogens (soy) – inconsistent evidence of efficacy
Figure 1

Thermoregulatory zone

↑ in hot flashes
Narrower zone in menopause
(↓ estrogen → ↑ neurotransmitters → ↓ thermoregulatory set point)

Core body temperature

Figure 2

Osteoblast

OPG

RANK-L

RANK receptor

Osteoclast progenitor

RANK-L

RANK receptor

Osteoclast progenitor

Bone resorption

Osteoclast

OPG

RANK-L

Osteoclast progenitor

References:

- Casper, RF. Clinical manifestations and diagnosis of menopause. In: UpToDate, Post TW (Ed), UpToDate, Waltham, MA. (2017)
- Martin, KA, Barbieri, RL. Treatment of menopausal symptoms with hormone therapy. In: UpToDate, Post TW (Ed), UpToDate, Waltham, MA. (2018)