



Approach to the Perimenopausal Patient

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Menopause has been successfully promoted as an estrogen-deficient state. Prescriptions in the United States for noncontraceptive estrogen formulations increased from 16 million to 39 million between 1982 and 1992; progestin sales reached 4.7 million by 1992 after their introduction in 1986.¹ A condition for which half of the population becomes eligible for pharmacologic treatment for 30 years or more of their life spans is worthy of family physicians' attention. Counseling of women regarding menopause has also been incorporated into the Health Employer Data Information Set (HEDIS) for measuring the quality of care provided by health care plans.

The women of the generation born from 1946 to 1965 are now 36 to 55 years old. About half will at some time seek medical attention for relief of symptoms believed to be related to the menopausal transition.² The clinical picture, however, can be confusing; women at midlife are susceptible to diseases that may affect or be affected by the menopausal transition. Life cycle changes can also provoke dysphoric symptoms similar to those of menopause or aggravate symptoms that already exist.

NATURAL HISTORY

A woman's hormonal rhythm changes gradually, usually in the early to middle forties. Ovarian mass decreases progressively; production of ovarian hormones decreases as well. The menstrual cycles tend to be somewhat shorter. Follicle-stimulating hormone (FSH) and estrogen levels fluctuate. Estrogen levels may be transiently higher than in former years in response to higher FSH levels, recruiting more ovarian follicles. Anovulatory cycles are more frequent. Perimenopausal menstrual irregularity typically lasts for approximately 4 years; the large majority of women experience such irregularity for 1 to 7

KEY POINTS FOR CLINICIANS

- Laboratory testing is not indicated to initiate treatment of perimenopausal symptoms.
- While estrogens are the best established of the options to treat vasomotor symptoms at perimenopause, they are not a proven treatment for major depression or poor libido.
- Little evidence exists regarding the benefits and risks of androgens for perimenopausal women, suggesting a cautious approach to their use.
- Routine use of hormone replacement therapy, especially beyond 5 years' duration, is not recommended because of uncertainties regarding risks and benefits.

years.² For 10% of women, menses simply cease without prior menstrual irregularity.

The best estimate of mean age at menopause in the United States, based on a cohort of primarily Caucasian women, is 51.3 years.² Smokers experience menopause 1.8 years earlier than nonsmokers (50.2 versus 52.0 years). Less than 10% of women reach menopause before age 46, while approximately 30% do so before age 50.² A recent review³ concluded that the lifetime number of ovulatory cycles is predictive of age at menopause: earlier for women with shorter cycles and nulliparous women, later for multigravid women and those with a history of oral contraceptive use. A familial tendency toward similarity in age at menopause has been noted.

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Each Applied Evidence review article considers a common presenting complaint or disease and summarizes the best available evidence for clinicians. The collected reviews are published online at www.jfponline.com. Explanations of the Levels of Evidence can be found at <http://cebm.jr2.ox.ac.uk/docs/levels.html>.

TABLE 1 TREATMENT OF VASOMOTOR SYMPTOMS

Strength of Recommendation	Treatment	Comment
A	Estrogens	Many preparations with both oral and transdermal delivery have been studied
A	Estrogen + MPA	Other progestins not well studied
B	Transdermal progesterone	One RCT ³⁸
B	Estrogen + testosterone	One RCT ²⁷ ; long-term safety is a theoretical concern
B	Megasterol	Cohort ³⁵ ; long experience with cancer patients gives some assurance of safety
C	Behavioral approaches	One small RCT ³⁹ ; deep breathing was beneficial
C	Clonidine	Small RCTs ^{36,37} with important loss of subjects because of side effects
D	Antidepressants	Pilot studies of sertraline, ⁴⁰ venlafaxine, ⁴¹ and paroxetine ⁴²
D	Phytoestrogens	Conflicting RCT results
D	Exercise	Weak observational studies suggest benefit ^{74,76}
No benefit seen		
B	Black cohosh	No benefit seen in one RCT ³¹
B	Dong quai	No benefit seen in one RCT ³²
B	Red clover	No benefit seen in systematic review ³³

Grades of recommendation are based on Oxford Centre for Evidence-Based Medicine guidelines. MPA denotes medroxyprogesterone; RCT, randomized clinical trial.

Premature menopause or premature ovarian failure is defined as cessation of menstrual periods before 40 years of age. The prevalence of premature ovarian failure is approximately 1% by age 40 and 0.1% by 30 years of age.⁴ Premature ovarian failure is frequently an autoimmune disorder.⁵

DIAGNOSIS OF MENOPAUSE

The gold standard for diagnosing menopause is to do so retrospectively, 1 year after the last menstrual period. In general, a diagnosis of menopause based on menstrual history or hormone levels is not considered necessary to begin treatment for perimenopausal symptoms, which often begin several years before the onset of menopause.

Laboratory Diagnosis

The extent to which FSH or other serologic markers can be used to diagnose menopause is controversial. The most important clinical reason to do so is to discontinue contraceptive methods safely. Some consider an FSH level greater than 40 mIU/mL to be diagnostic. This value was chosen because it is about 2 standard deviations above the periovulatory peak in FSH levels in regularly cycling women. However, longitudinal studies^{6,7} during the perimenopausal years have demonstrated that hormonal patterns that include FSH values greater than 40 mIU/mL often

abruptly revert to premenopausal patterns and are accompanied by ovulatory cycles. For the individual patient, hormone levels do not appear to rule out fertility reliably.⁸ Studies defining test characteristics (sensitivity, specificity, likelihood ratios) of hormone assays for the diagnosis of menopause are needed.

History and Physical Examination

A large population-based survey of Swedish women⁹ found that the most common climacteric symptoms are, in order of frequency, vasomotor symptoms (hot flashes), mood disturbances, sleep disturbances, decreased libido, and vaginal dryness. Several obser-

vational studies¹⁰⁻¹³ have shown that vasomotor symptoms have the clearest temporal association with the menstrual cycle changes of the climacteric. These symptoms result from a sudden change in the hypothalamic control of temperature regulation,¹⁴ although the precise triggers have not been elucidated. Hot flashes occur commonly among women in their late thirties and forties who have regular menstrual cycles.¹⁵ Several studies^{2,10,13,16} have shown that the prevalence of hot flashes peaks in the year immediately following the final menstrual period. A typical pattern prevalence of hot flashes is 25% in premenopausal women, 69% in perimenopausal women, and 39% in late-postmenopausal women (more than 4.5 years).¹⁷ Fifteen years after menopause, 10% of women may continue to have moderate to severe hot flashes,¹⁸ which can be lifelong.

Irritability and mood swings are common climacteric complaints. Women often compare them with their earlier premenstrual symptoms. Studies of depressive symptoms in menopausal women indicate that menopause is not associated with increased rates of major depression.¹⁹ Stressful life context and poor health status appear to be more important risk factors for depression than symptoms of menopause in climacteric women.²⁰

Many perimenopausal women complain of poor sleep, often attributed to nocturnal hot flashes.

TABLE 2

SUMMARY OF RISKS AND BENEFITS OF TREATMENTS FOR PERIMENOPAUSAL SYMPTOMS						
Treatment	VMS	Mood	Libido	Bone	CAD	Breast CA
Estrogens	Benefit	Benefit	No benefit	Benefit	Uncertain	Risk
Estrogen + MPA	Benefit	? benefit	No benefit	Benefit	Uncertain*	Risk†
Progesterone	Benefit	Risk	No benefit	NS	Uncertain	NS
Testosterone	Benefit	NS	? benefit	Benefit	NS	NS
Phytoestrogens	? benefit	NS	NS	No benefit	NS	NS
DHEA	NS	? benefit	? benefit	NS	NS	NS

* Not beneficial for secondary prevention. † Increased risk over estrogen alone. CA denotes cancer; CAD, coronary artery disease; DHEA, dihydroepiandrosterone; MPA, medroxyprogesterone acetate; NS, not studied; VMS, vasomotor symptoms.

Subjective impairment of sleep quality that is associated with climacteric vasomotor symptoms does not manifest as abnormalities in polysomnographic sleep recordings.²¹ It does not appear to be related to sleep apnea.

Sexual dysfunction is common in women at midlife and beyond. Dyspareunia, associated with vaginal dryness, increases in frequency with increasing time after menopause.⁹ The other complaint is decreased libido. Multiple factors may contribute to lack of sexual interest. Both aging and the menopause are independently associated with decreases in sexual responsiveness.²² The roles of declining endogenous sex steroid hormones in this process have not been elucidated.

TREATMENT

Vasomotor Symptoms

Table 1 summarizes treatment options for vasomotor symptoms. Numerous well-designed clinical trials have demonstrated the effectiveness of oral or transdermal estrogen replacement therapy (ERT) for hot flashes.^{18,23-25} Low-dose oral contraceptive formulations are approved until 50 years of age for non-smoking women.²⁶ In a well-designed randomized controlled trial (RCT) of 93 women, low-dose estrogen (0.625 mg conjugated equine estrogens daily) plus 1.25 mg methyltestosterone daily was shown to be more effective than low-dose estrogen only and as effective as high-dose estrogen (1.25 mg conjugated estrogens daily).²⁷

Phytoestrogens may be helpful, but have not yet been studied extensively. One RCT²⁸ of 104 postmenopausal women comparing ingestion of 60 g soy protein daily with that of 60 g casein (placebo) daily showed a 45% relative reduction of hot flashes at 12 weeks in the group taking soy versus the control group. A second RCT²⁹ of 51 women comparing soy protein with carbohydrate placebo showed a decrease in severity, but not frequency, of hot flashes. Another well-designed RCT³⁰ including 69

women treated with 40 g soy daily versus whey protein for 24 weeks showed no difference between treatment groups and improvement in symptom scores over time in both groups. It is difficult to include a 40-g to 60-g protein supplement in the daily diet because of the accompanying caloric intake required. Recent reports of randomized placebo-controlled trials of black

cohoosh³¹ and dong quai³² and a systematic review³³ of controlled trials of red clover have found no benefit.

Alternatives to estrogen for treatment of hot flashes include methyldopa, clonidine, transdermal progesterone, and megestrol acetate. Megestrol, which reduces symptoms by 70%, appears to be the most effective of these.³⁴ Although long-term use of megestrol acetate by cancer survivors for the treatment of hot flashes has been demonstrated to be effective and well tolerated,³⁵ it is not customarily used at menopause. A 20% reduction in hot flashes can be expected with clonidine at a dose of 0.1 to 0.2 mg daily,^{34,36} although this regimen may cause an increase in difficulty sleeping³⁷ as well as dry mouth, constipation, and low blood pressure. Transdermal progesterone cream alone has been shown to improve vasomotor symptoms, although without protective effect regarding bone loss.³⁸ One small study³⁹ of behavioral approaches showed symptom reduction with deep-breathing relaxation techniques. Pilot studies of sertraline,⁴⁰ venlafaxine,⁴¹ and paroxetine⁴² show promise in the treatment of hot flashes.

The remainder of this article focuses on hormonal treatment effects and risks for menopausal women. A summary appears in Table 2.

Mood Disorders

In a meta-analysis⁴³ including 26 RCTs of the effects of hormone replacement therapy (HRT) on depressed mood, estrogen showed limited effectiveness in improving mood. The addition of synthetic progestins reduced the estrogen effect. More recent short trials of unopposed transdermal estrogen showed benefit.^{44,45} Other reviews^{46,47} have concluded that ERT or HRT has little effect in the treatment of psychological symptoms, including anxiety, cognitive, and affective symptoms. As an adjuvant to psychotropic therapy, it may have limited effect. There is insufficient evidence to support prophylactic ERT or HRT to prevent depression in women whose

TABLE 3 RESOURCES FOR PATIENT EDUCATION ABOUT MENOPAUSE

Organization	Contact Information	Description
Ottawa Health Decision Centre	ldrake@civich.Ottawa.on.ca 613-798-5555	<i>Making Choices: Hormones After Menopause</i> (audiotape and workbook)
American Academy of Family Physicians	www.aafp.org 1-800-274-2237	Brochures: "Menopause: What to Expect When Your Body Is Changing"; "Osteoporosis: Keeping Your Bones Healthy and Strong"
American College of Obstetricians and Gynecologists	www.acog.org 1-800-410-ACOG	Brochures: "Midlife Transitions: A Guide to the Menopause Years"; "Hormone Replacement Therapy"

medical history includes prior postpartum depression.⁴⁷ Estrogens do not affect the ability of a woman with moderate to severe vasomotor symptoms to cope with stress.⁴⁸ Clinical trials reporting the effects of testosterone treatment on mood in women were not identified.

Women with mild psychological and predominantly vasomotor symptoms may benefit from a trial of HRT before psychotropic medication. For women who meet criteria for a diagnosis of major depression, initial treatment with an antidepressant alone or concurrent with HRT is advisable.

Sleep Disturbance

In a survey of more than 6000 women aged 40 to 64 years, 30% of HRT users reported sleep improvement that they attributed to therapy.⁴⁹ Other standard approaches to insomnia, such as sleep hygiene measures and progressive relaxation techniques, can also be used. If sleep apnea is suspected, a sleep study may be indicated.

Sexual Dysfunction

In a systematic review⁵⁰ of HRT for climacteric sexual dysfunction, vaginal dryness improved with ERT in 7 of 8 studies. Dyspareunia improved in only 1 of 6 studies using transdermal 17-beta-estradiol. Orgasm increased in only 1 of 5 trials using ethinyl estradiol. Sexual interest increased in none of 7 studies that used conjugated estrogens. However, taking testosterone appeared to increase sexual interest. The evidence regarding the safety and efficacy of androgens (testosterone and dehydroepiandrosterone [DHEA]) for the treatment of sexual dysfunction in perimenopause is incomplete; therefore, these drugs should not routinely be prescribed.⁵¹

Bone

Although HRT prevents the rapid bone loss observed in the early menopausal period, this effect is lost when treatment is stopped. The positive effect

of estrogen alone on bone mineral density was not diminished by medroxyprogesterone acetate (MPA) or micronized progesterone over a 3-year follow-up period.⁵² The long-term effects of MPA on fracture risk in postmenopausal women have not been reported. Use of

transdermal progesterone alone does not prevent bone loss.⁵⁸

Cancer

Estrogen alone for women with an intact uterus is currently considered unacceptable because adding the hormone poses endometrial cancer risk. An exception is low-dose estrogen administered intravaginally; this method does not alter the endometrium.⁵³

Estrogen alone or in combination with progestins has been associated with an increased risk of breast cancer in many observational studies and meta-analyses. A comprehensive reanalysis⁵⁴ of 51 mostly observational studies, including 52,705 cases of breast cancer and more than 100,000 controls, examined the association of breast cancer with HRT, predominantly unopposed estrogen. These authors concluded that there is an increase in incidence of breast cancer of 0.2%, 0.6%, and 1.2% with 5, 10, and 15 years of use, respectively. Thus, 1 additional case of breast cancer occurs for every 167 women treated for 10 years (number needed to harm [NNH] = 167). Two recent observational studies have documented up to a fourfold increase in breast cancer with estrogen plus progesterone over estrogen alone.^{55,56}

Cardiovascular Disease

HRT has been widely advocated for prevention of coronary artery disease (CAD), based on many observational studies. A meta-analysis⁵⁷ of 25 studies published through 1997 gave a relative risk (RR) of 0.7 (CI 0.65-0.75) for coronary events in women using HRT. However, a consistent bias in these studies of selecting healthy, compliant women for inclusion may explain the observed benefit.

A meta-analysis⁵⁸ of 22 trials of 4124 women comparing HRT with placebo, no therapy, or vitamins, in which cardiovascular events were secondary endpoints, revealed that there was no benefit regarding cardiac events and there were small increases in absolute risk of stroke and venous thromboembolism

(VET). In the Heart and Estrogen/Progestin Replacement (HERS) study,⁵⁹ conjugated equine estrogens (CEE) plus MPA, administered to women with established CAD for a mean of 4.1 years, did not reduce risk of cardiovascular events. An increase in events, particularly VET and stroke,⁶⁰ occurred in the first year of use. Small increases in the absolute risks of stroke^{61,62} and VTE^{63,64} have also been described in observational studies.

Randomized trial evidence is currently lacking for a role of HRT in the primary prevention of cardiovascular disease. A large study of low-risk postmenopausal women, the Women's Health Initiative,⁶⁵ is currently under way. Its objective is to investigate strategies for the prevention and control of some of the most common causes of morbidity and mortality in postmenopausal women. The study includes 27,000 women randomized to CEE plus MPA or placebo. Results are expected in 2007. The American Heart Association now recommends against estrogen therapy with or without progestin solely for the prevention of heart disease.⁶⁶ Long-term effects of androgens on cardiovascular risk have not been studied; concerns exist about their use.⁵¹

Other Effects

A meta-analysis⁶⁷ of trials of HRT for urinary incontinence showed no benefit. The HERS study⁶⁸ showed an increase in urinary incontinence episodes with combined HRT for women with incontinence at baseline (NNH = 8). HRT also increases the risk of gallbladder disease⁶⁹ and may worsen cognitive function for women with mild to moderate dementia.⁷⁰

PROGNOSIS

The symptoms of perimenopause are not life threatening and are usually limited in time. Climacteric symptoms are generally more severe and difficult to treat in women who have undergone bilateral oophorectomy before experiencing natural menopause.⁷¹ Women with multiple chronic medical conditions,^{13,72,73} psychiatric illnesses,^{15,74} or a history of premenstrual syndrome^{11,12,75} are also likely to experience more difficulty with symptoms attributed to the menopausal transition. Table 3 provides a list of resources for patient education regarding menopause.

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