

Knowledge gaps and challenges in care for menopausal women

The lack of discussion in society, and the lack of clinician knowledge around the menopausal transition and its overall effects for women, result in too many women not feeling empowered to seek help for and address their disruptive symptoms

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The transition to menopause begins with ovarian fluctuation and hormonal changes, often beginning before significant changes in menstruation. Reproductive aging with loss of follicular activity progresses over a wide age range (42 to 58 years) with an average onset at approximately age 47, ranging from 4 to 8 years. Although most women have heard about menopause, defined as 12 months after the last period, they often lack understanding about perimenopause or that the menopausal transition usually begins 5 years before menopause.¹

Perimenopause, defined as early and late menopause transition stages, may be viewed as a window of potential vulnerability for women who develop or have worsening menstrual-related mood disorders. Over time, hormonal fluctuations often lead to menstrual cycle irregularity (either shorter or longer). Changes occurring during perimenopause may be confusing as it may not

be clear whether symptoms are related to menopause, aging, or stress. Often not recognized or treated adequately, perimenopausal symptoms may be challenging to navigate for both women and clinicians.

The perimenopausal process is often even more confusing for women with early menopause—whether due to bilateral oophorectomy, chemotherapy or radiation therapy, genetics, or an autoimmune process—because of lack of recognition that an early menopausal transition is occurring or what solutions are available for symptoms. While there is support in the workplace for women during pregnancy and breastfeeding, there remains little support or recognition for the oft challenging perimenopausal transition leading to menopause.

Perimenopause: Common symptoms and treatments

Symptoms may be related to either estrogen level deficiency or excess during perimenopause, and these level changes may even occur within the same cycle.

Cyclic breast tenderness may develop, worsened by caffeine or high salt intake (which can be potentially improved, although without clinical trial evidence, with decreased caffeine or a trial of evening primrose oil or vitamin E).

Changes in menstrual flow and frequency of menses are typical. Flow may be lighter or heavier, longer or shorter, and

IN THIS ARTICLE

Myths and truths of menopause

page 24

Extended use of HT

page 25

Knowledge gaps

page 26



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The author reports participating in a multicenter clinical trial on nonhormone therapy for hot flashes, for which the University of Virginia received fees from Bayer.

doi: 10.12788/obgm.0203

there may be cycle variability, missed menses, or midcycle spotting.² Bleeding may be heavy, with or without cramping. In addition to imaging with vaginal ultrasonography or hysteroscopy to identify structural issues, symptoms may be managed with nonsteroidal anti-inflammatory drugs (NSAIDs), hormonal therapy (HT) with short hormone-free interval contraceptives, oral progestogens, or progestin intrauterine systems. Newer medical treatments include antifibrinolytic drugs and selective progesterone-receptor modulators. Uterine ablation to decrease or stop bleeding is effective if there are no structural abnormalities, such as fibroids or polyps or the presence of adenomyosis, where glands will regrow into the endometrium after ablation. Endometrial biopsy is indicated for persistent abnormal uterine bleeding or those with risk factors such as chronic anovulation.

Worsening headaches or menstrual migraines may be triggered by hormonal changes, which may respond to NSAIDs; dihydroergotamine; triptans; the combination of aspirin, acetaminophen, and caffeine; or estrogen the week before menses. For women taking oral contraceptives (OCPs), adding estradiol the week before menses, or using the OCP continuously, may decrease headache frequency. These short-term prophylactic strategies during the perimenstrual time are often effective. If not, preventive therapy is available for women with frequent, severe headaches.

Mood complaints and poor sleep are independently associated with menstrual irregularity, and can lead to fatigue or anxiety, worsening premenstrual syndrome, or depressive moods. Sleep is disrupted premenstrually for up to one-third of women, and sleep disruption is particularly prevalent in those with premenstrual mood disorders and worsens during perimenopause.³

Reproductive hormones act on the neurotransmitter systems in the brain involved in mood regulation and emotion. The fluctuating hormones occurring during perimenopause may exacerbate pre-existing menstrual-related mood disorders. A subset of women experience depressive moods

due to perimenopausal elevations in ovarian hormones.⁴ Others may exhibit increased mood sensitivity with the ovarian hormone withdrawal accompanying late menopause transition and early postmenopausal phase.⁵ There is significant comorbidity between premenstrual mood disorder (PMDD) and postpartum depression.⁶ During perimenopause and early menopause, clinicians should ask about prior hormonally-related depression (puberty, postpartum) and recognize that current or past premenstrual syndrome may worsen into a more severe premenstrual dysphoric disorder. Evidence-based treatments for PMDD include selective serotonin reuptake inhibitors (SSRIs); either taken continuously or only during the luteal phase; drospirenone-containing oral contraceptives, often with shorter pill-free intervals; GnRH analogues with or without hormone add-back; and cognitive behavioral therapy.⁷ For women whose perimenopausal moods improve with HT or develop worsened mood sensitivity with ovarian hormone withdrawal, clinicians should recognize that mood may worsen when treatment is ceased.⁵

Menopausal symptoms

Vasomotor symptoms (VMS), hot flashes, or night sweats occur in up to 75% of women as they develop more menstrual irregularity and move closer to their final period and menopause.

Hot flashes are transient episodes of flushing with the sensation of warmth (up to intense heat) on the upper body and face or head, often associated with sweating, chills or flushing, an increase in heart rate, and lowered blood pressure. Hot flashes can sometimes be preceded by an intense feeling of dread, followed by rapid heat dissipation. The etiology of hot flashes is still not clear, but the neurokinin receptors are involved. They are related to small fluctuations in core body temperature superimposed on a narrow thermoneutral zone in symptomatic women. Hot flashes are triggered when core body temperature rises above the upper (sweating) threshold. Shivering occurs if the

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Fluctuating hormone levels during perimenopause may exacerbate pre-existing menstrual-related mood disorders, with a subset of women experiencing depressive moods or exhibiting increased mood sensitivity

core body temperature falls below the lower threshold. Sleep may be disrupted, with less rapid eye movement (REM) sleep, and associated with throwing covers on and off or changing sheets or nightclothes. On average, hot flashes last 7.2 years,⁸ and they are more bothersome if night sweats interfere with sleep or disrupt performance during the day. In the Stages of Reproductive Aging Workshop (STRAW + 10), women reported VMS within 1-3 years after the menopausal transition.⁸ Four trajectories of hot flashes were identified in the Study of Women's Health Across the Nation (SWAN) trial,⁹ including low levels throughout the menopause transition, early onset, late onset, and a group which had frequent hot flashes, starting early and lasting longer. Serum estrogen levels were not predictive of hot flash frequency or severity.

Hot flashes have been associated with low levels of exercise, cigarette smoking, high follicle-stimulating hormone levels and low estradiol levels, increasing body mass index, ethnicity (with hot flashes more common among Black and Hispanic women), low socioeconomic status, prior PMDD, anxiety, perceived stress, and depression.⁸ Women with a history of premenstrual syndrome, stress, sexual dysfunction, physical inactivity, or hot flashes are more vulnerable to depressive symptoms during perimenopause and early menopause.⁵

Depression may co-occur or overlap with menopause symptoms. Diagnosis involves menopausal stage, co-occurring psychiatric and menopause symptoms, psychosocial stressors, and a validated screening tool such as PQ9. Treatments for perimenopausal depression, such as antidepressants, psychotherapy, or cognitive behavioral therapy, are recommended first line for perimenopausal depression. Estrogen therapy has not been approved to treat perimenopausal depression but appears to have antidepressant effects in perimenopausal women, particularly those with bothersome vasomotor symptoms.⁵

Anxiety can worsen during menopause, and may respond to calming apps, meditation, cognitive behavioral therapy, hypnosis, yoga or tai chi, HT, or antianxiety medications.

TABLE 1 Top changes women report during perimenopause

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- Irregular menstruation and ovulation cycles
 - Loss of sexual urge
 - Vasomotor symptoms (hot flashes and night sweats)
 - Insomnia
 - Increase in abdominal fat (“belly fat”)
 - Changes in the breast size and shape (increased fat accumulation)
 - Heart palpitations
 - Loss of memory and difficulties in concentration
 - Mood changes (depression, irritability, easier anger, mood fluctuations)
 - Fatigue
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Weight gain around the abdomen (ie, belly fat) is a common complaint during the menopausal transition, despite women reporting not changing their eating or exercise patterns. Increasing exercise or bursts of higher intensity, decreasing portion sizes or limiting carbohydrates and alcohol may help.

Memory and concentration problems, described as brain fog, tend to be more of an issue in perimenopause and level out after menopause. Counsel midlife women that these changes are not due to dementia but are related to normal aging, hormonal changes, mood, stress, or other life circumstances. Identifying and addressing sleep issues and mood disorders may help mitigate brain fog, as can advising women to avoid excess caffeine, alcohol, nicotine, and eating before bed. Improvements in memory, cognition, and health have been found with the Mediterranean diet, regular exercise, avoiding multitasking, and engaging in mentally stimulating activities.

Sleeping concerns in peri- and postmenopausal women include sleeping less and more frequent insomnia. Women are more likely to use prescription sleeping aids during these times of their lives. The data from SWAN⁹ show that the menopausal transition is related to self-reported difficulty sleeping, independent of age. Sleep latency interval is increased while REM sleep decreases. Night sweats can trigger awakenings in the first half of the night. The perceived decline in sleep quality also may be attributed to general aging

FAST TRACK

Common symptoms of menopause include hot flashes, depression, anxiety, weight gain, memory and concentration problems, sleeping concerns, and sexuality issues

CONTINUED ON PAGE 24

Demystifying 4 myths of menopause by providing accurate information

Myth 1: All hot flashes are the same

The truth: Seventy-five percent of women will have hot flashes, but only 25% are severe enough to cause women to seek treatment. Duration varies with identified patterns, including starting early or late, being mild or starting early, and going late. Ethnicity affects the duration of hot flashes, with longer durations seen in Black and Hispanic women. About 15% of women have had hot flashes for more than 15 or 20 years.^{1,2}

Myth 2: There is no help for hot flashes

The truth: For some women, lifestyle changes are helpful, such as dressing in layers, turning down the thermostat at night, avoiding hot beverages or alcohol, or using technology (Femtech) for cooling devices. Over-the-counter products that are available, but are not clearly proven to help more than placebo, include soy (which may be estrogenic), black cohosh supplements, and nutritional supplements. Cognitive behavioral therapy, hypnosis, weight loss, or mindfulness may help.³ Nonhormone medications such as low-dose antidepressants or gabapentin have shown benefit. Newer treatments in testing, including neurokinin receptor antagonists, appear to work quickly and as effectively as HT. When initiating HT, healthy women with bothersome hot flashes under age 60 or within 10 years of menopause are the best candidates for HT; many lower doses and oral and non-oral therapies are available.

Myth 3: Compounded bioidentical hormones made by a compounding pharmacy are safer and more effective than FDA-approved ones

The truth: Compounded bioidentical hormones are touted as safer or more effective, but there is no good evidence to back up those claims. Whether US Food and Drug Administration (FDA)-approved or compounded, hormones come from the same precursors and have potential risks. With custom compounded HT, there is additional concern about precisely what is in the compounded product, whether levels are similar batch to batch, and the degree of absorption of progesterone, which is better absorbed oral.⁴⁻⁶ FDA-approved bioidentical HTs have been tested for safety, proven to contain consistent, effective levels of hormones, and are monitored by the FDA. For menopausal symptoms, FDA-approved therapies are available as estradiol (oral, patch, spray, gel, lotion, and vaginal ring) and progesterone (as an oral compound or combined with estradiol). Pellets made of compounded hormones have shown higher serum levels and more adverse events.^{5,7}

Myth 4: Menopause causes weight gain

The truth is that fluctuating and declining hormones and the slowing of metabolism affect weight. Weight gain is not inevitable, just harder to prevent. Many women gain an average of 5 lb (2.27 kg) at midlife, which is mainly related to aging and lifestyle and not to menopause or HT. However, menopause may be related to body composition and fat distribution changes. Counsel women to decrease portion sizes, limit carbs, and increase exercise intensity, including strength training. The goal is 30 minutes of moderate aerobic activity per day, all at once or through smaller time increments, to improve their energy, mood, and sleep.

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effects, nocturnal urination, sleep-related disorders such as sleep apnea or restless legs, or chronic pain, stress, or depression.¹⁰ Suggestions for management include sleep apps, cognitive behavioral therapy, low-dose antidepressant therapy, addressing sleep routines, and HT. Hypnotics should be avoided.

Sexuality issues are common complaints during the menopausal transition. Cross-sectional data reported from a longitudi-

nal, population-based Australian cohort of women aged 45 to 55 years, found a decrease in sexual responsiveness, sexual frequency, libido, vaginal dyspareunia, and more partner problems.¹¹ Low libido may be related to relationship issues, dyspareunia with vaginal narrowing, loss of lubrication, levator spasm, stress, anxiety, exhaustion or mood disorder, lowered hormone levels, excess alcohol intake, underlying health concerns, or a

TABLE 2 Key takeaways about menopausal women

- Perimenopause may be challenging to navigate due to the hormonal changes and fluctuations with menstrual cycle irregularity, with potentially many other symptoms.
- Most women undergo the menopause transition while still in the workplace; thus, accommodations must become available.
- Women most likely to have more benefits than risks from HT started at menopause are healthy, symptomatic, under age 60, and within 10 years after menopause onset.
- Due to compounded HT's unique safety concerns, FDA-approved bioidentical HTs are recommended over compounded non-FDA-approved bioidentical HTs.
- Lower doses and non-oral (transdermal) HTs allow providers to individualize HT treatment options over time.
- Observational studies suggest that the risks of thromboembolism and stroke are lower with transdermal therapy.
- HT is recommended for women with early menopause without contraindications until the natural age of menopause, when risks and benefits should be re-evaluated.
- Despite data suggesting benefits for coronary heart disease and dementia when HT is initiated closer to menopause, HT is not recommended to prevent coronary heart disease or dementia.
- Nonhormone medical therapies that reduce hot flashes more than placebo include selective serotonin-reuptake inhibitors, serotonin-norepinephrine reuptake inhibitors, and gabapentinoids.
- Neurokinin receptor antagonists, currently in testing, appear as effective as HT and may provide a highly effective non-HT in the future.
- Local vaginal hormone therapies, including vaginal estrogen and dehydroepiandrosterone, are recommended for women with genitourinary symptoms.

Abbreviation: HT, hormone therapy.

side effect of medications for depression or pain. There is no direct correlation between testosterone levels and libido.

When HT at menopause may be helpful

For healthy symptomatic women without contraindications who are younger than age 60, or within 10 years of menopause onset, the benefits of initiating HT most likely outweigh the risks to relieve bothersome hot flashes and night sweats.¹²⁻¹⁷ For older women, or for those further from menopause, the greater absolute risks of coronary heart disease, stroke, venous thromboembolism, and dementia, in general, outweigh the potential benefits.¹²⁻¹⁷ Extended durations of HT have less safety and efficacy data and should be considered primarily for those with persistent menopausal symptoms, with periodic re-evaluation.^{13,14} For bothersome genitourinary syndrome of menopause symptoms that do not respond to vaginal moisturizers or lubricants, low-dose vaginal HTs are encouraged.¹³⁻¹⁷

Early-onset menopause

According to observational studies,¹⁸ early menopause is associated with a higher risk of osteoporosis, coronary heart disease, cognitive changes, vaginal dryness, loss of libido, and mood changes. Studies have shown that women with early menopause who take HT, without contraindications, to the average age of menopause (age 52) decrease the health risks of early menopause (bone loss, heart disease, mood, and cognition changes).^{13,14,18}

Women with early menopause, whether spontaneous or following bilateral oophorectomy or cancer treatment, should be counseled to get adequate calcium (dietary recommended over supplementation) and vitamin D intake, eat a healthy diet, and exercise regularly. Evaluation should include risk for bone loss, heart disease, mood changes, and vaginal changes.

Extended use of HT

Up to 8% of women have hot flashes for 20 years or more after menopause.¹⁹ The decision to continue or to stop HT is not always clear for women:

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Women most likely to have more benefits than risks from HT started at menopause are healthy, symptomatic, under age 60, and within 10 years after menopause onset

TABLE 3 What do menopausal women need from their providers?

- During perimenopause, clinicians need to ask about cycle duration, cramping, sleep disruption, worsening headaches, mood or anxiety, life stressors, contraceptive needs, presence of PMS or PMDD, or depression.
- Providers should be knowledgeable about the stages of perimenopause and menopause and help diverse women navigate the physical, emotional, and mood challenges that arise.
- Perimenopause is a time of vulnerability as ovarian hormonal fluctuations may cause worsening of mood disorders.
- Demystify menopause – ask what patients are reading to understand where their information comes from and what myths they may believe.
- Provide evidence-based information about lifestyle changes and tested, effective nonmedical and medical therapies tailored to the individual patient.
- Recommend FDA-approved products over compounded bioidentical products.
- Provide accurate information about concerns and risks of compounded bioidentical HT. Avoid prescribing unless allergies to specific ingredients in an FDA-approved drug product are a concern, or a type or dosage of a product is not available. Do not use patient preference alone to determine the use of compounded bioidentical HT preparations.¹
- Recommend cancer screenings (Pap tests, mammography, colon cancer screening) and screenings for other health risks (blood pressure, diabetes, cholesterol, bone density, and mood disorders).

Abbreviations: FDA, US Food and Drug Administration; HT, hormone therapy; PMDD, premenstrual dysphoric disorder; PMS, premenstrual syndrome.

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Therapies for GSM can include vaginal moisturizers and lubricants, estradiol, conjugated estrogen, dehydroepiandrosterone, oral selective estrogen-receptor modulators, and pelvic therapy

- with persistent hot flashes after a trial period of HT discontinuation
- with bone loss that cannot be treated with bone-specific medications
- who request continuation for quality of life.

Extended use of HT should include an ongoing assessment of its risks and benefits, periodic trials off of HT, and documentation of rationale and informed discussions about continuing. Lower doses and transdermal therapies appear safer, as does micronized progesterone instead of more potent synthetic progestins.¹³⁻¹⁷

Genitourinary syndrome of menopause

Once women are further into menopause, they may notice vaginal dryness, vulvar itching or burning, bothersome vaginal discharge, or urinary urgency or frequency. The development of painful intercourse frequently occurs, a combination of the loss of estrogen with thinning of the vaginal mucosa, a loss of the acidic vaginal milieu with less elasticity, and spasm of the levator muscles. Some women develop urinary tract infections after intercourse or have more frequent reoccurrences. First-line therapy is often vaginal moisturizers and

lubricants. Vaginal therapies (estradiol, conjugated estrogen, or dehydroepiandrosterone) or oral selective estrogen-receptor modulators (SERMs; ospemifene) improve vaginal dryness and dyspareunia.^{13,14} Pelvic therapy has also proved valuable for incontinence, pelvic floor dysfunction, and levator spasms.²⁰

Where are there gaps in clinician knowledge?

Studies on emotional health, mood, and sleep need to incorporate measures of menstrual timing into data collection and analyses. Does the sleep disruption occurring premenstrually during perimenopause disproportionately contribute to a woman's vulnerability to depressive disorders? The risk of clinically significant depressive symptoms increases 1.5- to 2.9-fold in the menopause transition.⁵ Research into premenstrual dysphoria during the menopause transition may identify different trajectories in the timing of symptoms related to either cycle itself or the ovarian hormone fluctuations or both.²¹ Gamma-aminobutyric acid (GABA)-modulating drugs, such as sepranolone, which blocks allopregnanolone's actions at the GABAA

CONTINUED ON PAGE 28

receptor, may allow treatment of menstrual-related mood disorders without the need for hormonal interventions.²¹

Despite extended observational trial data, more data are needed to inform us about the long-term risks and benefits of using menopausal HT, particularly when initiated at menopause and to help address the timing of HT discontinuation. Furthermore, there are many unanswered questions. For instance:

- How much safer are lower dose and transdermal therapies?
- Do untreated hot flashes increase the risk of cardiovascular disease or dementia?
- Will newer non-HT options, such as the neurokinin receptor antagonists that are in testing but are not yet available, lower cardiovascular or dementia risks?
- What will be the risks and benefits for the newer estrogen in testing (estetrol, or E4), considered a natural estrogen and which appears to have lower thrombotic risks?
- What will be the role of intravaginal energy-based therapies, such as vaginal laser or radiofrequency devices?
- How do we address diverse populations and the effects of menopause on race, gender, culture, prior trauma, and socioeconomic status?

Lack of recognition of menopausal symptoms, particularly in the workplace

Clinicians need to understand the varied physical and emotional symptoms that may

occur with hormonal changes as women traverse perimenopause and early menopause. We need to recognize that the lack of discussion about women's health during this time may make women feel ashamed and fearful of bringing up their symptoms due to fear of being dismissed or stigmatized.²² Women may not seek help until a crisis at home or work occurs, as they may fear that admitting symptoms or a need for help or time away from work will threaten how they are viewed at work or affect their chances of promotion. Although there are economic costs around menopause for appointments, tests, therapies, and missed time at work, not addressing menopausal health leads to poorer performance, workplace absences, and additional medical costs.²²

Conclusion

Menopause occurs naturally as a part of a woman's life cycle. However, women need assistance navigating perimenopausal hormonal fluctuations and decisions about HT once in menopause. Increased awareness and education about perimenopause and menopause will allow compassionate, individualized, informed care, including lifestyle changes, behavioral or complementary strategies, or medical therapies, hormonal or nonhormonal.²⁷ As a medical society, we need to challenge the stigma associated with aging and menopause and educate ourselves and our patients to help women navigate this challenging time. ●

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