PeriMenopause

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Objectives

- Discuss the perimenopause transition
- Identify symptoms related to perimenopause
- Review treatment options for common symptoms of perimenopause

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Definition - "around menopause"

- The time when a woman's body begins transitioning to menopause
- Ovaries gradually stop ovulating
- Begins with the first onset of menstrual irregularity and ends after one year of amenorrhea has occurred

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Definition

- Average age at start 40-44
- Marked by changes in menstrual flow and length of cycle
- Loss of ovarian reserve during perimenopause
- Menopause = follicle failure —> granulosa cells no longer respond to FSH signal resulting in loss of estradiol production

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STRAW stages of reproductive aging surrounding menopause transition

- **Late Reproductive**
  - Cycles regular to slightly irregular
  - Normal to variable FSH
  - Ovarian reserve low
- **Early Perimenopause**
  - Cycles and FSH variable
  - Ovarian reserve low
- **Late Perimenopause**
  - Cycles > 60 days apart
  - FSH high
  - Ovarian reserve low
- **Menopause**
  - Menses have ended
  - FSH high
  - Ovarian reserve undetectable

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Early Perimenopause

- Follicle cohort is relatively preserved, rises in FSH cause folliculogenesis to occur more rapidly
- Increase in luteal phase follicle growth (eg next cycle's dominant follicle has already started to grow)
- Ovulations follow rapidly upon one another
- Short follicular phase, relatively longer luteal phase so increased PMS symptoms
- Lower luteal progesterone, higher FSH
- Erratic estrogen secretion

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Late Perimenopause

- Menses highly irregular, menstrual periods are scarce
- Estradiol low
  - Loss of negative feedback from estradiol results in increased FSH and LH
- Long periods of amenorrhea
- When there is a menstrual cycle - it may be ovulatory, anovulatory with high estrogen levels, or anovulatory with low estrogen levels

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Perimenopausal AUB = diagnosis of exclusion

- Endometrial tissue sampling should be performed in patients with AUB who are older than 45 years as a first line test
- Endometrial tissue sampling should also be performed in patients younger than 45 years with h/o unopposed estrogen exposure (obesity/pcos), failed medical mgmt, and persistent AUB

*ACOG Practice Bulletin no 148 Diagnosis of AUB in Reproductive-Aged Women

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Perimenopausal AUB: treatment

- Hormonal contraception
  - OCP
  - Levonorgestrel IUD
- Endometrial ablation
  - Should only be done if sterilization has and will concomitantly occur
- Hysterectomy
- Tranexamic acid

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Perimenopaual Symptoms

- Hot flushes
- Poor sleep
- Vaginal dryness/dyspareunia
- Depressed mood
- Increased anxiety
- Other - brain fog, generalized joint pain

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Hot Flashes

- Reported in 30-70% of pre menopausal women
- Increase in prevalence during early perimenopause to up to 85%
- Highest incidence in African-American and Native American populations
- Lowest incidence in Chinese and Japanese women

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Hot Flashes

- High BMI: worse hot flashes during perimenopause, fewer milder hot flashes in menopause
- Elevated FSH is predictive of hot flashes (not necessarily estradiol level)
- Higher incidence in patients with anxiety, depression, and in smokers

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Hot Flashes

- Duration up to 10 years is common
  - 20% women in their 50s
  - 10% women in their 60s
  - 5% women in their 70s

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Hot Flashes - Health implications

- Decreased quality of life
- Increased cardiovascular disease risk
- Increased risk dementia

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Sleep Changes

- Changes in sleep patterns start age 40s and worsen through perimenopause - incidence up to 40%
- Many postmenopausal patients report insomnia
- Due in part to hot flashes but likely multifactorial

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Vaginal Dryness

- Up to 33% of women during perimenopause
- Does not improve without treatment

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Depressed Mood/Anxiety

- Depression and anxiety symptoms more likely to be reported by women who are perimenopausal
  - In SWAN study, baseline depression symptoms 20.9%, 27.8% in early perimenopause, 25.2% late perimenopause, 22% post-menopause
- Major depression more common during the late perimenopause stage
  - SWAN study Major Depression OR 2.27 in perimenopause, 3.57 in post-menopause
- Anxiety scores seemed to worsen as perimenopause progresses

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Treatment: vasomotor symptoms (VMS)

- Hormone therapy most effective at improving quality of life
  - Contraindications: ER+ cancer; h/o stroke, mi or VTE; thrombophilia, severe active liver disease
  - May slow progression of CVD when used during ages 45-55
- Menopausal hormone therapy dose about 1/4 equivalent estrogen dose as oral contraceptive pill
- If breakthrough bleeding - OCP indicated
  - Best to use continuous OCP rather than placebo week to avoid symptoms

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Treatment: VMS

- Remember to use progestin in patients using estrogen therapy with a uterus to avoid endometrial cancer
- Concurrent use of estrogen and continuous levonorgestrel intrauterine system
- Non-oral estrogen is preferred due to decreased risk for VTE

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Treatment: VMS

- Some SSRIs and SNRIs have been shown to reduce VMS by up to 69%
- Paroxetine salt 7.5 mg (long acting): FDA approved for vasomotor symptoms
- SSRI: citalopram, escitalopram
  - No significant improvement in VMS with sertraline or fluoxetine
- SNRI: desvenlafaxine, venlafaxine

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Treatment: VMS

- Gabapentin
  - improves the frequency and severity of VMS
  - Start with 100-300 mg at night, titrate to goal 900 mg/day; max dose 2400 mg/day
  - AE: drowsiness, dizziness, impaired balance/coordination
  - Of note, pregabalin is not recommended for VMS

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Treatment: VMS

- Clonidine
  - Has been shown to be modestly more effective than placebo
  - AE: hypotension, lightheadedness, headache, dry mouth, dizziness, sedation, constipation; sudden cessation can cause acute hypertension
  - Not recommended because there are more effective therapies with fewer AE's

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Treatment: VMS

- Oxybutynin
  - Doses range 2.5 mg or 5 mg bid up to 15 mg XR daily
  - Several studies show significant improvement for moderate to severe VMS
  - AE: dry mouth, urinary difficulty, cognitive decline (with prolonged use)

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Treatment: VMS

- Fezolinetant (Veozah)
  - FDA approved NONHORMONAL treatment for VMS in POSTmenopause
  - Neurokinin B antagonist
    - With loss of estrogen suppression, there is hyperactivity of the KNDy neurons, resulting in hypersecretion of neurokinin B (NKB)
    - NKB then stimulates the adjacent thermoregulatory center in the hypothalamus to cause VMS

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Treatment: VMS

- Elinzanetant (Lynkuet)
  - New FDA-approved NON-hormone option for treatment of VMS due to menopause
  - Dual neurokinin (NK) targeted therapy
    - NK1 and NK3 receptor antagonist
  - Side effects: headache, dizzy, fatigue, somnolence, transaminitis
  - Check baseline alt, ast, alkaline phosphatase, bilirubin, T bili and then at 3 months of therapy

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Treatment: VMS

- Cognitive behavioral therapy CBT
  - Has been shown to clinically reduce the degree to which VMS are rated as a problem (eg still have VMS but are not bothersome)
- Clinical hypnosis
  - Has been shown to reduce VMS frequency and severity

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Treatment: vaginal dryness

- Vaginal estrogen
  - Cream dose: 0.5 g daily x 2 wk then twice weekly
  - Goal is to treat distal 1/3 of vagina
  - Increases vaginal wall thickness, decreases vaginal pH, improves vaginal dryness, dyspareunia, and sexual function

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Treatment: vaginal dryness

- Vaginal hyaluronic acid
  - Draws water into tissue
  - Increases the thickness of the vaginal epithelium
- Vulvar moisturizer
  - Produces moist film over epithelium of vagina to lubricate vaginal walls
  - Improves vaginal pH, dryness, dyspareunia, and sexual function

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Treatment: vaginal dryness

- CO2 and Erbium laser
  - Laser applied to vaginal epithelium so that fractional beams of light penetrate tissues creating small wounds in the epithelium. This leads to stimulation of collagen remodeling and regeneration
  - Improves subjective and objective atrophy, urinary symptoms, sexual function, dyspareunia, and dryness

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Treatment: Genitourinary Syndrome of Menopause GSM

- Ospemifene
  - SERM which activates estrogen receptors in the vagina to increase wall thickness and reduce pain due to vulvar vaginal atrophy
- Topical DHEA
  - Converts to estrogen in vulvar vaginal tissues
  - Increases vaginal wall thickness, decreases vaginal pH, improves vaginal dryness, dyspareunia, and sexual function
- Vaginal testosterone
  - Induces proliferation of vaginal epithelium
  - Improves atrophy, dryness, and sexual function

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Treatment: GSM

In Postmenopausal Women Looking for Alternate Treatments to Local Estrogen With…	Guideline*	Intervention (Grade)†
Objective signs of atrophy	We recommend	Vaginal DHEA (A)
	We suggest	Vaginal hyaluronic acid (C), testosterone (B), CO_2 laser (B), erbium laser (B), ospemifene (B), polycarbophil-based vaginal moisturizer (B), tibolone (B)
Subjective atrophic symptoms such as dryness and dyspareunia	We recommend	Vaginal DHEA (A)
	We suggest	Vaginal hyaluronic acid (C), testosterone (B), CO_2 laser (B), erbium laser (B), ospemifene (B), polycarbophil-based vaginal moisturizer (B), tibolone (B)
Concerns about sexual function due to atrophy	We recommend	Vaginal DHEA (A)
	We suggest	CO_2 laser (B), ospemifene (B), polycarbophil-based vaginal moisturizer (B), testosterone (B), and tibolone (B)
Concerns about impaired quality of life due to GSM	We suggest	Vaginal hyaluronic acid (B), vaginal DHEA (B), and CO_2 laser (B)
Symptoms of urinary symptoms due to atrophy	We suggest	Ospemifene (B), tibolone (B), CO2 laser (B), erbium laser (B)
Concerns about effects on the uterus or endometrium	We suggest	CO2 and erbium laser, vaginal DHEA, vaginal hyaluronic acid, polycarbophil-based vaginal moisturizer, testosterone, and tibolone because they have no increased risk vs estrogen or placebo (C)
Concerns about adverse events	We suggest	Using with caution due to increased mild to moderate AEs ospemifene, vaginal DHEA or tibolone (C), CO_2, and erbium laser (B)
A personal history of breast cancer	We suggest	Vaginal DHEA 6.5 mg vaginal suppositories nightly (A), polycarbophil-based vaginal moisturizer (B), or CO_2 laser (B) Caution with use of tibolone among women with breast cancer because it may increase the risk of recurrence (ungraded statement)

DHEA, dehydroepiandrosterone; CO_2, carbon dioxide; AE, adverse event.
* "We recommend" refers to a strong recommendation for which most patients would want the recommended course of action and only a small proportion would not. "We suggest" refers to a weaker recommendation for which the majority of people in the situation would want the recommended course of action, but many would not.
† A=high certainty of evidence; future research is unlikely to change the conclusion. B=moderate certainty of evidence; future research may change the conclusion. C=low certainty of evidence; future evidence may substantially change the conclusion. D=very low certainty of evidence; the estimate of effect is very uncertain and precludes a conclusion.

OBSTETRICS & GYNECOLOGY

- Casiano Evans, Elizabeth A MD, et al. Nonestrogen Therapies for Treatment of Genitourinary Syndrome of Menopause: A Systematic Review. *Obstetrics & Gynecology* 142(3):p 555-570, September 2023.

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Treatment - poor sleep

- Cognitive behavioral treatment - insomnia
- Melatonin
- Gabapentin 100-300 mg at night

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Case Discussion

- 47 year old female patient presents with menstrual changes, hot flushes, night sweats, poor sleep, moodiness. Periods typically regular until a few years ago. Periods are now irregular and heavy in flow. She has family history of breast cancer and is worried about using hormones.

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Case Discussion

- Evaluate AUB (TVUS, Embx)
- Treatment options
  - OCP
  - Levonorgestrel IUD + estrogen patch
  - Endometrial ablation or hysterectomy alone will not address all of her symptoms

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