From perimenopause to menopause: Science, self-care, and support for a healthier you


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Abstract

Menopause, a natural biological transition, significantly impacts women's health due to declining estrogen levels. This hormonal shift contributes to metabolic syndrome, cardiovascular disease, osteoporosis, vasomotor symptoms, mood disturbances, sleep disorders, and sexual dysfunction. Management strategies include menopausal hormone therapy (MHT), nonhormonal medications, and lifestyle interventions. While MHT remains the most effective treatment, risks such as breast cancer and thromboembolism necessitate individualized approaches. Emerging treatments, including estetrol and neurokinin 3 receptor antagonists, offer promising alternatives. Comprehensive care involving screening, symptom tracking, and risk assessment is crucial for improving postmenopausal quality of life.

Keywords: Menopausal Hormone Therapy (MHT), Vasomotor Symptoms, Osteoporosis, Nonhormonal Treatment, Estetrol, Neurokinin 3 Receptor Antagonists

1. Introduction

Aging leads to reproductive decline in vertebrates, but certain whales and humans experience menopause and live for years post-transition. Menopause, confirmed after 12 months without menstruation (1), brings physiological changes affecting long-term health. In the U.S., it typically occurs between 45 and 51 years, lasting 7 to 14 years. Women experiencing menopause before 42 have double the risk of stroke (2), and postmenopausal women face higher risks of stroke and cardiac arrest, contributing to cognitive decline (3). Estrogen decline during menopause is linked to mild cognitive dysfunction and may indicate early Alzheimer's disease (AD) (4). It also triggers chronic inflammation, accelerating ovarian and brain aging (5). Studying menopause is challenging due to genetic, lifestyle, and environmental factors (6). Since rodents do not naturally undergo menopause, models are used to simulate conditions.

Progesterone and estrogen (estrone [E1], 17β-estradiol [E2], and estriol [E3]) levels decrease during menopause, but follicle-stimulating hormone (FSH) and luteinizing hormone (LH) levels rise (7). This increases the risk of heart disease, osteoporosis, diabetes, stroke, and Alzheimer's disease (8), as well as extra fat in the abdomen, cholesterol, and body mass index (9). Hormone replacement therapy (HRT) trials, such as the Women's Health Initiative (WHI), Heart and Estrogen/Progestin Replacement Study (HERS), and Women's Estrogen for Stroke Trial (WEST), show no significant reduction in stroke or cognitive decline risks (10), and are associated with cardiovascular disease and breast cancer, despite estrogen's anti-inflammatory benefits (11).

2. Menopausal transition process

The American Society for Reproductive Medicine's Stages of Reproductive Aging Workshop (STRAW) divides a woman's reproductive life into seven stages, ranging from menarche to postmenopause (1). In the U.S., 1.3 million women reach menopause annually, with the transition lasting up to 14 years. Given that women's life expectancy exceeds 80 years, many spend one-third of their lives postmenopausal, facing immune, metabolic, and neurodegenerative risks (12). Additionally, 1% experience premature menopause before 40. Genetics play a crucial role, and sex chromosome abnormalities may contribute to ovarian failure (13,14).

Immune function, bone health, and cognition are all impacted by estrogen decline, whether it is natural or the result of oophorectomy (15). Amenorrhea, elevated gonadotropins, and estrogen deficiency before the age of 40 define premature menopause, which increases the risk of early mortality, neurological diseases, sexual dysfunction, mood disorders, osteoporosis, ischemic heart disease, and infertility (14). Environmental xenoestrogens such as Bisphenol A (BPA) and phthalates disrupt estrogen activity and promote inflammation in the central nervous system (16). These substances mimic or block hormones, resulting in epigenetic changes that deplete ovarian reserves and shorten reproductive lifespan (17).

3. Systemic changes

3.1. Metabolic changes

- Estrogen promotes fat breakdown, while testosterone encourages visceral fat accumulation.
- Menopause increases free testosterone and abdominal fat while decreasing sex hormone-binding globulin (SHBG).
- This change increases the risk of diabetes, heart disease, and stroke by promoting insulin resistance and metabolic syndrome (18).

3.2. Vasomotor symptoms

- Hot flushes cause sudden warmth, palpitations, and sweating, leading to distress and sleep disturbances.
- Prevalence increases from 6–13% premenopause to 79% postmenopause (19).
- A more powerful indicator is elevated follicle-stimulating hormone (FSH) levels rather than estradiol withdrawal (20).
- Influenced by race, BMI, smoking, depression, and alcohol intake.

3.3. Mood and psychiatric changes

- Psychological distress peaks in early menopause (28.9%) and declines postmenopause (22%) (21).
- Major depressive episodes affect weight, sleep, and cognition, often going undiagnosed.

3.4. Sleep disturbances

- Sleep issues include difficulty falling asleep, early awakenings, and interruptions.
- Factors include vasomotor symptoms, mood swings, stress, obesity, and metabolic syndrome.

3.5. Sexual concerns & contraception

- Low estradiol leads to vaginal dryness; fluctuating testosterone affects libido (22).
- Combined oral contraceptives (COCs) help manage symptoms but increase cardiovascular risks (23).

3.6. Genitourinary symptoms

- Vaginal dryness increases from 3% (reproductive stage) to 47% (postmenopause).
- Estrogen decline weakens pelvic structures, causing infections, incontinence, and prolapse.

3.7. Skeletal symptoms

- Menopause accelerates bone loss, increasing fracture risk.

- FSH and gonadal peptides influence bone density (24).
- Vitamin D and calcium supplementation are recommended.

4. Managing menopausal symptoms

Managing menopausal symptoms requires assessing overall health, symptoms, and risks for conditions like heart disease and osteoporosis. Screening and preventive measures are essential. Tracking menstrual history during perimenopause is crucial for identifying abnormal bleeding before considering menopausal hormone therapy (MHT). Treatment includes lifestyle changes, medications (hormonal and non-hormonal), and contraception assessment if needed.

Premature ovarian insufficiency increases health concerns for women and requires extensive management. Until the typical menopausal age, MHT is advised (unless contraindicated) to lower the risk of osteoporosis and heart disease (25). After weighing the advantages and disadvantages, MHT is the most successful treatment and is usually safe (26). In women under 60, estrogen treatment also aids in the management of osteoporosis or reduced bone density (27).

4.1. Non-pharmacological approaches

Lifestyle changes such as regular exercise, weight control, and alcohol reduction increase overall well-being but may not directly reduce symptoms. Hot flashes can be controlled and sleep quality enhanced using cognitive behavioral treatment (CBT) (28).

4.2. Menopausal hormone therapy (MHT)

MHT improves mood, sleep, and cognitive function while successfully lowering hot flashes. The MHT regimen consists of the following:

- Estrogen-only therapy (for post-hysterectomy women to prevent endometrial problems).
- For women who have uterus, combined estrogen-progestogen therapy:
    - Cyclic MHT: Intermittent progestogen and continuous estrogen.
    - Continuous combined MHT: Daily administration of both hormones.
- Tibolone: Good for postmenopausal ladies, especially those who don't have much libido.

Women should be informed about potential side effects like nausea and breast tenderness. A follow-up after 6–12 weeks allows dosage adjustments, with annual reviews ensuring treatment suitability (29). Cyclic MHT may cause regular vaginal bleeding, which typically stabilizes. Persistent heavy bleeding after six months requires evaluation. MHT duration is individualized, with counseling on long-term risks (Australasian Menopause Society).

4.2.1. Estrogen in MHT

The main component of MHT, estrogen, usually consists of conjugated equine estrogens or estradiol (30). Estradiol comes in oral, transdermal, and gel formulations and is recommended because it resembles natural estrogen. A low-to-medium dosage is used at the beginning of treatment and is modified according to symptoms. Genitourinary problems like vaginal dryness and urinary tract infections are successfully alleviated with estrogen(31). Although systemic MHT takes care of these problems, some women need extra low-dose vaginal estrogen (tablets, pessaries, creams), meaning progestogen is not necessary (30).

4.2.2. Progestogens and combination therapy

Progestogens inhibit endometrial hyperplasia in women who have uterus. MHT type depending on menopause status:

- Cyclic MHT: A progestogen given every 12–14 days for perimenopausal women.
- For postmenopausal women, continuous combined MHT entails taking both hormones every day.

Cyclical MHT is recommended prior to switching to continuous medication after a year since perimenopausal women on continuous MHT may develop irregular bleeding. There are other progestogens with different characteristics, such as norethisterone, dydrogesterone,

drospirenone, and micronized progesterone (32). Compared to previous progestogens, micronized progesterone and dydrogesterone may have a lower risk of breast cancer (33).

Progestogens, which contain norethisterone and estradiol, are sold as transdermal patches, oral tablets, and capsules. An alternative is the levonorgestrel-releasing intrauterine device (IUD), which provides contraception and relief from heavy bleeding and can be used with estrogen for up to five years. Combination hormonal contraception, which relieves symptoms and regulates the cycle, may be an option for women under 50.

4.2.3. Tibolone

Postmenopausal women with reduced libido benefit from using tibolone, a synthetic steroid with estrogenic, progestogenic, and androgenic properties. The usual dosage is 2.5 mg per day; lesser dosages can prevent bone fractures. Because of the danger of bleeding, tibolone should be started a year after menopause. Due to the risk of stroke, it is not advised for women over 60 and contraindicated in those with a history of breast cancer (34).

5.The risk of cardiovascular disease and MHT

Menopause raises the risk of cardiovascular disease. According to the "timing hypothesis," which postulates that there are cardiovascular advantages to commencing MHT early, women who begin MHT before the age of 60 or within ten years after menopause had lower rates of heart disease risk and mortality (35,36). MHT helps women with premature ovarian insufficiency but is not advised for major heart disease prevention.

5.1. Contraindications to MHT

MHT is unsuitable for women with:

- Unexplained vaginal bleeding
- Breast or endometrial cancer history
- Recent cardiovascular events (e.g., heart attack, stroke)
- Blood clot disorders

Transdermal estrogen is a safer alternative for women with:

- Atherosclerotic heart disease
- Migraine with aura
- Hypertension or high cholesterol
- Increased blood clot risk
- Liver disease

This individualized approach minimizes risks. Other contradictions for MHT are given in Table 1.

5.2. MHT-related risk

MHT hazards are minimal and exceeded by advantages for the majority of women under 60 or within ten years after menopause (29). Table 1 lists the circumstances for which caution is advised while prescribing MHT.

Table 1. Menopausal hormone treatment (MHT) precautions

MHT contraindications	Situations in which using MHT with caution is advised
• Hormone-dependent malignancies, such as endometrial and breast tumors [NB1]. • Unidentified vaginal hemorrhage • Acute venous thromboembolism [NB2] • Acute cardiovascular event • Porphyria tarda cutanea • Severe liver damage	• Previous myocardial infarction, transient ischemic attack, or stroke [NB3] [NB4] • Venous thromboembolism risk is high [NB3]. • Liver disease in progress [NB3] • Aura-accompanied migraine [NB3] • Hypertriglyceridemia [NB3] • Diseases of the liver and kidneys [NB3] • Age over 65 and no history of MHT use • High risk of breast cancer1

NB1: Patients who have had stage 1 endometrial cancer treated can usually safely utilize MHT.
NB2: If the patient is anticoagulated, think about using transdermal estrogen for MHT.
NB3: Transdermal estrogen is recommended for MHT; use cautious when taking oral estrogen.
NB4: Using MHT is not contraindicated in cases of treated hypertension.

5.3. Breast cancer risk

A higher incidence of breast cancer was associated with the combined MHT (medroxyprogesterone acetate + conjugated equine estrogens) in the Women's Health Initiative studies. A decreased risk was observed with estrogen-only therapy, indicating the role of progestogens (37). Higher risk is correlated with longer MHT use (32). Micronized progesterone and dydrogesterone may be less likely to cause breast cancer than older progestogens, according to observational research (33).

5.4. Blood clot risk

The liver's processing of oral estrogen raises the generation of clotting factors, which increases the risk of venous thromboembolism (VTE) by two to three times while the absolute risk is still modest. More research is required to determine whether the newer estrogens, such as estetrol and estradiol, have a lower risk of clotting. Transdermal estrogen (patches, gels) is advised for women with a high cardiovascular risk because it does not raise the risk of clots (38).

6. Nonhormonal treatment options

Nonhormonal drugs can treat symptoms in women who are unable or unwilling to take MHT; however, they may have negative effects and do not provide the heart and bone benefits of estrogen.
Table 2. Provides a list of typical dosages for nonhormonal drugs used to treat menopausal vasomotor symptoms.

Table 2. Nonhormonal medications for symptoms related to vasomotor

Medication [NB1]	The dosage	Negative consequences
Serotonin and Noradrenaline Reuptake Inhibitors (SNRIs)		
Desvenlafaxine	25–150 mg taken once a day	nausea, vertigo, and sexual dysfunction
Venlafaxine	37.5–150 mg taken orally each day	
Selective Serotonin Reuptake Inhibitors (SSRIs)		
Citalopram	10 to 20 mg taken orally each day	nausea, vertigo, and sexual dysfunction
Escitalopram	5 to 20 mg taken orally each day	
Paroxetine [NB2]	10 to 25 mg taken orally each day	
Other Medications		
Clonidine [NB3]	25 to 75 mg orally administered twice a day	feeling faint, fatigue, and constipation
Gabapentin	100 to 900 mg taken orally per day in three separate doses	fatigue, feeling faint, and probable withdrawal symptoms
Oxybutynin [NB4]	2.5 to 5 mg taken twice a day orally	weakened visual abilities, sleepiness, and dry mouth
NB1: Clonidine is the only medication in the table that is not approved by the Therapeutic Goods Administration to treat vasomotor symptoms. NB2: Tamoxifen and paroxetine shouldn't be used together as this reduces the effectiveness of tamoxifen by inhibiting cytochrome P450 2D6. NB3: Due to the negative effects of clonidine, it is no longer advised to take it. NB4: Oxybutynin may have positive effects for overactive bladder symptoms, but it may also have negative consequences, especially on cognitive decline in older adults (28).		

7. New & Emerging Treatments

- Estetrol: A naturally occurring estrogen that may have less of an impact on the liver and breast (39).
- Nonhormonal remedies for hot flashes include neurokinin 3 receptor antagonists. The fezolinetant trial conducted in 2023 demonstrated good tolerability and efficacy (40).

8. Conclusion

A variety of health issues arise during menopause, necessitating specialized management techniques. Although MHT relieves symptoms, it is important to assess risk factors including cardiovascular hazards, thromboembolism, and breast cancer to guarantee safety. Nonhormonal substitutes, such as gabapentin, clonidine, selective serotonin reuptake inhibitors (SSRIs), and serotonin-norepinephrine reuptake inhibitors (SNRIs), provide extra symptom alleviation but do not have the preventive effects of estrogen. Overall well-being is enhanced by lifestyle changes like stress management, exercise, and food. New treatments like estetrol and neurokinin 3 receptor antagonists have the potential to be safer and more efficient. Optimizing health outcomes for women going through menopause requires a patient-centered approach that includes routine screening and individualized care.

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