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Menopause: A primary care perspective

Abstract: Menopause signifies permanent cessation of ovarian function and the end of a woman's reproductive potential. Menopausal transition plays a major role in many symptoms common in middle age and may contribute to chronic conditions and disorders of aging. An evidence-based plan of care improves outcomes, enhancing quality of life.

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Permanent termination of ovarian function and menses is known as menopause. Menopause is more of a process than an isolated episode. Perimenopause, the period leading up to menopause, is when the ovaries are in transition with irregular menstrual cycles and additional menopausal symptoms.[1] A decline in ovarian follicles occurs during the approximate age of 49 to 52 years. When ovarian follicles degenerate, the female sex hormones estrogen and progesterone become depleted, giving rise to irregular menstrual cycles. Ultimately, menstruation is permanently arrested when estrogen levels decrease to the point where endometrial growth ceases.[2] Primary care providers benefit from up-to-date evidence-based guidance to address the needs of women transitioning into menopause.

Physiology

The primary role of the hypothalamic-pituitary-ovarian (HPO) axis is to control reproduction. The HPO axis is also critical during puberty, aging, and immune system function. The hypothalamus releases gonadotropin-releasing hormone (GnRH), which signals to the pituitary gland to secrete two hormones: luteinizing hormone (LH) and follicle-stimulating hormone (FSH). LH and FSH within the sex organs send a signal to produce estrogen and progesterone in women and testosterone in men (and, in smaller amounts, in women). The production of these hormones can be influenced in many ways, from lifestyle factors like not getting enough sleep to taking synthetic hormones.

The most significant change during the menopausal process, along with

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declining follicular function, is the change in circulating estradiol. Estradiol begins to decline 2 years prior to menopause and continues approximately 2 years after menopause until stable levels of estradiol are reached.[3] Estrogen, in the absence of follicular production, is now produced from ovarian stromal connective tissue and androstenedione from adrenal secretion enters the peripheral circulation as aromatized estrogen. The aromatized estrogen is known as estrone; nonfollicular sources continue to produce estrone as follicular production decreases. Estrone is the main source of estrogen in postmenopausal women.[4,5] Finally, high levels of serum circulating FSH is a sign that menopause has occurred.[6] Because of a reduction in renal clearance, FSH levels continue to remain higher than circulating LH levels.[2]

During embryonic development, germ cell differentiation and primordial follicle growth produce approximately 6 to 7 million oocytes in a growing 5-month-old fetus in utero.[7] The process of germ cell differentiation and primordial follicle growth is driven by FSH and LH that ultimately leads to surges of LH at menarche resulting in ovulation.[8] In a sexually mature female, ovulatory release of an oocyte transforms the follicle into the corpus luteum. The corpus luteum produces an increasing amount of progesterone. During pregnancy, progesterone is necessary for maintenance of pregnancy after fertilization and eventual embedding of the embryo into the uterine lining.[9]

Ovarian senescence is a natural continuous process that occurs within the ovaries. This process begins during fetal development and eventually reduces the number of oocytes from its peak of 6-7 million to about 300,000 by puberty. Follicular atresia and oocyte decline are driven by decreasing FSH. The production of androgens in ovarian theca cells correlates with decreasing amounts of circulating estrogen.[10,11]

The period prior to complete cessation of menses, known as perimenopause, occurs for about 2 to 8 years before complete termination of menses. Perimenopause is characterized by several hormonal changes that continue 1 year following menses termination. The variability of ovarian function is reflected in random changes in menstrual cycles, which may be ovulatory or anovulatory, such as shorter duration and irregular frequency. The perimenopausal changes are due to intensified LH/FSH secretion, lack of estrogen and follicular development, and decreasing estradiol production. As ovarian follicles continue to age, ovarian sensitivity to gonadotropin stimulation is decreased. With increasing LH and FSH levels causing stromal stimulation of the ovary, estradiol levels decrease and estrone levels increase. This hormonal shift alters the estrogen feedback mechanism to the hypothalamic-pituitary-ovarian axis. Occasionally the negative estrogen feedback fails to suppress LH during the follicular phase possibly resulting in an ovulatory cycle. Additionally, dysfunctional uterine bleeding and endometrial hyperplasia are seen during this time.[12-14]

A decrease in the ovarian hormone inhibin B begins in the menopausal transition. Inhibin B acts as negative feedback to prevent the anterior pituitary from secreting FSH in the early stages of menopause. Inhibin B levels decrease as the female advances in age; this decrease in inhibin B is due to decreasing number and function of follicles. Ovarian response to the increasing FSH secretion, due to lack of inhibition, is the secretion of estradiol; this renders estradiol levels normal or high secondary to elevated FSH levels and increased aromatase activity.[2]

Diagnosis, diagnostic studies, and differential diagnoses

The average age of menopause in the US is 52 years but can range from 40 to 58 years.[15] When diagnosing menopause, providers must understand that diagnostic criteria differ with age. For healthy women over age 45 with an intact uterus, menopause is defined retrospectively as amenorrhea for 12 months.[16]

In women ages 40-45 years, amenorrhea for 12 months is also considered menopause; however, the diagnosis necessitates exclusion of causative conditions such as pregnancy and other endocrine disorders such as thyroid disease and hyperprolactinemia.[15,17] In women younger than age 40, absence of menstruation is considered primary ovarian insufficiency (POI), previously known as premature ovarian failure.[15] The evaluation and diagnosis of POI is beyond the scope of this article.

In addition to age criteria, menopause is diagnosed differently for women who have had certain surgical or medical therapies. For women over age 45 years who have had a hysterectomy but not bilateral oophorectomy, or in whom the menstrual pattern is difficult to ascertain (for example, endometrial ablation), the diagnosis of menopause is made presumptively when classic menopausal symptoms are present (that is, hot

Considerations for MHT with estrogens and progestins[26,33]*

Indications	
For systemic use	Treatment of moderate to severe vasomotor symptoms (that is, moderate/severe hot flashes)
For intravaginal use	Treatment of moderate to severe symptoms of vulvar and vaginal atrophy (that is, moderate/severe vaginal dryness, dyspareunia, and atrophic vaginitis)
Contraindications and precautions	
Absolute contraindications	Undiagnosed abnormal genital bleeding
	Known, suspected, or history of cancer of the breast
	Known or suspected estrogen- or progesterone-dependent neoplasia
	Active deep vein thrombosis, pulmonary embolism, or history of these conditions
	Active or recent (for example, within the past year) arterial thromboembolic disease (for example, stroke, myocardial infarction)
	Liver dysfunction or disease
	Known or suspected pregnancy
Precautions	Elevated BP
	Hypertriglyceridemia
	Impaired liver function and past history of cholestatic jaundice
	Hypothyroidism
	Fluid retention (careful observation recommended with use of MHT in patients with conditions potentially worsened by fluid retention)
	Severe hypocalcemia
	Ovarian cancer
	Endometriosis (risk of exacerbation with administration of estrogens)
	Asthma, diabetes mellitus, migraine, systemic lupus erythematosus, epilepsy, porphyria, and hepatic hemangioma (risk of exacerbation of these conditions with administration of estrogens)

*Not a complete list of all possible contraindications and considerations.

flashes or night sweats).[15] In this population, a history of amenorrhea is noncontributory, and hormone levels fluctuate in the years prior to menopause.[8] Thus, the diagnosis of menopause may be supported but not confirmed by repeat elevations in FSH levels and decreased estradiol levels less than 20 pg/mL.[15] Menopause may also be induced by bilateral oophorectomy, chemotherapy, or pelvic radiation therapy.[15,18,19] Bilateral oophorectomy causes immediate menopause. Chemotherapy or pelvic radiation may slow or stop menstruation, but menstruation may resume 12 months or more after treatment. This variability plus lack of diagnostic biomarkers make the diagnosis of menopause in these women difficult.[18]

Measurement of FSH to diagnose menopause is commonplace. However, the North American Menopause Society (NAMS), the American College of Obstetricians and Gynecologists (ACOG), and other professional societies agree that confirmatory testing of FSH is not indicated to diagnose menopause for healthy women over age 45 years.[15,19] Measurement of FSH is also not recommended for women taking combined estrogen-progesterone or high-dose, progesterone-only contraceptives.[17] Measuring FSH may be considered in evaluating women ages 40-45 with menopausal symptoms and menstrual changes.[15,18] An FSH level of 40 IU/L or higher is generally considered postmenopausal.[20]

In addition to FSH, other biochemical measurements and diagnostic studies are used to evaluate ovarian reserve. These include anti-Müllerian hormone, inhibin B, and estradiol. Although useful in assessing ovarian reserve, these tests are mostly reserved for evaluating infertility, POI, and ovarian tumors, not for predicting the onset of menopause.[15,19,21] Ultrasound

measurements including ovarian volume and antral follicle count have the same indications as other markers of ovarian reserve.[15,17]

Clinical manifestations

Normal estrogen production can begin to decline in women as early as in their late 30s. In addition to menstrual changes, this estrogen deficiency is associated with several common symptoms.[17] Approximately 75% of menopausal women in the US report vasomotor symptoms (VMS) including hot flashes and night sweats.[18] VMS manifest as a sensation of heat starting in the face and upper chest, often becoming generalized and lasting up to 4 minutes. Night sweats generally occur in the first 4 hours of sleep and are associated with sleep disruption.[18] VMS often last several years, but may persist for up to 10 years for postmenopausal women.[22] Onset of VMS earlier in the menopausal transition has been associated with longer duration of symptoms.[18] VMS have complex etiology and have been associated with decreasing estrogen and alteration in thermoregulation by increased norepinephrine and serotonin activity.[9]

In addition to VMS, menopause has been associated with genitourinary symptoms, mood changes, and musculoskeletal complaints. Genitourinary syndrome of menopause (GSM) due to lack of estrogen substrates and receptors cause decreased collagen synthesis and blood flow to the vaginal area resulting in vaginal dryness, irritation or burning, decreased lubrication, dyspareunia, dysuria, urinary urgency, and urinary tract infections.[17,18] Symptoms of GSM increase the longer a woman has been menopausal. Signs of GSM include decreased labial size, loss of vulvar fat pads, narrowing of the introitus, and thinning of the vaginal epithelium.[18]

Genitourinary complaints and decreased libido are associated with decreased sexual function. Mood and cognitive changes include depression, anxiety, irritability, difficulty concentrating, and memory problems.[18,17] Cognitive symptoms may be exacerbated by sleep disturbances.

Twenty-five percent of women have severe menopausal symptoms that adversely affect their quality of life, and the prevalence of symptoms varies according to race. For example, Black women experience greater VMS, and Hispanic women are more likely to have consistently higher depressive symptoms over midlife.[3]

Women in menopause also report musculoskeletal complaints including joint and muscle aches.[17] Estrogen has a protective benefit in bone health. Decreasing estrogen is associated with menopausal transition. The sharp decrease in estrogen can adversely impact and is linked with bone loss. Therefore, the chance of developing osteoporosis increases as women transition to menopause. Detailed risk assessment utilizing a validated tool such as FRAX® is critically important in menopausal women to evaluate for risk of fracture.[23]

Management

Lifestyle modification. Lifestyle modification may be beneficial as data suggest staying cool and reducing stress can help relieve some hot flash symptoms.[24] Avoidance of warm rooms, hot beverages, caffeine, and cigarette smoking may improve symptoms. Reduction of stress is correlated with more restful sleep. Regular exercise, meditation, acupuncture, and massage are linked to improved sleep by reducing the time it takes to fall asleep. Limited data have shown a lack of convincing benefit for nonprescription options such as herbal supplements.[24,25]

Menopausal hormone therapy. Menopausal hormone therapy (MHT) is broadly used to describe unopposed estrogen use for women who have undergone hysterectomy and combined estrogen-progestin therapy for women with an intact uterus.[26] Women with an intact uterus need progestin to prevent unopposed estrogen-associated endometrial hyperplasia. Thorough risk versus benefit analysis should be completed to assure a patient's candidacy for MHT.

The main goal of MHT is relief of hot flashes. Women requiring symptom relief of moderate to severe hot flashes require systemic estrogen. Moderate to severe hot flashes and/or night sweats are defined by interference with daily activities, impaired quality of life, and/or interrupted sleep.[27,28] Women with symptoms of GSM should receive treatment with low-dose vaginal estrogen.

Considerations for timing of MHT vary with age of initiation relative to age of onset of menopause. While there is a risk of cardiovascular events across for all ages with use of MHT, some data suggest that this risk may be less for women starting MHT at the natural age of menopause than those starting later. Women who start MHT near the time of menopause may be at greater risk of developing breast cancer versus patients who start MHT later after menopause. However, the increased risk may be due to likely increased duration of use rather than age at menopause.[24-29] There are absolute contraindications to MHT as well as precautions to

consider requiring clinical decision-making (see *Considerations for MHT with estrogens and progestins*).

Routes of administration. Estrogen is available in many forms: oral, transdermal, topical, and vaginal. Depending on severity of symptoms, transdermal or oral preparation is most often used as a starting strategy for VMS. Oral route should be avoided with hypertrigylceridemia and active gallbladder disease, as they are considered relative contraindications for therapy. Transdermal route allows for first pass effect.[26,28] Current best practice is to start with the lowest dosage and titrate up to symptom relief.[26] Standard recommendations for duration of use are 3 to 5 years. However, extended use may be necessary for women with persistent, severe hot flashes.

Other considerations in use of MHT. Those with hot flashes who see complete resolution of symptoms and are able to tolerate MHT may continue its use for several years unless health status changes warrant reconsideration of therapy. Tapering of dosages may begin between 3 and 5 years of MHT. The total length of treatment with MHT must be considered when carefully weighing risks versus benefits of continuing MHT.[24-29] Women starting MHT earlier, such as patients with early onset of menopause in their mid- to late-40s can consider longer MHT before first taper and the goal is often to decrease the dose rather than stopping MHT.[30]

Below are some factors to consider:

- *Factors affecting oral estrogen metabolism*–Exogenous estrogen metabolism is altered by many factors. Increased metabolism may result in lower serum estrogen concentrations. Decreased metabolism can result in higher serum concentrations.
- *Antiepileptic drugs*–Seizure medications such as phenytoin and carbamazepine increase the hepatic clearance of estrogen and steroid hormones. Transdermal estrogen may be the best route to avoid first pass hepatic metabolism.[30]
- *Thyroid hormone replacement*–Oral estrogens increase thyroxine-binding globulin more than transdermal preparations. The result is lower bioavailable thyroxine (T4). Women receiving thyroid hormone replacement therapy taking oral estrogen may require increased thyroid hormone dosage.[31] Thyroid-stimulating hormone levels are easily monitored to assess thyroid hormone dosage requirements.
- *Other*–Alcohol intake while taking oral estradiol has been correlated with a threefold rise in serum estradiol. The slowing of metabolism of estradiol is impacted by alcohol ingestion. Women taking exogenous estrogen should be encouraged to limit alcohol intake.[29,30]

Low-dose vaginal estrogen

Low-dose vaginal estrogen is a very effective treatment for vaginal dryness or dyspareunia (pain with intercourse). Treatment for women with dyspareunia can continue for many years due to minimal systemic absorption. Low-dose vaginal estrogen is considered a safer option for patients with breast cancer, history of myocardial infarction or stroke, or other cardiovascular risk factors. However, it is important to consult with specialists, such as oncologists, prior to start of treatment.[24-29]

Alternative treatment options. Patients with hot flashes who are not estrogen candidates or those desiring nonhormonal options do have effective treatment options for hot flashes showing symptom improvement. Nonestrogen treatments for hot flashes are effective for many women, some of which are discussed below.[27]

Paroxetine (Brisdelle) is specifically approved for hot flashes at a lower dose than is used for treatment of depression.[24-28] Caution should be taken when prescribing paroxetine to patients taking tamoxifen for breast cancer as it can decrease effectiveness of tamoxifen.

There are absolute contraindications to MHT as well as precautions to consider requiring clinical decision-making.

Other antidepressants that multiple studies have associated with hot flash symptom relief include venlafaxine (Effexor), desvenlafaxine (Pristiq), citalopram (Celexa), and escitalopram (Lexapro); however, none aside from paroxetine are FDA-approved for this purpose.[24-29] Antidepressant medications are recommended as a first-line treatment for hot flashes in women who are not estrogen candidates. Fluoxetine (Prozac) and sertraline (Zoloft) do not relieve hot flash symptoms quite as well as other antidepressant options in studies.[27-29]

Gabapentin is a seizure medication which has shown relief of hot flashes as an off-label use in some women. A common adverse reaction is somnolence. This medication may be an option especially for patients with insomnia; a once-daily dosage at bedtime may be considered.[25-28]

Patient education

Plant-derived estrogens (phytoestrogens) are an alternative to hormones for women with menopausal symptoms. Phytoestrogens are found in many foods, including soybeans, chickpeas, lentils, flaxseed, grains, fruits, vegetables, and red clover. Isoflavone supplements are a type of phytoestrogen. However, most studies have not found benefit or symptom relief. Further, concern exists regarding phytoestrogens as they may mimic estrogen. Experts recommend caution for women with a history of breast cancer.[24-26]

Cognitive behavioral therapy or other mental health support may be beneficial for symptoms of depression or anxiety. Education about the importance of managing stress, incorporating relaxation, mindfulness breathing, or calming exercises such as yoga may be helpful for some women. Alternative approaches such as acupuncture or hypnosis may be helpful with reducing hot flashes.[25-27] However, some experts note this may be attributable to the placebo effect. Current use of MHT may prevent more severe VMS. Severe hot flashes are a risk factor for depression.[32] Identification of risk factors for depression, which may include social determinants of health, age at onset of menopause, and severity of menopausal symptoms, is an important consideration when assessing mental health.

Herbal treatments are often used as natural remedies for hot flashes. Many postmenopausal women have reported taking black cohosh for hot flashes. Clinical studies have shown no greater benefit than placebo.[24-28] Data are conflicting regarding the safety of black cohosh, especially in patients with breast cancer, as it may mimic estrogen in breast tissue. Herbal supplements are not recommended for menopausal symptoms. Additional studies would be beneficial to further assess efficacy and safety.

Implications for practice

It is recommended to start with the lowest dosage of MHT and titrate up. The most commonly used routes for treatment of VMS are oral or transdermal. The focus of MHT therapeutic dosage range is on that which is needed for symptom relief. Patients with severe symptoms may warrant a higher starting dose to provide more rapid relief of symptoms.[25-29]

Women experiencing recurrent hot flashes after stopping estrogen may consider nonhormonal options for management of symptoms. Persistent symptoms impacting quality of life may require continuation of MHT at the lowest possible dosage for carefully selected patients.[24-29]

Conclusion

Menopause is a normal physiologic event reflecting the permanent cessation of ovarian function and is the culmination of declining ovarian follicles over one's lifetime. The hormonal changes of menopause are complex and include decreased estradiol production from the ovarian follicles replaced by nonfollicular sources of aromatized estrogen from the ovarian stromal connective tissue and adrenal gland.

Symptoms of menopause include the classic VMS of hot flashes and night sweats as well as genitourinary symptoms, mood and cognitive changes, sexual difficulties, and musculoskeletal pain. In otherwise healthy women over the age of 45 who are not taking hormonal contraception, the diagnosis of menopause is based solely on a history of amenorrhea for 12 consecutive months; in the setting of no uterus but intact ovaries in women over the age of 45, the presence of classic symptoms such as hot flashes is diagnostic. No confirmatory testing is indicated in this age group. For women ages 40 to 45 with amenorrhea for 12 months, menopause is likely, but secondary etiologies should be ruled out.

MHT with estrogen can be administered by oral, transdermal, topical, or vaginal routes in women without contraindications. Oral and transdermal estrogen are the most effective in treating VMS and should be started at the lowest effective dose and then titrated up as needed. Potentially beneficial nonhormonal treatments include lifestyle modifications, certain antidepressants, gabapentin, and cognitive behavioral therapy or other mental health support. Phytoestrogens and herbal treatments for menopausal symptoms have not been found to provide benefit and require further study before their use can be recommended. NP

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