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# Perimenopause: Considerations for the Endocrinologist

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*Perimenopause is a clinically defined reproductive transition characterized by menstrual-cycle variability, fluctuating ovarian hormone secretion, and symptoms that often overlap with endocrine disease. Endocrinologists are well positioned to distinguish physiological reproductive aging from thyroid disease, hyperprolactinemia, pregnancy, premature ovarian insufficiency, and other causes of oligo-amenorrhea; to identify abnormal uterine bleeding requiring gynecologic evaluation; and to address the concurrent emergence of cardiometabolic and skeletal risk. Management should be symptom-directed and should explicitly separate the need for contraception and cycle control from the use of menopausal hormone therapy. This review presents a practical, evidence-based approach to diagnosis, risk assessment, and treatment for the endocrinology setting.*

## Introduction

Perimenopause spans the menopausal transition and the first year after the final menstrual period. The Stages of Reproductive Aging Workshop (STRAW)+10 framework defines early transition by a persistent difference, often a shortening, of at least seven days between consecutive cycle lengths, whereas late transition is characterized by amenorrhea lasting 60 days or longer.[1] The underlying physiology is driven not by a simple linear decline in estradiol, but by diminishing follicular reserve, which produces variable inhibin B and anti-Müllerian hormone, rising and increasingly erratic follicle-stimulating hormone (FSH), intermittent anovulation, and marked intra- and inter-cycle fluctuations in estradiol and ovulatory function.[1,2] Consequently, patients may experience heavy or irregular bleeding, vasomotor symptoms, sleep disruption, mood changes, breast tenderness, migraine, and genitourinary symptoms despite intermittently normal or high estradiol levels. For the endocrinologist, the central task is to recognize a physiological transition without attributing all midlife symptoms to menopause.

## Diagnosis: Clinical First, Selective Testing

In otherwise healthy patients aged 45 years or older, perimenopause is usually diagnosed clinically, making routine measurement of FSH, estradiol, anti-Müllerian hormone, or ovarian reserve unnecessary. A single FSH value is particularly unhelpful because secretion fluctuates and does not reliably predict either the final menstrual period or the need for contraception.[1,3] Laboratory testing should instead be reserved for evaluating a specific alternative diagnosis. Pregnancy testing is appropriate whenever pregnancy is biologically possible. Thyroid-stimulating hormone is appropriate in patients with new cycle disturbances or symptoms suggestive of thyroid dysfunction, whereas prolactin measurement is indicated for those with galactorrhea, marked oligomenorrhea, or amenorrhea. Targeted evaluation for hyperandrogenism or hypothalamic-pituitary disease should be guided by the phenotype. New-onset flushing accompanied by diarrhea, wheezing, episodic hypertension, or other atypical features warrants investigation beyond menopause.

Age influences the threshold for evaluation. Menstrual irregularity or symptoms of estrogen deficiency before age 40 should prompt assessment for premature ovarian insufficiency (POI), generally using one elevated FSH measurement above 25 IU/L and oligomenorrhea.[4] Between the ages of 40 and 45, early menopause should also be considered given the implications of prolonged estrogen deficiency for bone and cardiovascular health. Because hormonal contraception can obscure bleeding criteria and complicate laboratory interpretation, menstrual history before initiation of contraception, treatment goals, and age are more informative than indiscriminate testing.

## Abnormal Uterine Bleeding is Not an Endocrine Diagnosis

Although anovulation is common during the transition period, heavy, prolonged, intermenstrual, or postcoital bleeding should not be presumed physiological. Initial assessment should include pregnancy testing, complete blood count, ferritin, medication review, and evaluation for structural and non-structural causes using the polyp; adenomyosis; leiomyoma; malignancy and hyperplasia; coagulopathy; ovulatory dysfunction; endometrial; iatrogenic; and not yet classified (PALM–COEIN) framework. Thyroid testing is appropriate when clinically indicated, but thyroid disease should not become a default explanation that delays uterine assessment. Transvaginal ultrasonography is the preferred first-line imaging modality when structural pathology is suspected. Endometrial sampling is generally recommended for abnormal uterine bleeding in patients aged 45 years or older and in younger patients with persistent bleeding or risk factors for endometrial hyperplasia, including obesity, chronic anovulation, diabetes, or prolonged unopposed estrogen exposure.[5,6] Iron deficiency may precede anemia and should be treated while the bleeding source is investigated.

## A Cardiometabolic and Skeletal Inflection Point

Although midlife aging and ovarian aging occur together, longitudinal data support menopause-related changes in body composition and cardiovascular risk beyond those attributable to chronological aging alone. Across the transition, fat mass and waist circumference increase, lean mass declines, and adverse changes in lipids, blood pressure, insulin sensitivity, and metabolic syndrome become more common.[7,8] These observations should be interpreted without implying that menopause makes weight gain inevitable or that hormone therapy is a weight-loss treatment. Patients may benefit from attention to sleep, engaging in resistance exercise, improving dietary quality, ensuring protein adequacy, avoidance of alcohol and medications that promote weight gain, and evidence-based obesity treatment when indicated. For those with diabetes, changes in body composition and sleep may complicate glycemic control. Oral estrogen may affect triglycerides and binding proteins, whereas transdermal estradiol usually produces fewer hepatic metabolic effects.

Perimenopause provides an opportunity for a useful prevention visit. Evaluation should include blood pressure, adiposity, smoking and alcohol use, sleep, physical activity, and screening for diabetes and dyslipidemia according to local guidelines. A history of hypertensive disorders of pregnancy, gestational diabetes, preterm birth, or early menopause can further refine lifetime cardiovascular risk. Menopausal hormone therapy (MHT) should not be prescribed to prevent cardiovascular disease, but neither should it be

withheld from appropriately selected symptomatic patients who are younger than 60 years or within 10 years of menopause, a group in whom there is generally a more favourable benefit–risk profile than that for older initiators.[3,9]

Bone loss accelerates during late perimenopause and continues through the early postmenopausal years.[10] Routine dual-energy x-ray absorptiometry is not required solely because perimenopause has begun; however, earlier testing is appropriate for patients with POI, early menopause, fragility fracture, prolonged glucocorticoid exposure, low body weight, malabsorption, or other major risk factors. Counselling should emphasize resistance and weight-bearing exercise, adequate protein and calcium intake primarily from food, vitamin D sufficiency, fall prevention, smoking cessation, and moderation of alcohol use.

## Symptom Clusters and Competing Diagnoses

Vasomotor symptoms are often the most recognizable manifestation of perimenopause, but the clinical burden frequently arises from the interaction of multiple symptom clusters. Night sweats can fragment sleep, and poor sleep can worsen quality of life, energy, appetite regulation, concentration, and mood. Heavy menstrual bleeding can produce iron deficiency that can mimic or amplify fatigue and cognitive complaints. The term "not feeling like myself" has been tied to perimenopause.[11] A symptom inventory should therefore be paired with a basic differential rather than viewed as evidence of estrogen deficiency. Palpitations may accompany vasomotor symptoms such as hot flashes but still require appropriate cardiovascular assessment. Similarly, diffuse hair loss may reflect iron deficiency or thyroid disease; and new-onset severe headache, focal neurologic symptoms, or rapidly progressive cognitive change is not typical "brain fog."

Subjective cognitive symptoms during perimenopause commonly involve attention, word retrieval, and verbal learning difficulties. Longitudinal studies suggest a modest, time-limited decrement in verbal memory across the transition rather than a global loss of executive function.[12] Although reassurance is useful, active treatment of contributors—including insomnia, depression, vasomotor symptoms, medication effects, alcohol, anemia, thyroid dysfunction, and sleep-disordered breathing—are equally important. Obstructive sleep apnea may present in midlife women with insomnia, fatigue, mood changes, or morning headaches rather than classic witnessed apneas. Chronic insomnia should be diagnosed and treated as a distinct condition, with cognitive behavioural therapy for insomnia as first-line care. MHT is most likely to improve sleep when vasomotor symptoms are the principal driver.[13]

## Treatment: Separate Contraception from Hormone Therapy

Treatment should be driven by symptom burden, bleeding pattern, contraceptive requirements, comorbidities, and patient preferences. Combined hormonal contraception suppresses ovulation, stabilizes hormonal fluctuation, controls bleeding, and provides contraception, making it a useful option for medically eligible patients with irregular cycles and vasomotor symptoms. Eligibility must be reassessed over time, as age-related vascular risk accumulates, particularly in the presence of smoking, hypertension, migraine with aura, obesity, or thromboembolic history.[14] A 52 mg levonorgestrel intrauterine system is highly effective for both heavy bleeding and contraception, and systemic estrogen may be added for vasomotor symptoms, although local regulatory approval for endometrial protection with MHT varies.[15]

MHT does not reliably suppress ovulation and is not a contraceptive method. It becomes attractive when contraception is no longer required or can be provided separately, particularly during the late transition. In patients with a uterus, systemic estrogen requires adequate endometrial protection, often with a progestogen. In still-cycling patients, a sequential regimen often produces more predictable bleeding than continuous combined therapy, though either is acceptable when individualized to the patient's needs. Transdermal estradiol avoids first-pass hepatic effects and is generally preferred in patients with elevated triglycerides or increased risk of venous thromboembolism.[3,9] Oral micronized progesterone may offer a more favourable metabolic and thrombotic profile than some synthetic progestins, although the choice of regimen must ensure endometrial protection. Custom-compounded hormones and salivary hormone testing are not recommended when regulated products are available.[16]

For patients with vasomotor symptoms who cannot or prefer not to use estrogen, evidence-based options for vasomotor symptoms include neurokinin receptor antagonists, carefully selected selective serotonin reuptake inhibitors or serotonin-norepinephrine reuptake inhibitors, gabapentin, and oxybutynin.[3,17] Cognitive behavioural therapy and hypnosis can reduce the impact of vasomotor symptoms. Mood symptoms require screening for major depression, anxiety, suicidality, sleep disorders, and substance use. Although estradiol may help some patients with perimenopausal depression, it should not displace established psychiatric treatment when diagnostic criteria for a mood disorder are met.[18,19] Genitourinary symptoms can begin before the final menstrual period; moisturizers and lubricants are appropriate for mild symptoms, while low-dose vaginal estrogen or dehydroepiandrosterone is effective for persistent genitourinary syndrome with minimal systemic absorption.[3]

## Practical Endocrine Follow-up

Follow-up at approximately three months permits assessment of symptom response, bleeding patterns, blood pressure, adherence, and adverse effects, with subsequent monitoring individualized to clinical need. Persistent or new unscheduled bleeding requires evaluation rather than repeated empiric hormone adjustment. The endocrinologist should also revisit contraception requirements because fertility declines but does not disappear until menopause is confirmed. For contraceptive purposes, one year of amenorrhea in those aged over 50 years is acceptable, or two years before age 50. Treatment duration should not be governed by an arbitrary age threshold; instead, the benefits, risks, dose, route of therapy, and the ongoing indication should be reviewed periodically.[3,9]

## Conclusion

Perimenopause is best approached as a dynamic clinical transition rather than a laboratory diagnosis. Endocrinologists contribute particular value by excluding endocrine mimics selectively, recognizing POI and early menopause, integrating bone and cardiometabolic prevention, and prescribing hormone therapy with attention to route, progestogen, and contraceptive needs. Equally important is recognizing when abnormal bleeding or atypical symptoms require gynecologic or broader medical investigation. A structured, individualized approach can relieve symptoms while using midlife as an opportunity for long-term health protection.

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## Financial Disclosures

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