

Bioidentical Hormones in Perimenopause

Why starting in the transition — not years after the last period — changes the benefit-risk story



AUTHOR

Dr. Maria Granzotto ND

Naturopathic Doctor • Women's Health & Hormones • Co-founder, Tri-Health

Vaughan / Woodbridge, Ontario

Educational review for the public and clinicians • September 2026

The short version

Perimenopause is not a short dress rehearsal for menopause. It is the years when estrogen and progesterone swing, then fall — often beginning in the early-to-mid forties. Hot flashes, wrecked sleep, anxiety, heavy or chaotic cycles, joint pain, and a thickening middle commonly start here, long before the last period.

Waiting until “you are fully menopausal” is the advice many women still hear. That advice was shaped by a trial of older women on a different hormone recipe than most clinics use today. For healthy symptomatic women under 60, or within 10 years of their last period, major menopause societies now say the benefit-risk ratio of hormone therapy is favorable.

“Bioidentical” in evidence-based practice means 17 β -estradiol (the human estrogen) plus micronized progesterone (the human progesterone) — preferably transdermal estradiol when clot risk matters. It does not automatically mean an unregulated custom cream from a compounding pharmacy.

Starting while vessels, bone, and brain are still responding to estrogen is the timing hypothesis. It is strongest for arteries and bone. It is not a promise that hormones prevent dementia or heart attacks if you start them at 68. Early is not the same as forever, and it is not for every woman.

Part I — For patients and the public

What perimenopause actually is

Menopause is one day: twelve months after the final menstrual period. The average age in North America is about 51 or 52. Perimenopause is the stretch before that day, when the ovaries become unreliable. Cycles lengthen, then bunch, then skip. Estradiol can spike higher than it did in the thirties, then crash. Progesterone, made after ovulation, is often the first hormone to go missing in months without a true ovulation.

That is why a woman can have night sweats, rage-crying, and a 10-day bleed while her FSH is still “normal.” The laboratory is a snapshot. The ovaries are a weather system. SWAN — the Study of Women's Health Across the Nation — showed that cycle length starts drifting years before the last period, and that up to 80% of women report hot flashes at some point in the transition. Frequent flashes last a median of 7.4 years, not the two years many pamphlets still imply.

If you wait for the official menopause date to take symptoms seriously, you have already spent several hard years without a plan.

Why “start early” is not a slogan

Three clocks start running in the late transition. None of them wait for your last period.

- **Bone.** SWAN found that the fastest bone-density loss begins about one year before the final period and runs hard for roughly three years (the “transmenopause”). Over ten years around that window, spine density falls about 10%. Women who lose more bone in the transition fracture more later. Waiting until a first fracture to discuss estrogen is late by definition.
- **Arteries.** Estrogen helps keep the lining of blood vessels flexible. After years without it, plaque is already there. Giving estrogen to a clean vessel is a different experiment from giving it to a stiff, calcified one. That is the timing hypothesis in one sentence.
- **Sleep, mood, and metabolic shape.** Night sweats fragment sleep. Poor sleep drives insulin resistance and belly fat. Midlife weight shift is not only calories. Estradiol decline changes where fat is stored. Treating flashes often treats the cascade that follows them.

The 2022 North American Menopause Society position statement is blunt: for healthy women younger than 60, or within 10 years of menopause, benefits of hormone therapy generally outweigh risks for bothersome hot flashes and for bone. After 60, or more than 10 years past the last period, the same drugs carry more stroke, clot, and heart-disease risk. Starting late is not the same medicine as starting on time.

What “bioidentical” should mean

The word is used two ways, and mixing them up is how clinics lose trust.

Body-identical hormones are molecules that match what the ovary made: 17 β -estradiol and micronized progesterone. These exist as regulated prescriptions — patches, gels, an oral estradiol-progesterone capsule, and oral micronized progesterone (often Prometrium). That is the evidence-based version of “bioidentical.”

Custom-compounded creams, troches, and pellet mixes are a different product class. Some women need compounding for a dose or allergy reason. Many compounded products are under- or over-dosed, and progesterone cream in particular has weak proof that it protects the lining of the uterus. ACOG and menopause societies prefer approved estradiol and micronized progesterone whenever they will do the job. A saliva kit plus a 40-ingredient cream is not automatically safer because the brochure says natural.

The regimen most of the newer safety data points toward is transdermal estradiol plus oral micronized progesterone if you still have a uterus. Transdermal estradiol skips the liver’s first pass, and large observational work (ESTHER and later syntheses) finds little or no extra clot risk compared with oral estrogen. Micronized progesterone looks kinder to breast and vessels than the synthetic progestin used in the Women’s Health Initiative (medroxyprogesterone acetate).

The trial that frightened a generation — and what it actually enrolled

The Women’s Health Initiative (WHI) started most women in their sixties on oral conjugated equine estrogen plus medroxyprogesterone acetate. That is not a 48-year-old on an estradiol patch and micronized progesterone. When WHI results landed in 2002, prescriptions collapsed. Women in perimenopause were told hormones cause breast cancer and heart attacks. The average participant was the wrong age, on the wrong recipe, for the question most midlife women are asking.

Re-analyses by age tell a different story. Women who started closer to menopause did not show the same heart-disease harm; some analyses showed fewer events. Estrogen-alone in women without a uterus even showed fewer breast cancers in long follow-up. None of that makes hormones a vitamin. It does mean the scare headline was not written for the woman who cannot sleep through a Tuesday in her forties.

What early treatment is for — and what it is not

Hormone therapy remains the most effective treatment for hot flashes and night sweats. It treats genitourinary syndrome of menopause (dryness, pain, recurrent urinary symptoms) better than moisturizer alone when symptoms are bothersome — and low-dose vaginal estrogen can be used even when systemic hormones are not. It prevents bone loss and reduces fractures.

It is not licensed as a first-line drug to prevent heart attacks or dementia. Cognition trials (KEEPS, ELITE cognitive arms, WHIMS in older women) did not prove that midlife hormones stop Alzheimer's. Starting after 65 for "brain protection" is the setting where WHIMS saw more dementia, not less. Early start looks neutral for cognition in healthy women, not magical.

A 2025 conference analysis of tens of millions of records suggested that estrogen begun in perimenopause associated with lower later rates of breast cancer and heart attack than never-use. That is intriguing and observational. It is not a reason to put every 42-year-old on estrogen. It is a reason to stop treating perimenopause as a waiting room.

Who should not start — or should start only with a specialist

- Current or recent breast cancer, unless an oncologist is driving the plan.
- Unexplained vaginal bleeding until it is investigated.
- Active clot, or a high-risk thrombophilia, especially if the only option is oral estrogen.
- Active liver disease, or cardiovascular disease that is already clinical — timing works against you here.

Smoking, obesity, and migraine with aura do not automatically forbid treatment. They usually push the prescription toward a patch or gel and a careful progestogen, not toward "nothing until you suffer more."

What a thoughtful start looks like

Labs help — estradiol, FSH, thyroid, iron, and sometimes a DUTCH or comprehensive hormone panel — but symptoms and cycle pattern decide more than a single number. In perimenopause, cyclic or pulsed progesterone can settle heavy bleeds and sleep before full continuous combined therapy is needed. Dose is the lowest that works. Review every 3–12 months. Add strength training, protein, and vitamin D because hormones are not a substitute for the rest of midlife physiology.

If you are in premature or early menopause (last period before 40, or 40–45), the recommendation is stronger: replace hormones at least until the average age of natural menopause unless there is a clear reason not to. The bone, heart, and mood costs of early estrogen loss are not theoretical.

Part II — For clinicians

Definitions that keep prescribing honest

- **Perimenopause / menopause transition (STRAW+10).** Variable cycle length, then ≥ 60 -day gaps. Hormonal chaos precedes the FMP by years. Do not require FSH >25 or 12 months of amenorrhea before treating disabling VMS.
- **Body-identical MHT.** 17 β -estradiol + micronized progesterone (or a levonorgestrel IUS for endometrial protection). Distinct from CEE/MPA and from unregulated multi-hormone compounds.
- **Timing / window hypothesis.** Net vascular effect of estrogen depends on the state of the endothelium at initiation. Early: slower CIMT progression. Late: neutral or harmful on CHD, stroke, VTE, dementia.

Guideline position, 2022–2025

NAMS 2022: most effective therapy for VMS and GSM; prevents bone loss and fracture. Favorable benefit–risk under age 60 or within 10 years of onset, no contraindications. Less favorable after that because absolute risks of CHD, stroke, VTE, and dementia rise. Transdermal routes and lower doses may reduce VTE and stroke. Continue in POI/early menopause at least to the mean age of menopause.

ESE 2025 menopause and perimenopause guideline: initiate MHT within 10 years of onset or under 60 for bothersome climacteric symptoms; inform patients that MHT prevents bone loss and may have positive cardiovascular effects; do not use MHT primarily for CVD prevention or as routine treatment of clinical depression.

The timing evidence, ranked

Vascular — moderate, consistent direction

ELITE (Hodis et al., NEJM 2016): oral 17 β -estradiol $\pm$ cyclic progesterone. CIMT progressed slower than placebo when therapy started <6 years after menopause (0.0044 vs 0.0078 mm/year, $P=0.008$). No CIMT benefit when started ≥ 10 years after ($P=0.29$). Interaction $P=0.007$. Coronary calcium did not differ. Surrogate endpoint, but the trial was built to test timing.

KEEPS: recently menopausal women, oral CEE or transdermal estradiol plus cyclic progesterone. Neutral CIMT; favorable vascular-function signals; no excess coronary events in a low-risk early cohort.

WHI age-stratified and Cochrane-style syntheses in women <60 or <10 years from menopause: CHD RR in the region of 0.5–0.8 and lower all-cause mortality in some pooled estimates, with higher VTE on oral estrogen. These are not a license to prescribe for primary prevention. They are why “hormones cause heart attacks” is the wrong sentence for a 52-year-old.

Bone — high

SWAN: BMD loss begins ~ 1 year before FMP; 7.4% of a 10.6% decade spine loss occurs in the 1-year-before to 2-years-after window. TBS (bone quality) starts falling ~ 1.5 years before FMP. MHT reduces hip, vertebral, and total fracture in RCT meta-analysis (roughly 20–37%). Estrogen is first-line skeletal protection in premature menopause until age ~ 52 , not a bisphosphonate by default.

Breast — formulation-dependent, not settled

WHI CEE+MPA increased breast cancer; CEE-alone did not, and long-term follow-up showed fewer cases. French E3N cohort: estrogen plus micronized progesterone was not associated with higher breast-cancer incidence in

the first five years, unlike estrogen plus synthetic progestins. Meta-analytic RR for micronized progesterone vs other progestogens has been reported around 0.67. Still observational. Counsel duration, mammographic density, and family history. Do not sell “bioidentical equals zero breast risk.”

VTE and stroke — route-dependent

Oral estrogen raises clotting-factor synthesis. Transdermal estradiol in ESTHER and subsequent reviews sits near baseline VTE risk. Micronized progesterone and dydrogesterone look safer than norethindrone progestogens and MPA. Prefer patch/gel in smokers, BMI ≥ 30 , prior VTE discussion, and migraine with aura.

Cognition — do not over-claim

WHIMS (start ≥ 65): more dementia with CEE+MPA. KEEPS and ELITE cognitive follow-up: no clear midlife benefit or harm. Window theory is weaker for brain than for CIMT. Treat VMS and sleep; do not prescribe estradiol as dementia prophylaxis.

Perimenopause-start observational data — hypothesis-generating

2025 Menopause Society presentation (large EHR cohort): estrogen use through perimenopause associated with substantially lower later breast-cancer and event odds versus never-use, with a less favorable stroke signal when start was delayed until after menopause. Residual confounding is likely. Quote it as supportive context, not as Level I.

Prescribing in the transition

Situation	Typical approach	Why	Watch
Early peri, cyclic, VMS + sleep	Transdermal E2 low dose $\pm$ luteal micronized P 200 mg $\times$ 12–14 d, or P-only at night	Preserve some cycling; P helps sleep and endometrium	Unscheduled bleeding; titrate E2 slowly
Late peri / postmenopausal, uterus in situ	Transdermal E2 + continuous micronized P 100 mg, or cyclic P; or LNG-IUS	Endometrial protection; continuous P if amenorrhea preferred	Spotting first 3–6 months
No uterus	Estradiol alone	No progestogen required	Dose to symptoms, not a target E2 of 400
GSM only	Low-dose vaginal E2 or DHEA	Local effect; minimal systemic exposure	Does not treat VMS or bone
POI / early menopause	Full replacement to $\sim$ age 51–52, then reassess	Observational CV, bone, cognitive benefit of treating the deficit	Do not apply late-WHI risk language here

Compounded bi-est/tri-est and topical progesterone as sole endometrial protection remain poorly supported. If compounding is used (allergy, unavailable dose), document why, measure serum levels when doses look implausible, and do not skip a progestogen that has endometrial data.

What remains uncertain

We still lack a large RCT of transdermal estradiol plus micronized progesterone started in early perimenopause with hard CV and breast endpoints at 10 years. ELITE used oral estradiol. KEEPS was underpowered for events. EHR studies of perimenopausal start cannot fully adjust for healthy-user bias. Duration beyond 5–7 years is individualized, not automatic. Androgens (testosterone) for desire have a narrower evidence base and are a separate consent.

How we approach this at the clinic

At Tri-Health, perimenopause is treated as a whole-person transition, not a prescription reflex. Hormone work sits beside cycle history, sleep, iron, thyroid, body composition (InBody), gut and metabolic health, and — when it fits — strength training and nutrition. Body-identical estradiol and micronized progesterone are the default molecules. Route follows risk. Dose follows symptoms. We do not wait for a commemorative last period if a woman is already losing sleep, bone trajectory, or her week.

This article is educational. It is not a prescription. Contraindications, unexplained bleeding, and cancer histories belong with a clinician who has examined the patient and the chart.

Selected references

The 2022 hormone therapy position statement of The North American Menopause Society. *Menopause*. 2022;29(7):767-794.

Hodis HN, et al. Vascular effects of early versus late postmenopausal treatment with estradiol. *N Engl J Med*. 2016;374:1221-1231. (ELITE)

Harman SM, et al. Arterial imaging outcomes and cardiovascular risk factors in recently menopausal women: the KEEPS trial. *Ann Intern Med*. 2014.

Manson JE, et al. Menopausal hormone therapy and health outcomes during the intervention and extended poststopping phases of the Women's Health Initiative. *JAMA* / subsequent WHI age-stratified reports.

Greendale GA, et al. Bone mineral density loss in relation to the final menstrual period: SWAN. *J Clin Endocrinol Metab* / *JBMR*. 2012.

SWAN. Bone health over the menopause transition. Fact sheet; trabecular bone score analyses JCEM 2020.

European Society of Endocrinology clinical practice guideline for evaluation and management of menopause and the perimenopause. *Eur J Endocrinol*. 2025;193(4):G49-.

Fournier A, et al. E3N cohort: estrogen-progestogen combinations and breast cancer; micronized progesterone analyses.

Canonica M, et al. ESTHER study: hormone therapy and venous thromboembolism by route of estrogen.

Prior JC / Hitchcock CL. Oral micronized progesterone for vasomotor symptoms. RCT evidence ~55% symptom reduction at 300 mg nightly.

ACOG Clinical Consensus. Compounded bioidentical menopausal hormone therapy. 2023.

Boardman HMP, et al. Cochrane / AHA-cited meta-analysis of hormone therapy and CHD by timing of initiation.

The Menopause Society 2025 Annual Meeting abstract: timing of estrogen therapy — perimenopausal benefits and postmenopausal risks (large EHR analysis).

Narrative reviews 2025–2026: estradiol plus micronized progesterone — VTE, breast, bone, and QoL (e.g., PMC12565450).

Avis NE, et al. Duration of menopausal vasomotor symptoms: SWAN. *JAMA Intern Med*. 2015; median 7.4 years.

Dr. Maria Granzotto ND • Tri-Health Wellness Centre • Vaughan / Woodbridge • trihealth.ca

Educational briefing. Not a prescription. Hormone therapy requires individualized assessment, endometrial protection when a uterus is present, and follow-up.