Understanding Menopausal Hormone Replacement Therapy: Estrogen Routes, Progesterone Roles, and Long-Term Considerations

Menopausal hormone therapy (MHT) remains one of the most effective tools for managing vasomotor symptoms, preserving bone density, and improving quality of life. Yet the details — oral vs transdermal estrogen, the role of progesterone, duration of therapy, and receptor biology — often raise questions.

History

Women's Health Initiative (WHI) started in the 1990s, an observational study to check the risk of coronary heart disease in postmenopausal women taking estrogens showed a 25% to 50% reduction compared to the risk in women not taking estrogens. An important goal of the study was to check the risks and benefit of estrogen treatment. The study was terminated early in 2004 by the National Institutes of Health by the recommendation of safety monitoring board (DSMB). Due to the increase in risks (hazard ratios: coronary heart disease, 1.29; invasive breast cancer, 1.26; stroke, 1.41; pulmonary embolism, 2.13; colorectal cancer, 0.63; hip fracture, 0.66), the Federal Food and Drug Administration (FDA) placed a box warning on all estrogen replacement therapy and estrogen-

progesterone replacement therapy products about the increased risk of breast cancer, endometrial cancer, cardiovascular disorders, and, probable dementia in women older than 65 years. (If the ratio is over 1, the risk is increased, if it is less then 1, the risk is decreased)

The new administration at the FDA held an expert panel on hormone treatment in July 2025 to discuss the matter to change the box warnings. According to many experts including the living members of the original WHI members, the safety of hormone replacement treatment (HRT) is not evidently safe. However, in November 2025, FDA announced its intention to remove most box warnings from the package inserts.

Cardiovascular prevention is not an indication

MHT should not be started for primary or secondary cardiovascular prevention at any age.

Breast cancer risk depends on regimen and duration

- Estrogen□only therapy (post□hysterectomy) shows neutral or even slightly favorable breast cancer risk in long□term follow□up.
- Combined estrogen–progestogen therapy increases risk with longer duration.
- Age itself is not the main determinant—duration and progestogen type matter more.

Estrogen Delivery Routes: Oral vs Transdermal vs Vaginal

Oral Estrogen

Oral estradiol is absorbed through the digestive tract and undergoes first-pass metabolism in the liver. This metabolic route increases clotting factors, inflammatory markers, and sex-hormone binding globulin. While oral estrogen can improve lipid profiles, it carries a higher risk of venous thromboembolism and stroke compared with non-oral routes.

Transdermal Estrogen

Transdermal patches, gels, and sprays deliver estradiol directly into systemic circulation. This bypasses the liver, resulting in:lower clotting risk more stable serum estradiol levels minimal impact on SHBG predictable dose–response for bone protection. Transdermal estradiol is often preferred for long-term systemic therapy. Unless there is a special situation, **monitoring blood hormone levels is not necessary.**

Vaginal Estrogen

Vaginal estradiol (tablets, creams, rings) is designed for local treatment of genitourinary symptoms. Systemic absorption is minimal, even with higher-dose creams. No clinical studies show that vaginal estradiol — including high-dose oral tablets used vaginally — can maintain serum estradiol levels above the threshold needed for bone preservation. Its

benefits remain localized to vaginal tissue, pH, lubrication, and urinary symptoms. If this method is to be used for reasons such as vaginal dryness or urinary incontinence, it should be planned for long-term use, and treatment should not be interrupted intermittently. Its effect on atrophic vaginitis does not appear before 15 days.

Estradiol Levels and Bone Density

To maintain bone strength after menopause, the body generally needs a certain minimum estrogen level, which transdermal therapy can achieve consistently. The lowest dose that improves vasomotor symptoms is not sufficient to protect bone health. A clinical review on estrogen therapy notes that estradiol doses sufficient to relieve hot flashes may not be high enough to protect bone, emphasizing that symptom relief does not guarantee adequate skeletal estrogen exposure. **However, unless there is a special situation, monitoring blood hormone levels is not necessary.** Random serum estrogen measurements are not reliable. Measuring estradiol in dried urine over a 24-hour period may help determine the average serum estrogen level and help avoid daily fluctuations after applying estrogen in cream or gel form.

Transdermal estradiol reliably reaches these levels in a dose-dependent manner. Vaginal estrogen does not. Oral estrogen can, but with higher systemic risks.

Duration of Hormone Therapy: Is It Lifelong?

Modern menopause societies no longer impose a strict time limit on hormone therapy. The outdated "5-year rule" has been abandoned.

Current consensus

- Therapy may continue as long as benefits outweigh risks.

- There is no mandatory stopping age, even beyond 60 or 65. However, the current consensus is that treatment should be continued **until the age of 60**. After that, patient consent and a more detailed examination of risk factors are required.
- For bone protection, long-term or lifelong therapy is often necessary because bone loss resumes quickly after discontinuation.
- For genitourinary symptoms, local estrogen is typically lifelong.
- The decision is individualized, based on symptoms, goals, and risk profile.

Estrogen Receptors After Menopause

Estrogen receptors (ER-α and ER-β) remain present and functional throughout the body long after menopause. Their expression patterns shift, but they do not disappear.

Bone Tissue

Bone cells retain estrogen receptors for life. Even decades after menopause, estrogen:

- reduces bone resorption
- slows bone turnover
- improves bone mineral density

This explains why women starting estrogen therapy later in life can still experience bone benefits.

The Role of Progesterone: Required or Optional?

Progesterone is added to estrogen therapy primarily to protect the endometrium from unopposed estrogen. If the uterus has been surgically removed, progesterone is not medically required.

When Progesterone May Still Be Used

Even without a uterus, some women choose micronized progesterone for:

- improved sleep
- reduced anxiety
- mood stabilization
- possible breast comfort

These effects stem from progesterone's neuroactive metabolites, particularly allopregnanolone, which enhances GABAergic activity.

Special Cases

Progesterone may be considered if:

- residual endometriosis remains
- a supracervical hysterectomy left endometrial tissue in the cervical stump

Otherwise, estrogen-only therapy is standard after hysterectomy.

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Micronized Progesterone vs Synthetic Progestins

These two categories differ profoundly in structure, receptor activity, and safety profile.

Micronized Progesterone

- Bioidentical to human progesterone
- Binds selectively to progesterone receptors
- Neutral cardiovascular profile
- Does not increase breast cancer risk in major cohort studies
- Improves sleep and reduces anxiety
- Better tolerated overall

Synthetic Progestins

- Structurally modified molecules
- Bind to multiple receptors (androgen, glucocorticoid, etc.)
- Some increase clotting risk
- Some worsen lipids
- Certain types (e.g., medroxyprogesterone acetate) are associated with higher breast cancer risk
- Do not produce calming neuroactive metabolites
- Large studies, including the E3N cohort, consistently show safer breast and cardiovascular profiles with micronized progesterone compared with synthetic progestins.

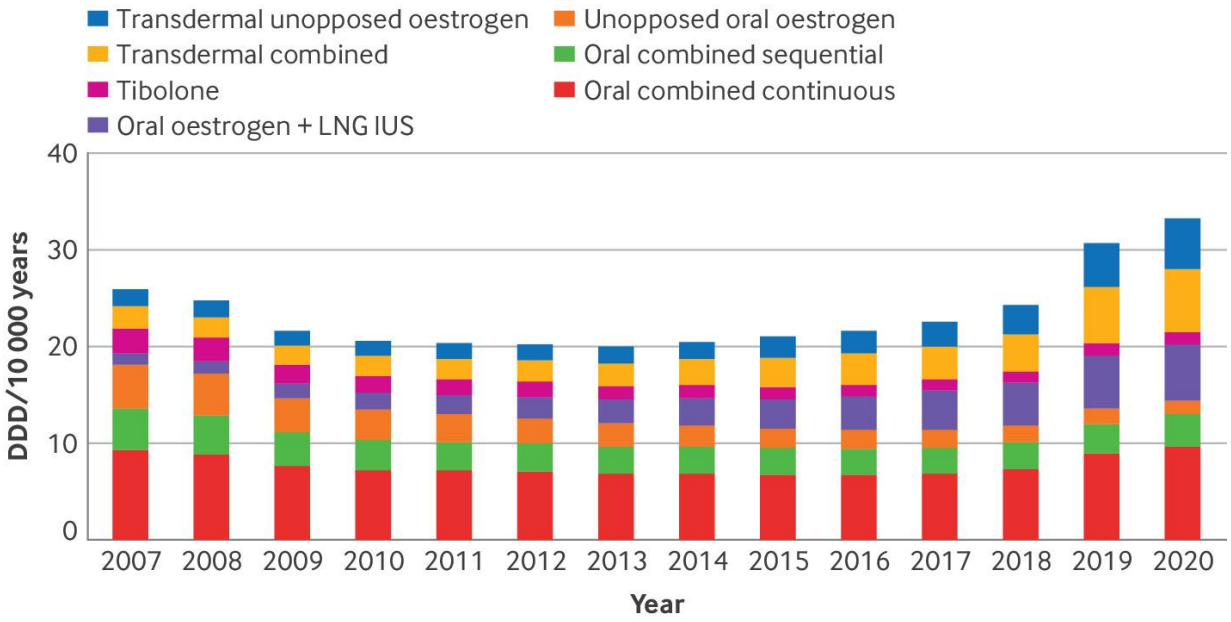
Conclusion

Menopausal hormone therapy is not a one-size-fits-all intervention. The choice of estrogen route, the decision to include progesterone, and the duration of therapy all depend on individual physiology, goals, and risk factors.

Key takeaways:

- Transdermal estrogen is the most reliable route for achieving systemic levels that protect bone.
- Vaginal estrogen is for local symptoms, not systemic replacement.
- Progesterone is unnecessary after hysterectomy, but micronized progesterone may offer optional neurocognitive and sleep benefits.
- Estrogen receptors remain functional for life, allowing estrogen to preserve bone even many years after menopause.
- Long-term therapy is acceptable when benefits outweigh risks.

Figure 1: Trends in menopausal hormone therapy use in Sweden among women aged 50-58 years. Defined daily dosages (DDD) of different types of menopausal hormone therapies from 2007 to 2020. LNG IUS=levonorgestrel intrauterine system



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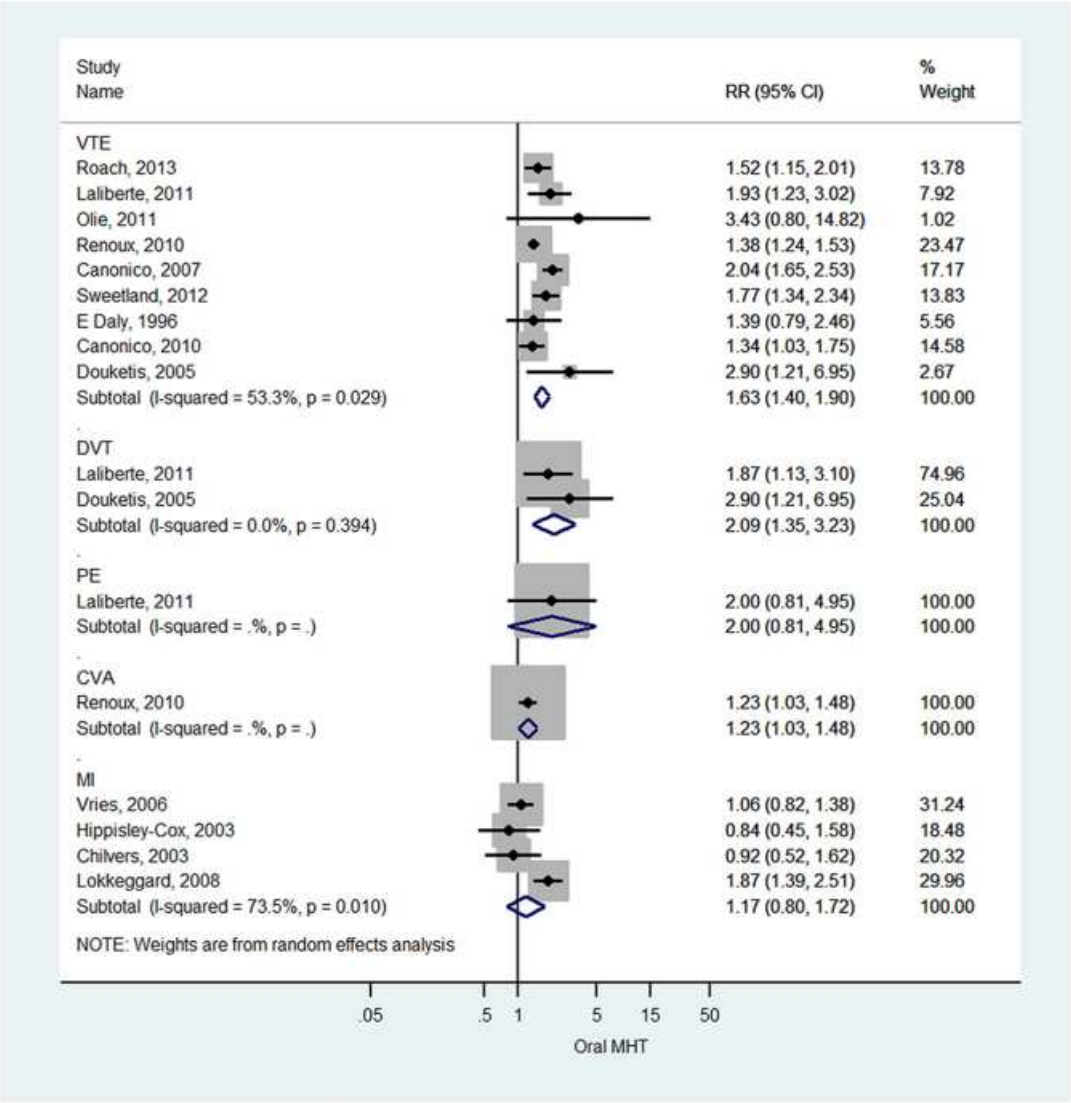

Figure 2. Meta-analysis of risk of vascular events in postmenopausal women using oral estrogen vs transdermal ET.

Considerations:

- Some experts, including the original member of the WHI study, do not approve that the risks are clearly identified and proposed more

studies about the risks. There is no randomized clinical trials comparing estrogen with placebo starting in perimenopause.

- No randomized studies comparing oral with patch formulations.