Penn Medicine
Lancaster General Hospital

Perimenopause and the Menopause Transition

Elizabeth Doherty MD, MSCP

Disclosures

- I have no relevant financial relationship(s) with ineligible companies to disclose

Learning Objectives

1) Describe and apply the Stages of Reproductive Aging Workshop (STRAW+10) nomenclature.
2) Recognize the breadth and depth of organ systems affected by the menopause transition.
3) Describe some of the most common perimenopause symptoms and treatment options:
    1) Vasomotor symptoms
    2) Body composition changes
    3) Sleep disturbance
    4) Mood and cognitive changes

Stages of Reproductive Aging

Stages of Reproductive Aging

Chronologic Aging

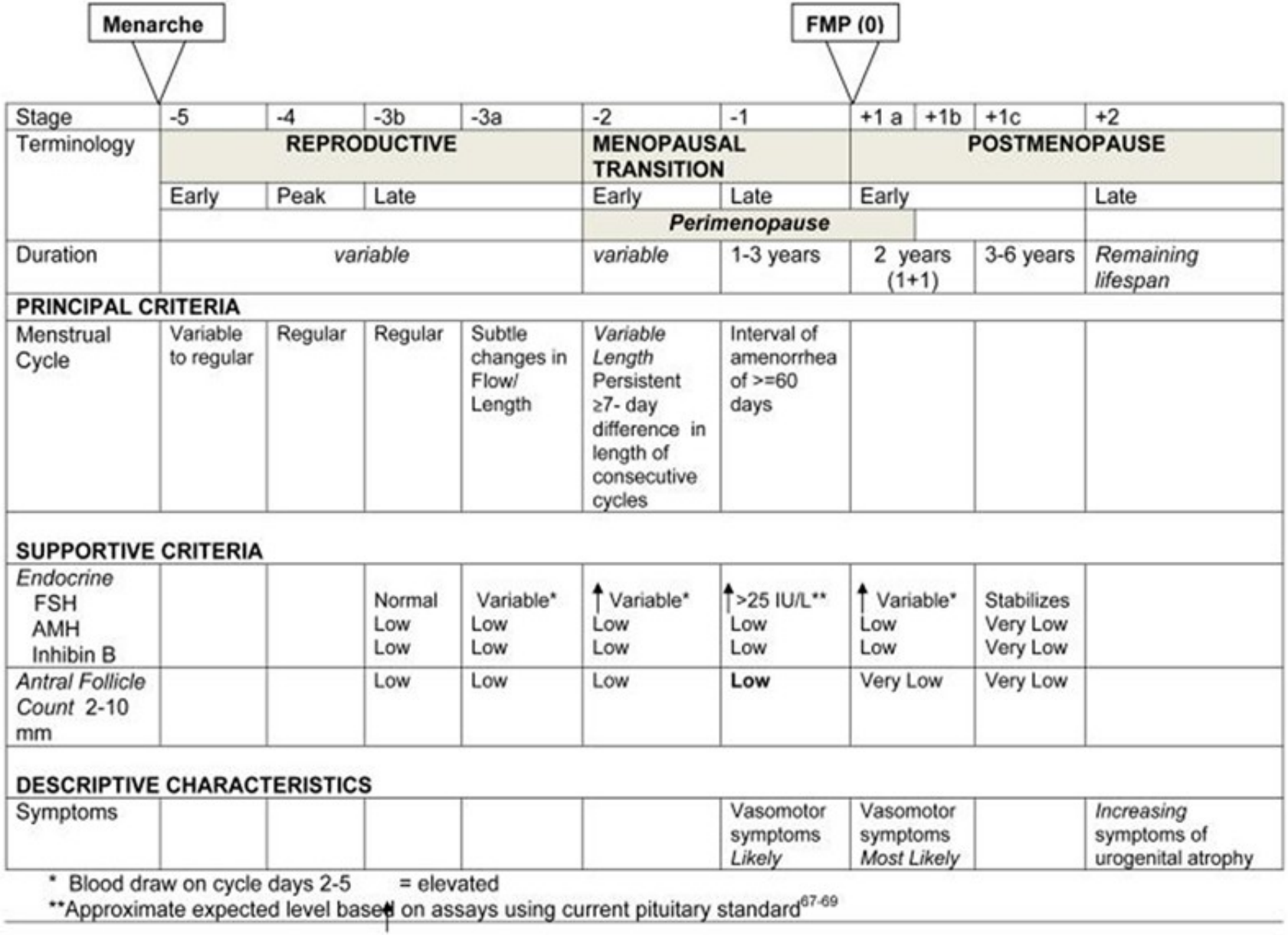
- Process of time-related physiologic deterioration that is genetically determined and environmentally modifiable

Reproductive Aging

- Progressive loss of oocytes by ovulation and atresia.

STRAW+10 Nomenclature

- Divides reproductive lifespan into three broad phases, further broken down into seven stages
  - Data analyzed from several cohort studies on midlife women
  - Centered on the final menstrual period (FMP) as Stage 0
  - Menstrual cycle criteria is the most important staging criteria
- Cannot be applied if:
  - primary ovarian insufficiency, irregular menstrual cycles, hysterectomy, or endometrial ablation



Stage	-5	-4	-3b	-3a	-2	-1	+1 a	+1b	+1c	+2
Terminology	REPRODUCTIVE				MENOPAUSAL TRANSITION		POSTMENOPAUSE			
	Early	Peak	Late		Early	Late	Early			Late
					Perimenopause					
Duration	*variable*				*variable*	1-3 years	2 years (1+1)		3-6 years	*Remaining lifespan*
PRINCIPAL CRITERIA										
Menstrual Cycle	Variable to regular	Regular	Regular	Subtle changes in Flow/ Length	*Variable Length* Persistent ≥7- day difference in length of consecutive cycles	Interval of amenorrhea of >=60 days				
SUPPORTIVE CRITERIA										
Endocrine FSH AMH Inhibin B			Normal Low Low	Variable* Low Low	↑ Variable* Low Low	↑ >25 IU/L** Low Low	↑ Variable* Low Low		Stabilizes Very Low Very Low	
Antral Follicle Count 2-10 mm			Low	Low	Low	**Low**	Very Low		Very Low	
DESCRIPTIVE CHARACTERISTICS										
Symptoms						Vasomotor symptoms *Likely*	Vasomotor symptoms *Most Likely*			*Increasing* symptoms of urogenital atrophy

* Blood draw on cycle days 2-5 = elevated

**Approximate expected level based on assays using current pituitary standard[67-69]

Perimenopause Symptoms

Clinical Assessment and Screening: Key Components for Menopause History

Symptoms effect on QOL and function

- Including, but not limited to, hot flashes, night sweats, genitourinary symptoms, decreased libido, insomnia, and changes in mood and cognition.
- Screening questionnaires can elicit symptoms and degree of bother or interference (eg, The Menopause Transition Scale [MTS])

Menstrual history

- Last menstrual period, frequency, duration, amount of flow, intermenstrual bleeding, history of polycystic ovary syndrome or endometriosis; age at menarche and final menses.

Type of menopause

- Natural vs induced.

Medications

- Specifically take note of anticoagulants, hormones, selective estrogen receptor modulators (SERMs), chemotherapy, antipsychotics, antidepressants, steroids, and opioids because they may influence symptoms.

Menopause Transition Scale

Please circle the answer that is closest to how you have felt in the last 2 wk.

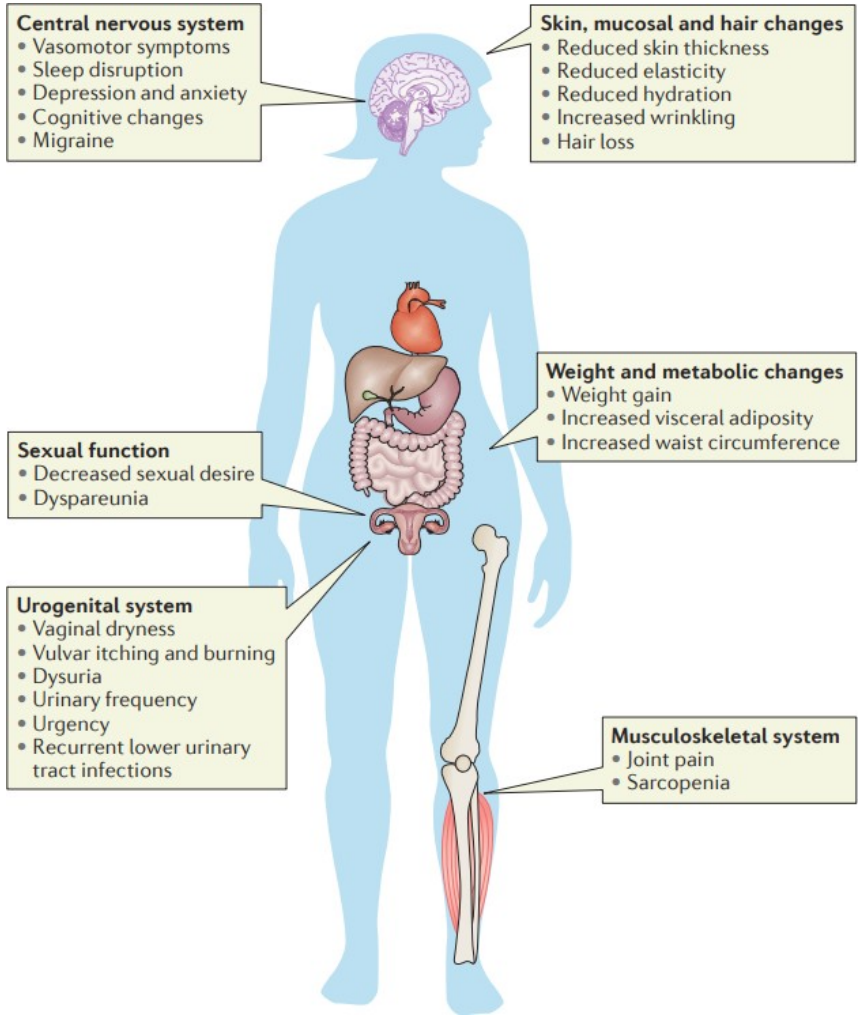
SYMPTOM	EASY (3)	MODERATE (2)	HARD (1)
Hot Flashes/ Night Sweats	Rare to none, no sweating, predictable, barely distracting	Somewhat frequent, sweating, predictable, somewhat distracted from activity	Frequent, sweating, unpredictable, very distracting from activity
Weight	Stable, healthy or overweight, losing	Overweight or not losing	Obese or gaining
Energy	Good, rested in AM, mostly good days	Moderate, mostly rested in AM, good and bad days	Tired, mostly not rested in AM, mostly bad days
Libido	Both partners initiate, both satisfied, relationship good predictable, no dysfunction	Only partner initiates, OK once going, relationship mostly OK	No one initiating, no desire, relationship stressed
Moods	Good mood-rare mild anxiety/ depressed mood, no one notices,	Some anxiety/depressed mood, others notice, not predictable, some dysfunction	Mostly anxious or depressed, others notice, not predictable, poor function in daily activities
Vaginal Dryness	Minor to no dryness, rare to no bladder symptoms, no pain with intercourse	Some dryness, some bladder symptoms, mild pain with intercourse	Mostly dryness, always bladder symptoms, mostly pain with intercourse
Vaginal Bleeding	None or light, predictable, not interfering with daily activities	Moderate to heavy, predictable, some interference with daily activities	Heavy, not predictable, interfering with daily activities

Anderson NJ, et al. *Menopause* 2022:868-876. doi:10.1097/GME.0000000000001975

Organ Systems Affected by the Menopause Transition

Genitourinary	Irregular periods/bleeding Vaginal dryness Changes in libido Urinary urgency and incontinence Recurrent UTIs
CNS	Headaches Paresthesias/electric shocks Difficulty with concentration Memory lapse Dizziness Formications (tactile hallucinations)
Gastrointestinal	Digestive issues (constipation, flatulence, cramps, abdominal bloating)
Psychological	Mood swings Sleeping difficulty New-onset or worsening anxiety/depression Panic disorder Formications

Breast	Breast tenderness or soreness Loss of breast fullness Breast sagging
Musculoskeletal	Joint aches and pains Muscle tightness/soreness Decreased skeletal muscle mass
Oral	Burning tongue Gum health issues
Integumentary	Dry, itchy skin Brittle nails Hair thinning or loss Change in body odor
Bone	Osteoporosis/bone loss
Cardiovascular	Hot flashes and hot flushes (redness seen) Night sweats Palpitations
Immunologic	Worsening allergies
General	Fatigue Weight gain Bloating/water retention



Iyer, T.K., Thacker, H.L. (2022). Menopause. In: Falcone, T., Hurd, W.W. (eds) Clinical Reproductive Medicine and Surgery. Springer, Cham. https://doi.org/10.1007/978-3-030-99596-6_9

Monteleone, P., Mascagni, G., Giannini, A. *et al.* Symptoms of menopause — global prevalence, physiology and implications. *Nat Rev Endocrinol* **14**, 199–215 (2018). https://doi.org/10.1038/nrendo.2017.180

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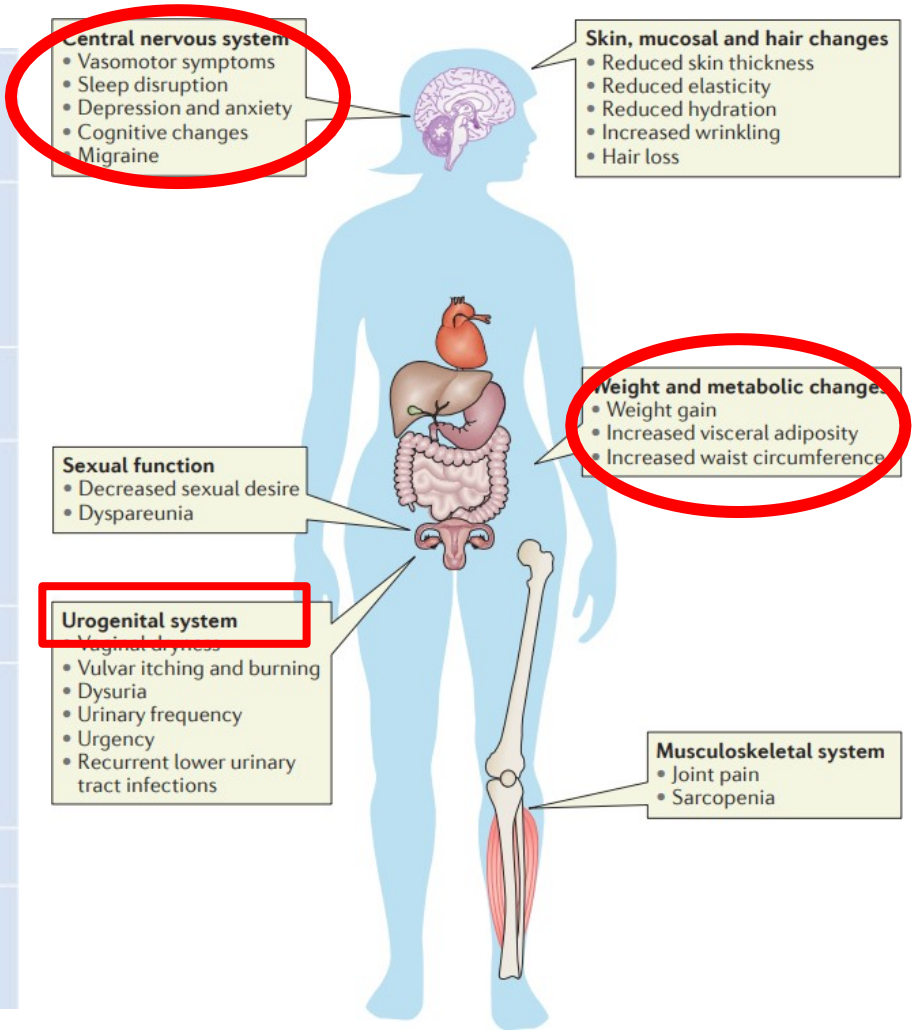

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Vasomotor Symptoms

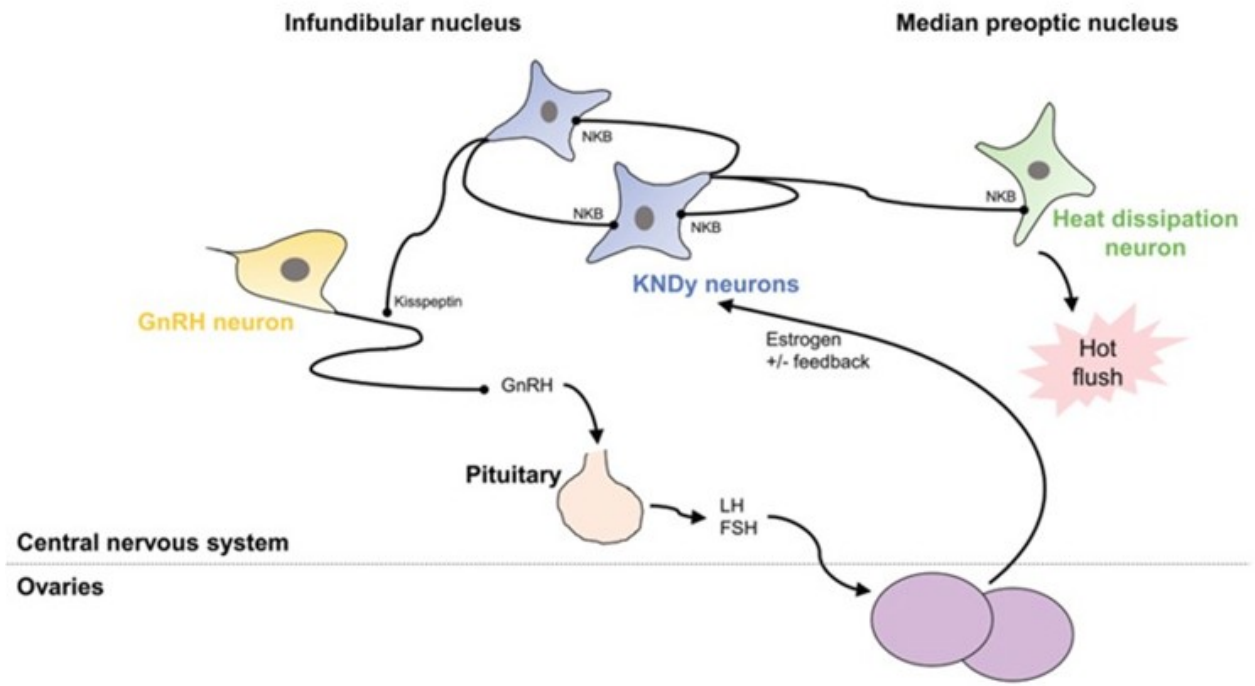
Vasomotor Symptoms

- Most commonly reported symptoms of the menopause transition (60-80% of women at some point during MT)
- Sudden intense sensation of heat in the upper body, particularly the face, neck and chest
- Typically between 30 sec and 5 min and may be accompanied by perspiration, chills, anxiety and palpitations
- Number of episodes and degree of bother vary
- Median duration of VMS is 7.4 years, but 10% can have them 20+ years

- Severity is often categorized:
  - Mild - sensation of heat without sweating
  - Moderate - sensation of heat with sweating, able to continue activity (or return to sleep)
  - Severe - sensation of heat with sweating, causing cessation of activity (or waking from sleep)

Avis NE, et al. *JAMA Intern Med* 2015;175:531-539. doi: 10.1001/jamainternmed.2014.8063; Richard-Davis G, et al. *JAMA Intern Med* 2015;175:540-541. doi: 10.1001/jamainternmed.2014.8099

Pathophysiology of Vasomotor Symptoms



Reproduced from Santoro N, Roeca C. The menopause transition: signs, symptoms, and management options. *J Clin Endocrinol Metab* 2021;106:1-15; by permission of Oxford University Press on behalf of the Endocrine Society. All rights reserved.

Freedman RR. *Semin Reprod Med* 2005;23:117-125. doi: 10.1055/s-2005-869479; Santoro N, et al. *J Clin Endocrinol Metab* 2021;106:1-15. doi: 10.1210/clinem/dgaa764

- Pathophysiology is multifactorial.
- Involves complex interplay between central nervous system and peripheral physiologic processes.
- Kisspeptin-neurokinin B-dynorphin (KNDy) neurons that control the gonadotropin-releasing hormone (GnRH) pulse generator are activated by decreasing estradiol serum concentrations in the menopause transition. This causes an activation cascade to the adjacent thermoregulatory center causing VMS.
- Blockade of neurokinin receptors on KNDy and thermoregulatory neurons reduces or eliminates VMS.
- Small increases in temperature trigger thermoregulatory mechanisms causing the sensation of a hot flush (vasodilation, sweating, and decreased skin resistance) due to a narrowing of the normal thermoregulatory zone.

Vasomotor Symptom Treatment Options – Non-pharmacologic

- Evidence based therapies:
  - Clinical hypnosis
  - Cognitive Behavioral Therapy
  - Stellate Ganglion Block (with caution)
- Lacking evidence:
  - Exercise including yoga
  - Paced respiration (slow deep breathing)
  - Soy foods and extracts
  - Multiple OTC supplements and herbal therapies including black cohosh, evening primrose, etc

Vasomotor Symptom Treatment Options – Non-hormonal

Drug	Dose Range	Starting Dose	Efficacy	Adverse Events
Selective serotonin reuptake inhibitors				
Paroxetine salt	7.5 mg/d	Single dose	40%-65%	Nausea, dizziness, fatigue (don't use with tamoxifen)
Paroxetine	10 mg-25 mg/d	10 mg/d		
Citalopram Escitalopram	10 mg-20 mg/d	10 mg/d	50%-65%	Nausea, dizziness, fatigue, drowsiness, headache, dry mouth
Serotonin-norepinephrine reuptake inhibitors				
Desvenlafaxine	100 mg-150 mg/d	50 mg/d	50%-65%	Nausea, constipation, dry mouth, †blood pressure, insomnia
Venlafaxine	37.5 mg-150 mg/d	37.5 mg/d		
Gabapentinoid				
Gabapentin	900 mg-2,400 mg/d	100-300 mg (before bedtime)	40%-65%	Dizziness, headache, drowsiness, disorientation, unsteadiness
Anticholinergic				
Oxybutynin	2.5 mg-5 mg twice/d or 15 mg extended release/d	2.5 mg twice/d	70%	Dry mouth and eyes, constipation; long-term use may be associated with cognitive decline
Neurokinin B Antagonist				
Fezolinetant	45 mg/d	Single dose	50%-70%	Abdominal pain, diarrhea, insomnia, back pain, headache, †Liver enzymes

Crandall CJ, et al. *JAMA* 2023;329:405-420. doi: 10.1001/jama.2022.24140; Lederman S, et al. *Lancet* 2023;401:1091-1102. doi: 10.1016/S0140-6736(23)00085-5; "The 2023 Nonhormone Therapy Position Statement of the North American Menopause Society" Advisory Panel. *Menopause* 2023;30:573-590. doi: 10.1097/GME.0000000000002200

Vasomotor Symptom Treatment Options – Hormonal

- Systemic HT reduces frequency and severity of VMS by 75% or more
- FDA approved as first-line therapy
- Variety of doses and formulations: oral, transdermal patches, topical sprays/gels
  - Transdermal HT bypasses first-pass liver effect; lower VTE than oral formulations in observational studies
  - Progestogens must be used with estrogen for prevention of endometrial hyperplasia/cancer from unopposed systemic estrogen therapy
- Use HT at lowest effective dose for duration necessary to meet treatment goals
- May take 6+ weeks to take effect

Vasomotor Symptom Treatment Options – Hormonal

Transdermal Continuous-Combined		
17β-estradiol + NETA	Combipatch	0.05 mg E + 0.1 4mg P; 0.05 mg E + 0.2 5mg P 2x/wk
17β-estradiol + LNG	ClimaraPro	0.045 mg E + 0.015 mg P once/wk
Transdermal Estrogen		
17β-estradiol matrix patch	Alora, Climara, Esclim, Fempatch, Menostar, Vivelle, Vivelle-Dot, various generics	0.014-0.1 mg delivered daily; applied once or twice/d
17β-estradiol reservoir patch	Estraderm	0.05-0.1 mg/d, applied twice/ wk
17β-estradiol transdermal gel	EstroGel, Elestrin, Divigel	0.52-0.75 mg/d
17β-estradiol topical emulsion	Estrasorb	2 packets/d
17β-estradiol transdermal spray	Evamist	1-3 sprays/d
Estradiol acetate ring	Femring	Device containing 12.4 mg or 24.8 mg releases 0.05 mg/d or 0.10 mg/d for 90 d

Liu JH, ed. Prescription therapies. *Menopause Practice: A Clinician's Guide*, 6th ed. The North American Menopause Society; 2019:277-317.

Vasomotor Symptom Treatment Options – Hormonal

Oral Tablets		
MPA	Provera, various generics	Continuous-combined: 2.5 mg/d Continuous-cyclic: 5 mg for 12-14 d
Norethindrone	Micronor, various generics	Continuous-combined: 0.35 mg/d Continuous-cyclic: 0.35-0.7 mg for 12-14 d
NETA	Aygestin, various generics	Continuous-combined: 0.5-1.0 mg/d Continuous-cyclic: 2.5 mg/d for 12-14 d
MP	Prometrium	Continuous-combined: 100 mg/d Continuous-cyclic: 200 mg/d for 12-14 d
Intrauterine System		
Levonorgestrel[a]	Mirena	20 µg/d

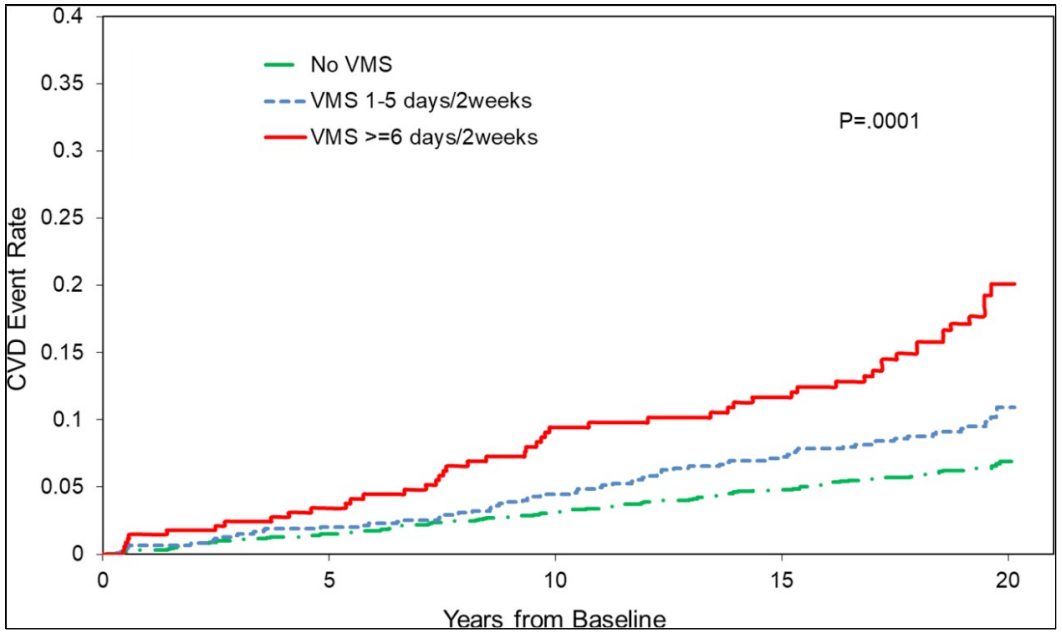
[a]Not FDA approved for endometrial protection with estrogen therapy.

Liu JH, ed. Prescription therapies. *Menopause Practice: A Clinician's Guide*, 6th ed. The North American Menopause Society; 2019:277-317.

Vasomotor Symptoms and Cardiovascular Disease Risk

- Women with VMS tend to have:
  - More dyslipidemia and insulin resistance
  - More likely to develop HTN
- Early and persistent VMS are associated with a 50-77% greater risk of future CVD events
  - Longitudinal cohort study of 3083 women age 42-52 followed for 22 years (SWAN)
- Risk not explained by CVD risk factors

Effective treatment of VMS does NOT mean CVD risk is reduced

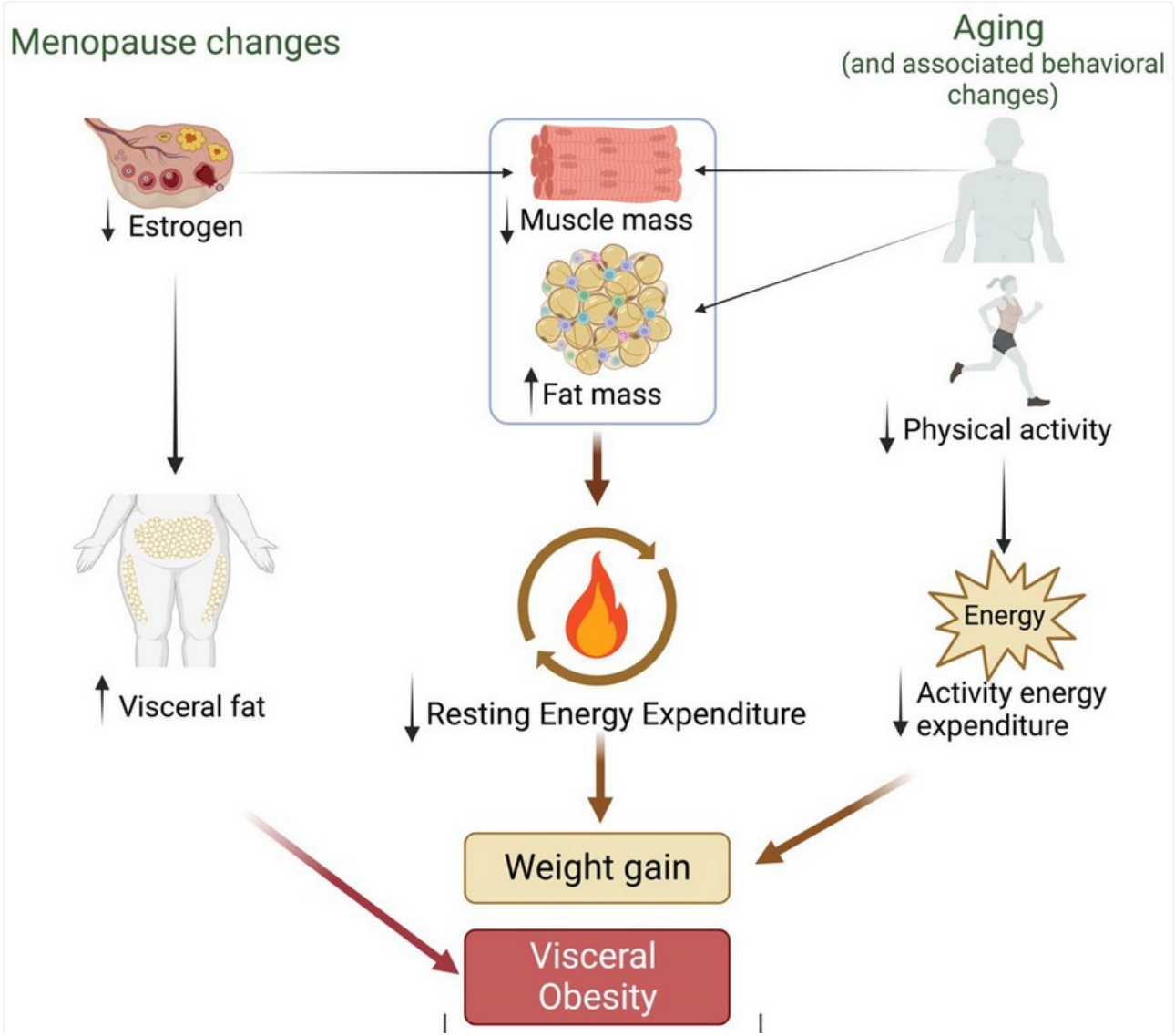


- "Timing hypothesis"
  - Less CVD risk (and potential CHD benefit) with HT use started closer to FMP
  - HT initiated further from menopause may be harmful

Thurston RC et al. Menopausal Vasomotor Symptoms and Risk of Incident Cardiovascular Disease Events in SWAN. J Am Heart Assoc. 2021 Feb 2;10(3):e017416. doi: 10.1161/JAHA.120.017416. Epub 2021 Jan 20. PMID: 33470142; PMCID: PMC7955448.

Body Composition Changes

- Weight gain primarily due to aging and lifestyle
- Body composition change due to the menopause transition
  - Increased abdominal/visceral fat
  - Decrease in lean body mass (independent of age)
- Utilize similar weight management options as with other ages/stages of life
  - Exercise is negligible for weight loss, but highly effective at reducing lean muscle loss and reducing visceral adiposity
  - Increase protein intake to 30% of caloric needs and prioritize diet high in fiber from whole foods
  - Focus on health behaviors over goal weight; Set/adjust expectations (ie. “bodies change”)



Curr Obes Rep. 2024 Feb 28;13(2):352–363. doi: 10.1007/s13679-024-00555-2

Sleep Disturbance

Sleep Disturbances

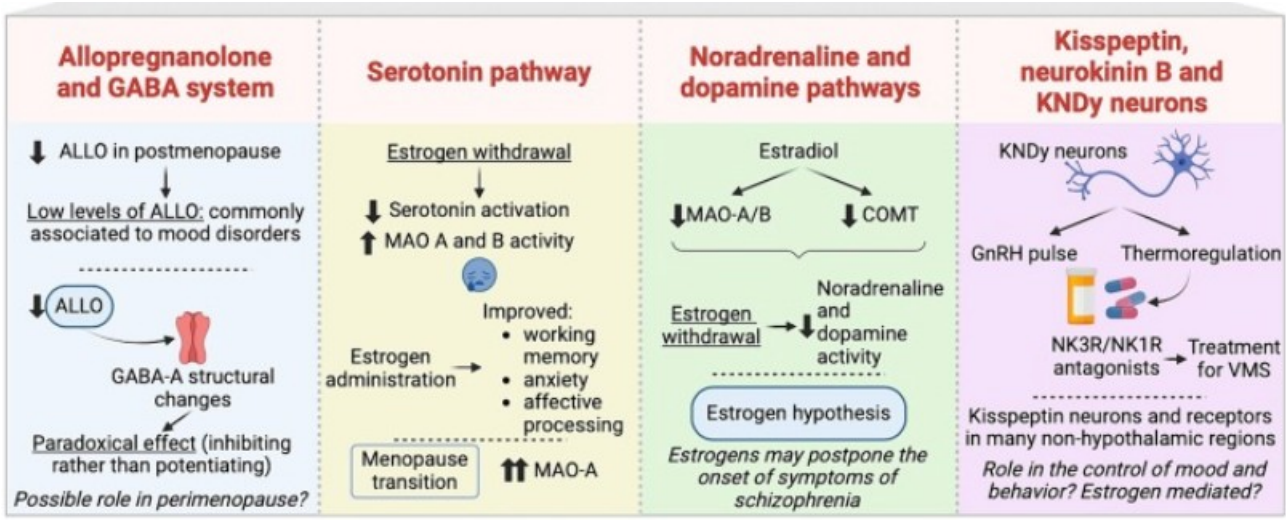
- Women with vasomotor symptoms are more likely to report disrupted sleep; sleep disturbance can be present whether or not women sense the hot flash
- SWAN: 38% of women aged 40-55 report difficulty sleeping; highest rates of sleeplessness in late perimenopause (45%) or surgical menopause (47%)
- Consider other contributing factors and/or co-morbidities:
  - Obstructive sleep apnea, restless leg syndrome, stress, anxiety/depression, medication, drugs/alcohol
- No form of hormone therapy is FDA approved to treat insomnia, but:
  - Oral estrogen improves nighttime restlessness and waking
  - Hormone therapy in general aids sleep quality by reducing hot flashes and night sweats
- Cognitive Behavioral Therapy for Insomnia (CBT-I) is first line
  - Effective in treating menopause-related sleep disturbances with long-lasting benefits
  - No head to head trials comparing effect sizes with hormone therapy

Nowakowski, Sara PhD, CBSM, DBSM1; Meers, Jessica M. MA2. Cognitive-behavior therapy for sleep disorders at midlife. Menopause 28(7):p 833-835, July 2021. | DOI: 10.1097/GME.0000000000001771

Mood and Cognitive Changes

Mood Changes

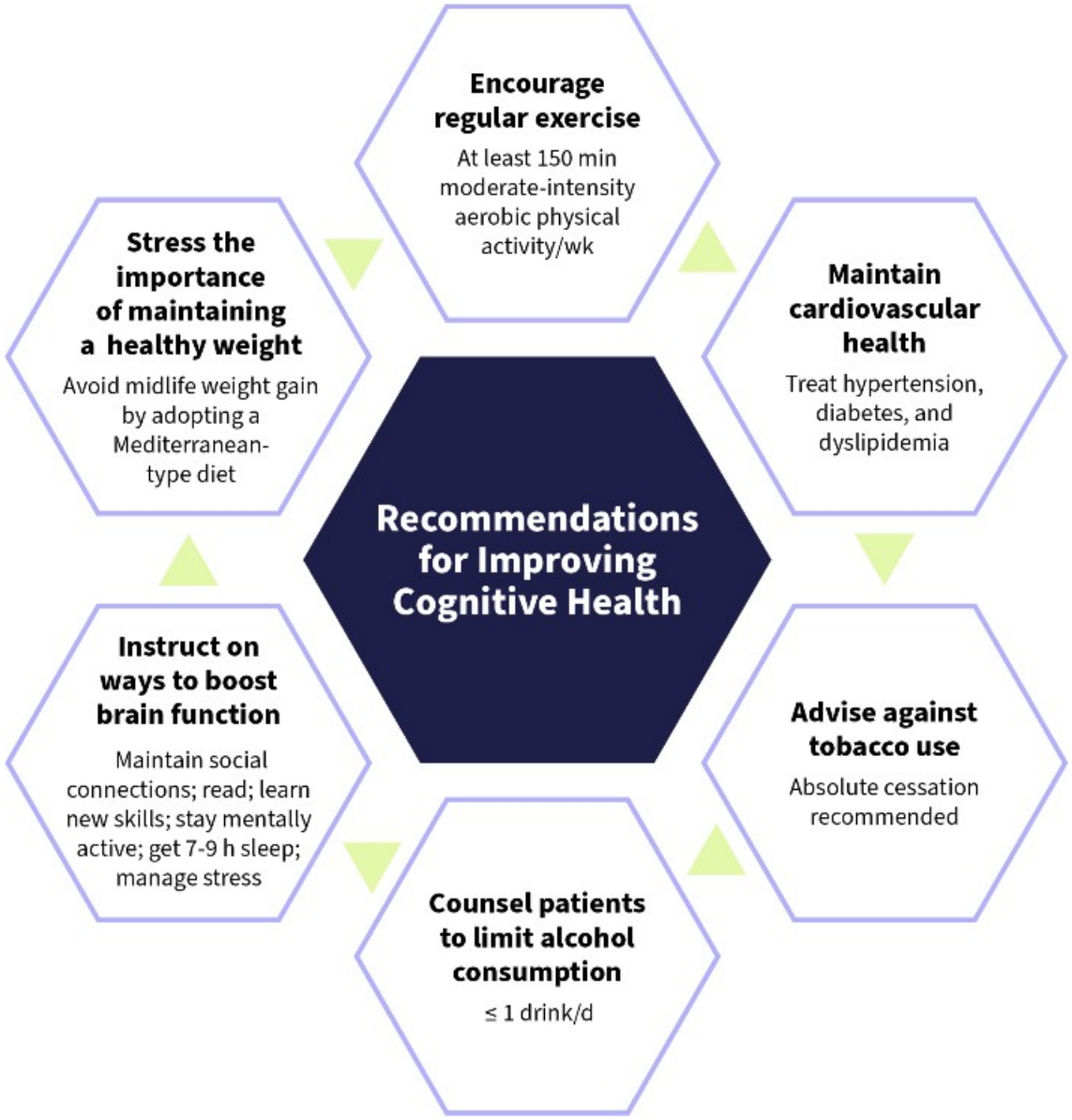
- Estrogen receptors are throughout the brain
  - Hypothalamus, PFC, hippocampus, brainstem
  - Areas involved in mood and cognitive regulation
- Depression and anxiety can be more severe in menopause
  - History of MDD associated with higher risk of depressive episodes during perimenopause
  - Bipolar disorder symptoms can worsen as well
- Antidepressants and psychotherapy are first line
- Hormone therapy
  - Efficacy of transdermal estrogen therapy for depressive disorders noted in some small trials with and without VMS
  - Estrogen therapy may augment clinical response to antidepressants



Cohen LS, et al. *Am J Psychiatry* 2003;160:1519-1522. doi: 10.1176/appi.ajp.160.8.1519; Joffe H, et al. *J Clin Endocrinol Metab* 2011;96:E1044–E1054. doi: 10.1210/jc.2010-2503; Morrison MF, et al. *Biol Psychiatry* 2004;55:406-412. doi: 10.1016/j.biopsych.2003.08.011; Rasgon NL, et al. *Am J Psychiatry* 2001;158:1738. doi: 10.1176/appi.ajp.158.10.1738; Rudolph I, et al. *Climacteric* 2004;7:301-311. doi: 10.1080/13697130400001802;https://doi.org/10.1016/j.maturitas.2024.108087

Cognitive Changes

- Menopause “brain fog” refers to attention and memory difficulties; not a sign of early dementia; typically improves postmenopause
- Studies link cognitive changes to estradiol levels as well as VMS, sleep disturbances and mood symptoms
  - Addressing other menopause symptoms may improve cognition
- Hormone therapy is not recommended for treatment or prevention of cognitive dysfunction at any age
  - No large scale trials in perimenopause
  - Effects between HT and cognition vary by formulation and timing of treatment



Andy C, et al. *Front Endocrinol (Lausanne)* 2024;15:1350318. doi: 10.3389/fendo.2024.1350318; Maki PM, et al. *Climacteric* 2022;25:570-578. doi: 10.1080/13697137.2022.2122792

Case Studies

Case Study #1

43-year-old woman experiencing intermittent hot flashes that are pretty mild and not that bothersome. Has had more trouble losing weight ever since having her second child five years ago. Still gets a monthly period, sometimes a couple days early or a couple days late. Occasionally has difficulty staying asleep. Waking up around 2-3 am. Started on citalopram 10 mg about a year ago for increasing anxiety. TSH was normal at that time. She feels okay overall, but wants her “hormone levels checked” to see if she is in perimenopause and wonders if she should start hormone therapy “to keep things from getting worse”. Another provider told her she couldn’t be in perimenopause because she was still getting a period.

	Menarche					FMP (0)				
Stage	-5	-4	-3b	-3a	-2	-1	+1 a	+1b	+1c	+2
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**Approximate expected level based on assays using current pituitary standard[67-69]

Case Study #1

- *43 years old*
- *Regular periods*
- *Mild intermittent hot flashes*
- *Difficulty losing weight*
- *Early morning waking*
- *Perimenopause? Hormones for prevention?*

- STRAW+10 – likely Stage -3a
  - Still in the “Reproductive Phase”
  - Discuss contraceptive options if patient does not desire pregnancy
- Perimenopausal symptoms can precede period irregularities
- Citalopram may be attenuating her hot flashes
  - Citalopram also associated with weight gain
- Hormone therapy does not “stop the clock”, but it can help patients manage the symptoms of the transition

Case Study #2

A 57-year-old woman with bothersome menopause symptoms, including frequent hot flashes and night sweats, sleep disturbances, and mood swings. The symptoms started 2 to 3 years ago, and she had her final menstrual period a little over a year ago. The patient is very active and adheres to a strict whole food, plant based diet. There is no significant past medical or family history. Last month she was seen by another healthcare professional who told her that she was “too old” for hormone therapy and to “get a portable fan and wear layers”.

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**Approximate expected level based on assays using current pituitary standard[67-69]

Case Study #2

- *57 years old*
- *Bothersome hot flashes, night sweats, sleep disturbance and mood swings*
- *Active with a heart healthy diet*
- *Postmenopausal since greater than 12 months from FMP*
- *"Too old" for menopause hormone therapy?*
- *Are hormones her only option?*

- STRAW+10 – likely Stage +1b
- Moderate to severe VMS are an FDA approved indication for hormone therapy
- "Timing hypothesis"
  - Within 10 years of FMP and age <60
- Assess for increased risk of CVD and breast cancer; risk/benefit discussion with patient
- Numerous non-hormone pharmacologic options to help patient's manage hot flashes:
  - SSRIs/SNRIs, Gabapentin, Feozolinant, etc
- New VMS in Stage +1c or +2 new work-up

Case Study #3

A 51-year-old woman presents to discuss menopause hormone therapy. Her final menstrual period was a little over 2 years ago. Initially, she experienced episodic hot flashes and night sweats, but she hasn't had any in the last couple months. She states, "even when I did have them, they weren't terribly bothersome." Her main concerns are weight gain, forgetfulness and "brain fog", and overall lack of energy. She has gained more than 20 lbs over the last couple years despite exercising several times a week and eating "mostly Keto". She is afraid that she is going to keep gaining weight and saw on social media that if she doesn't start hormone therapy she is more likely to get Alzheimer's dementia.

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	Early	Peak	Late		Early	Late	Early			Late
					Perimenopause					
Duration	*variable*				*variable*	1-3 years	2 years (1+1)		3-6 years	*Remaining lifespan*
PRINCIPAL CRITERIA										
Menstrual Cycle	Variable to regular	Regular	Regular	Subtle changes in Flow/ Length	*Variable Length* Persistent ≥7- day difference in length of consecutive cycles	Interval of amenorrhea of >=60 days				
SUPPORTIVE CRITERIA										
Endocrine FSH AMH Inhibin B			Normal Low Low	Variable* Low Low	↑ Variable* Low Low	↑ >25 IU/L** Low Low	↑ Variable* Low Low		Stabilizes Very Low Very Low	
Antral Follicle Count 2-10 mm			Low	Low	Low	**Low**	Very Low		Very Low	
DESCRIPTIVE CHARACTERISTICS										
Symptoms						Vasomotor symptoms *Likely*	Vasomotor symptoms *Most Likely*			*Increasing* symptoms of urogenital atrophy

* Blood draw on cycle days 2-5 = elevated

**Approximate expected level based on assays using current pituitary standard[67-69]

Case Study #3

- *51 years old*
- *Hot flashes resolved*
- *Weight gain, “brain fog”, fatigue*
- *Exercises and east “mostly Keto”*
- *Will she keep gaining weight?*
- *Is she less likely to get dementia if she starts hormone therapy?*

- STRAW+10 – likely Stage +1c
- Evidence does not support the use of hormone therapy for weight gain or cognitive changes
- “Brain fog” during perimenopause typically resolves postmenopause
- Heart healthy diet is a brain healthy diet
  - Whole food, plant predominant
  - Fruits, vegetables, whole grains (oatmeal not oat bars), beans/lentils, nuts/seeds
- Strength training can help attenuate the body composition changes with menopause

Penn Medicine
Lancaster General Hospital