Approach to the Patient with Menopausal Symptoms

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Many women experience menopausal symptoms during the menopausal transition and postmenopausal years. Hot flashes, the most common symptom, typically resolve after several years, but for 15–20% of women, they interfere with quality of life. For these women, estrogen therapy, the most effective treatment for hot flashes, should be considered. The decision to use hormone therapy involves balancing the potential benefits of hormone therapy against its potential risks. Accumulating data suggest that initiation of estrogen many years after menopause is associated with excess coronary risk, whereas initiation soon after menopause is not. Therefore, most now agree that short-term estrogen therapy, using the lowest effective estrogen dose, is a reasonable option for recently menopausal women with moderate to severe symptoms who are in good cardiovascular health. Short-term therapy is considered to be not more than 4–5 yr because symptoms diminish after several years, whereas the risk of breast cancer increases with longer duration of hormone therapy. A minority of women may need long-term therapy for severe, persistent vasomotor symptoms after stopping hormone therapy. However, these women should first undergo trials of nonhormonal options such as gabapentin, selective serotonin reuptake inhibitors, or serotonin norepinephrine reuptake inhibitors, returning to estrogen only if these alternatives are ineffective or cause significant side effects. Low-dose vaginal estrogens are highly effective for genitourinary atrophy symptoms, with minimal systemic absorption and endometrial effects. (*J Clin Endocrinol Metab* 93: 4567–4575, 2008)

A 49-yr-old woman was self-referred for possible estrogen therapy. She has been experiencing intermittent hot flashes and difficulty sleeping for the past year, but the severity and frequency of hot flashes have increased recently. She has frequent waking episodes and is finding it difficult to concentrate. Menses had occurred approximately every 6–8 wk for the past 2 yr, but her most recent period was 12 months ago. She has tried soy supplements and black cohosh without adequate relief. She also notes recent vaginal dryness and pain with intercourse. Medications include 0.1 mg levothyroxine for hypothyroidism, 1200 mg/d calcium, and 800 U/d vitamin D. She has no personal or family history of coronary heart disease, stroke, venous thromboembolism, or breast cancer. She is a nonsmoker. On examination, her height is 5 ft 4 in., weight 130 lb (body mass index 22.3 kg/m^2). Blood pressure is 110/70 mm Hg. Thyroid is 20 g without nodules. On breast examination there are no masses. Pelvic examination show a normal cervix, slightly pale vaginal mucosa, and no adnexal masses.

Case background

This patient has classic menopausal symptoms (hot flashes, sleep disturbances, and vaginal dryness). She has tried soy-based supplements and black cohosh without relief and is now interested in estrogen therapy. Estrogen therapy has been prescribed for many years for menopausal symptoms, in particular hot flashes and genitourinary atrophy symptoms. In recent decades, menopausal hormone therapy was also promoted as a strategy to prevent chronic diseases, including dementia, osteoporosis, but most importantly coronary heart disease (CHD). This approach was based on numerous observational epidemiologic studies reporting a 30–50% reduction in the risk of CHD with postmenopausal hormone therapy (1). However, subsequent large, randomized, clinical trials, including the Women's Health Initiative (WHI), demonstrated an early increase in the risk of CHD with combined estrogen-progestin therapy when used for primary (2, 3) or secondary prevention of CHD (4, 5). Other health risks and benefits reported in the WHI combined hormone therapy trial

Abbreviations: CHD, Coronary heart disease; SNRI, serotonin norepinephrine reuptake inhibitor; SSRI, selective serotonin reuptake inhibitor; WHI, Women's Health Initiative.

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included an increased risk of breast cancer, stroke, and venous thromboembolism and a decreased risk of osteoporotic fracture and colon cancer risk (2). In the WHI unopposed estrogen trial, an increased risk of stroke, but not CHD or breast cancer, and a reduced risk of fracture were observed (6, 7).

After publication of the initial WHI findings, which suggested greater overall harm than benefit with combined therapy, hormone therapy use decreased dramatically. However, accumulating data suggest that the effect of hormone therapy on CHD risk may depend on the timing of starting therapy in relation to the onset of menopause, a concept referred to as the timing hypothesis (8–10). As described below, this hypothesis suggests that hormone therapy may have a neutral or beneficial effect when started during the early menopausal years but a harmful effect if started in late menopause. The clinical implication of these observations is not that newly menopausal women should be given estrogen to prevent CHD but that these women can be reassured that short-term use of estrogen for menopausal symptoms is not associated with excess cardiac risk.

Menopausal symptoms

Clinical menopause is diagnosed after 12 months of amenorrhea and occurs on average between the ages of 50 and 51 yr (11). A variety of terms have been used to describe the stages of the menopausal transition, including those developed at the Stages of Reproductive Aging Workshop (12). This model identifies seven stages of reproductive aging, divided into regular menstrual cycles, menopausal transition stages (irregular menses and high serum FSH concentrations), and postmenopausal stages, beginning with the final menstrual period (Fig. 1).

As women progress through the menopausal transition, the intermenstrual interval increases, followed by the development of anovulatory cycles, which may be associated with irregular, and sometimes heavy, bleeding. Two symptoms that have been consistently associated with menopause in longitudinal studies are hot flashes and vaginal dryness (13). As described below, other symptoms such as sleep disturbances and depression may also be associated with menopause. The symptom intensity, duration, and frequency of these symptoms are highly variable.

Hot flashes

Hot flashes are most common in the late menopausal transition and early postmenopausal periods (14). A systematic review of menopausal symptoms estimated that vasomotor symptoms occur in 14–51% of women before the menopausal transition, 35–50% during the transition, and 30–80% after menopause (15). For about 15–20% of women, these symptoms are severe enough to interfere with quality of life. Untreated, hot flashes stop spontaneously within a few years of onset in most women (14–17). However, some women have hot flashes that persist for many years. The reported prevalence of women with persistent hot flashes is 12–15% for women in their 60s (17, 18), and 9% after age 70 yr (18). Ethnicity affects one's risk of hot flashes, as illustrated by the Study of Women's Health across the Nation, a longitudinal study of women followed up during the menopausal transition (14). Vasomotor symptoms were reported less often by Japanese and Chinese women but more often by African-American women when compared with Caucasian women Other factors that are associated with hot flashes include obesity, surgical menopause, less physical activity, smoking, and less education (16, 18).

Genitourinary atrophy

Estrogen deficiency leads to thinning of the vaginal epithelium, often resulting in vaginal atrophy (atrophic vaginitis), which may cause symptoms of vaginal dryness, itching, and dys-

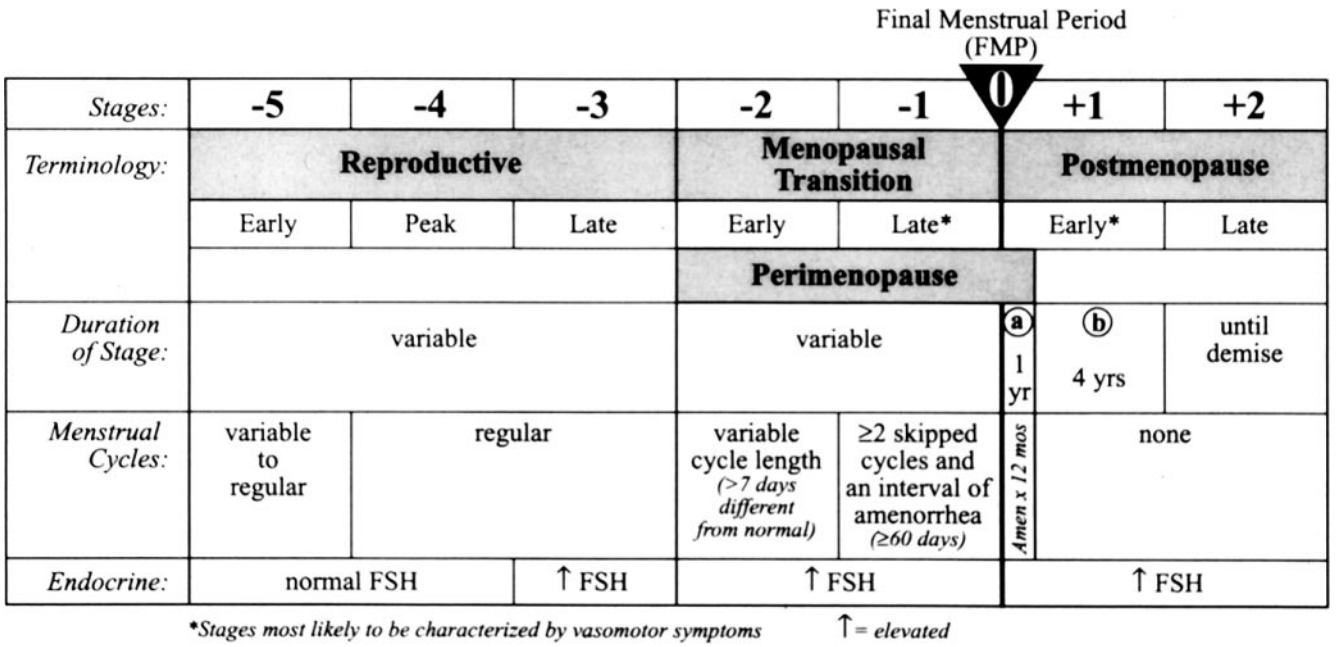

FIG. 1. The Stages of Reproductive Aging Workshop staging system: stages −5 to −3 represent the reproductive interval; stages −2 and −1 represent the menopausal transition, and stages 1 and 2 are the postmenopause. Adapted with permission from M. R. Soules, S. Sherman, E. Parrott, R. Rebar, N. Santoro, W. Utian, and N. Woods: Fertil Steril 76:874–878, 2001 (12). © The Endocrine Society.

pareunia. The prevalence of vaginal dryness in one longitudinal study was 3, 4, 21, and 47% of women in the reproductive, early menopausal transition, late menopausal transition, and 3 yr postmenopausal stages, respectively (19). Some women report diminished sexual function during the menopausal transition, possibly due in part to hypoestrogenemia and diminished vaginal blood flow (20). Vaginal estrogen therapy is the treatment of choice for women with isolated symptoms of genitourinary atrophy and no contraindications to estrogen use (21).

Other menopausal symptoms

Perimenopausal and postmenopausal women often report difficulty sleeping (22). Whereas hot flashes and mood changes may be associated with sleep disturbances (23), primary sleep disorders such as sleep apnea and restless legs syndrome are also common in this population (24). Some (20, 25) but not all (19), studies suggest that the risk of mood changes and depression are also increased during the menopausal transition. Diffuse joint pain (26) and a decline in memory have also been reported (27), but changes in cognitive function have not been consistently observed in longitudinal studies (28).

Differential diagnosis of menopausal symptoms

Hyperthyroidism should always be considered in the differential diagnosis of menopausal symptoms because irregular menses, sweating (although different from typical hot flashes), and mood changes are all potential clinical manifestations of hyperthyroidism. Other etiologies for menstrual cycle changes that should be considered include pregnancy, hyperprolactinemia, and thyroid disease. Sweating symptoms may be due to other disorders, such as medications, hypoglycemia, carcinoid, pheochromocytoma, or underlying malignancy.

Controversies and unanswered questions

As noted above, observational studies of postmenopausal hormone therapy have reported significant reductions in CHD risk, whereas clinical trial data have reported excess risk. Possible explanations for the discrepant findings have focused on the validity of the observational data, specifically that the CHD benefit may have resulted from the healthy populations studied (healthy user bias). However, a key difference between participants in observational studies and the WHI and other randomized clinical trials is the timing of initiation of hormone therapy in relation to the onset of menopause (8). Women in observational studies tend to be younger, and most start hormone therapy soon after menopause. For example, in the Nurses' Health Study, participants were aged 30–55 yr at baseline, and approximately 80% started hormone therapy within 2–3 yr of clinical menopause. In contrast, WHI participants were older (mean baseline age 63 yr) and typically started or reinitiated their hormone therapy more than 10 yr after menopause. The older age at the time of hormone therapy initiation would be expected to be associated with atherosclerotic lesions that may be more susceptible to the prothrombotic, proinflammatory effects of estrogen.

In contrast, women with presumably normal endothelium who start estrogen soon after menopause (within 5 yr) may not be at increased risk, (or may even derive cardiovascular benefit) because advanced, unstable atherosclerotic plaques have not yet formed (Fig. 2). This hypothesis has been referred to as the timing hypothesis and is supported by data from an observational study in postmenopausal women (29), a metaanalysis of clinical trials (30), secondary analyses from the WHI (Table 1) (3, 7, 31), and an ancillary substudy of the WHI (the WHI-Coronary Artery Calcium Study) (32). In this study, coronary-artery calcium, as measured by cardiac computed tomography at trial completion, was lower in women assigned to unopposed estrogen when compared with placebo, suggesting that estrogen therapy may reduce progression of atherosclerosis and subclinical CHD in younger women who do not yet have advanced plaque. Although the evidence in favor of the timing hypothesis is compelling, the data do not justify the use of hormone therapy for prevention of CHD in younger women due to other potential risks of the treatment. Major medical organizations, including the North American Menopause Society (10), U.S. Preventive Services Task Force (33), and American College of Obstetricians and Gynecologists (34), recommend against the use of hormone therapy at any age to prevent CHD. However, the findings provide reassurance for recently menopausal women considering short-term use of estrogen for treatment of menopausal symptoms. For women with premature ovarian failure (menopause before age 40 yr), hormone therapy is recommended until the average age at natural menopause (50 to 51 yr) (10).

In contrast to CHD risk, stroke risk appears to be increased, regardless of the number of years since menopause (31, 35). However, absolute rates of stroke are low in younger women and, in the WHI, the low baseline risk and modest hazard ratio in women ages 50–59 yr resulted in minimal absolute excess risk in stroke (31). Lower estrogen doses appear to be associated with lower stroke risks (35).

There are many other unanswered questions about postmenopausal hormone therapy, including the optimal route of estrogen administration, the impact of early hormone use on later cognitive function and dementia risk (36, 37), and the role of progestins on CHD and breast cancer risk. Two trials in progress (38, 39) in younger postmenopausal women will address the timing hypothesis in relation to noninvasive measures of atherosclerosis progression (the former trial will also examine the impact of lower estrogen doses, the transdermal route of administration, and the use of natural micronized progesterone).

Treatment considerations

Clinical decision making for women interested in hormone therapy involves balancing the potential benefits of hormone therapy against its potential risks. Benefits of hormone therapy include relief from hot flashes, night sweats, and vaginal dryness and possibly improvements in sleep, mood, and concentration. In addition, hormone therapy prevents bone loss and protects against osteoporotic fractures. Assuming the timing hypothesis is correct, a younger patient, during the menopausal transition, or a recently menopausal woman (final menstrual period <5 yr ago) at low baseline risk of CHD, stroke, and venous thromboembolism are reasonable candidates for short-term hormone therapy. In clinical practice, the majority of women seeking in-

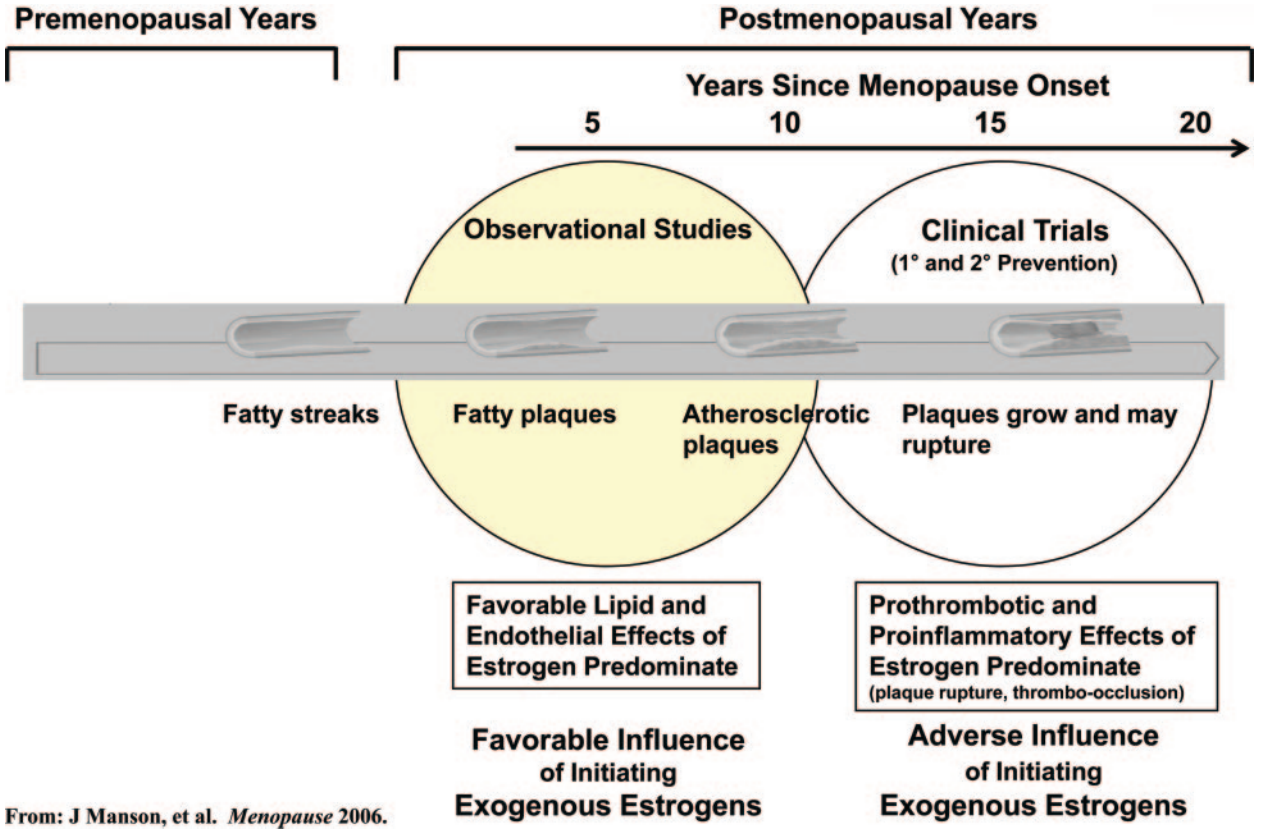

FIG. 2. Timing of hormone therapy initiation in relation to stage of atherosclerosis: observational studies *vs.* clinical trials. Adapted with permission from J. E. Manson, S. S. Bassuk, M. Harman, E. A. Brinton, M. I. Cedars, R. Lobo, G. R. Merriam, V. M. Miller, F. Naftolin, and N. Santoro: Menopause 13:139–147, 2006 (9). © The Endocrine Society.

tervention for hot flashes fall into this category. In contrast, an older woman many years past menopause (>10 yr), who is at higher risk of cardiovascular disease, is not a good candidate. Thus, the two key factors to consider in our patient with severe symptoms are where she is in the menopausal transition and whether she is in good cardiovascular health. In women who are between 5 and 10 yr past menopause, have cardiovascular risk factors at baseline, or are considering resuming estrogen because of persistent, severe hot flashes, an algorithm that estimates cardiovascular, fracture, and breast cancer risk may be helpful for clinical decision making (40, 41) (Fig. 3).

TABLE 1. Absolute excess risk of CHD and mortality

Outcome	Age (yr)			Years since menopause		
	50–59	60–69	70–79	<10	10–19	>20
CHD	−2	−1	+19[a]	−6	+4	+17[a]
Total mortality	−10	−4	+16[a]	−7	−1	+14
Global index[b]	−4	+15	+43	+5	+20	+23

Absolute excess risk of CHD and mortality (cases per 10,000 patient-years) by age and years since menopause in the combined trials (E+P and E-alone) of the WHI. Data from report published elsewhere (31).

[a] $P = 0.03$ compared with age 50–59 yr or less than 10 yr since menopause.

[b] Global index is a composite outcome of CHD, stroke, pulmonary embolism, breast cancer, colorectal cancer, endometrial cancer, hip fracture, and mortality.

Low-dose oral contraceptives

For nonsmoking, perimenopausal women with irregular or heavy menses and/or hormonally related symptoms that impair quality of life, low-dose combined oral contraceptives containing 20 μg ethinyl estradiol (roughly equivalent to 2.5 mg conjugated estrogen) are a good option. Unlike standard-dose hormone therapy, the higher doses of both estrogen and progestin in oral contraceptives suppress the hypothalamic-pituitary-ovarian axis, thereby providing contraception and bleeding control in addition to symptomatic relief. Contraindications to oral contraceptive use in this population include smoking, hypertension, migraine headaches, and diabetes because the cardiovascular risks of the pill would outweigh the benefits (42). Oral contraception should also be avoided in obese perimenopausal women because the risk of venous thromboembolism appears to be twice as high as for nonobese women (43).

The optimal timing for stopping the pill is uncertain. One approach has been to measure serum FSH concentration at the end of the placebo week to identify women who are postmenopausal and no longer need contraception. However, FSH measurements may be misleading because ovulatory women during the menopausal transition also have intermittent elevations of serum FSH (44). Another strategy is to stop the pill at age 50–51 yr, the average age of menopause, when the likelihood of ovulation is low (45, 46). The decision to then use postmenopausal hormone therapy would depend on the severity of symptoms (if

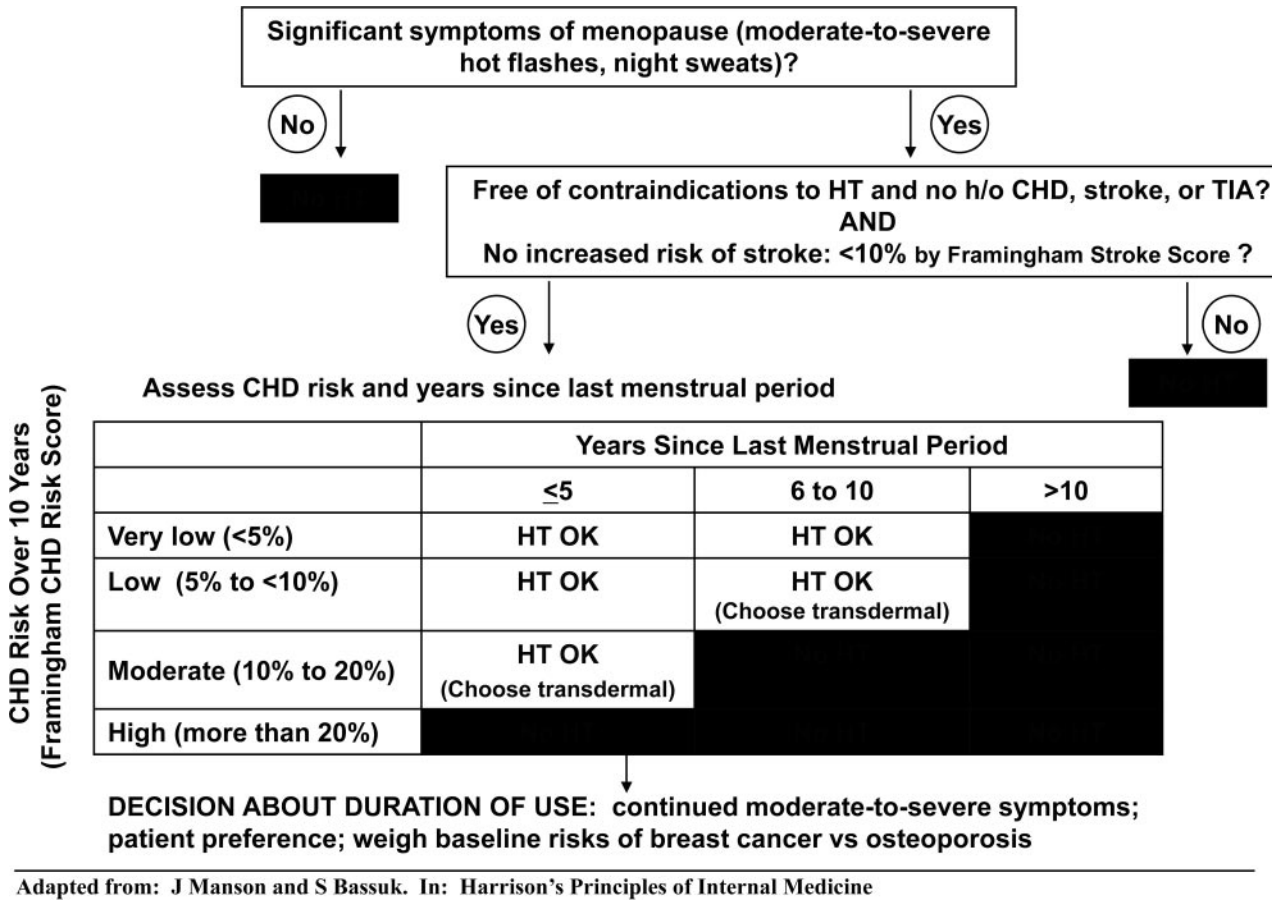

FIG. 3. Hormone therapy (HT) decision-making flow chart. TIA, Transient ischemic attack. [Adapted with permission from J. E. Manson and S. S. Bassuk: Harrison's principles of internal medicine, 17th ed. (edited by A. S. Fauci, E. Braunwald, D. L. Kasper, S. L. Hauser, D. L. Longo, J. L. Jameson, and J. Loscalzo), McGraw-Hill, New York, 2008, p 2334–2339 (40); and J. E. Manson and S. S. Bassuk: Hot flashes, hormones and your health, McGraw-Hill, New York, 2007 (41)].

they recur) and her risks for cardiovascular complications and venous thromboembolism as described above.

Postmenopausal hormone therapy

For women who are not experiencing heavy bleeding and do not need contraception, replacement doses of estrogen are used. Estrogen is the most effective therapy for hot flashes. The standard dose of estrogen used historically, and the one studied in the WHI, is 0.0625 mg conjugated equine estrogen. Equivalent doses of other estrogens include micronized 17β-estradiol (1 mg) and transdermal 17β-estradiol (50 μg/d). These doses given daily are sufficient to reduce hot flash frequency and severity by approximately 75% relative to placebo (47). In a systematic review and metaanalysis of trials of estrogen for hot flashes, conjugated estrogen and 17β estradiol (oral or transdermal) were equally effective (48). Common side effects include breast soreness and vaginal bleeding. Estrogen, especially in combination with a progestin, is also associated with increased breast density (49) and a higher rate of abnormal mammograms and breast biopsies (50, 51).

Estrogen therapy has also been shown to improve sleep and depression in some women (52, 53). Women with an intact uterus who are treated with estrogen need a progestin for prevention of endometrial hyperplasia and carcinoma. Combined estrogen-progestin therapy may be given in a cyclic or continuous regimen. Women who have undergone hysterectomy should not receive a progestin.

Low-dose estrogen

The lowest dose of estrogen that relieves menopausal symptoms should be used. Lower doses of estrogen, which have been shown to prevent bone loss, are also effective for relief of hot flashes in many women and are associated with less vaginal bleeding and breast tenderness (54). Examples of low-dose preparations include conjugated estrogen (0.3 mg), micronized 17β-estradiol (0.5 mg), and transdermal 17β-estradiol (0.025 mg). An even lower dose of estrogen is also available (transdermal estradiol 0.014 mg) (55). Progestin doses may be lowered with low-dose estrogen, but there is no consensus on optimal regimens.

Duration and stopping therapy

Ideally, hormone therapy is used for only 2–3 yr and rarely for more than 5 yr. Hot flashes and night sweats typically diminish in frequency and intensity after several years, whereas breast cancer risk increases with duration of hormone use, in particular, combined estrogen-progestin regimens. Observational studies report that 40–50% of women who start hormone therapy stop within 1 yr, and 65–75% stop within 2 yr, often with no assistance from their health care provider (56). However, for many

others, abrupt withdrawal of exogenous estrogen results in the return of hot flashes and other menopausal symptoms, sometimes requiring resumption of therapy (57). Although tapering hormone therapy doses before stopping is often recommended, the advantage of this approach remains unproven. In women with cardiovascular risk factors at baseline or in women who are considering resuming estrogen because of persistent, severe, hot flashes, an algorithm that estimates cardiovascular, fracture, and breast cancer risk may be helpful for clinical decision making (Fig. 3). Women with persistent symptoms after stopping estrogen should first undergo trials with nonhormonal options such as gabapentin or selective serotonin reuptake inhibitors (SSRIs)/serotonin norepinephrine reuptake inhibitors (SNRIs), returning to estrogen only if these alternatives are ineffective or cause significant side effects.

Bioidentical hormones

Some postmenopausal women are turning to natural or bioidentical hormone therapy because of safety concerns about conventional hormone preparations. However, available data suggest that whereas some of these products may decrease hot flushes, there is no evidence that they have any advantage over conventional hormone therapies. There are bioidentical conventional hormone therapy products (*e.g.* oral or transdermal 17β-estradiol, micronized progesterone) approved by the U.S. Food and Drug Administration (FDA) and available by prescription in retail pharmacies in a variety of doses; these are reasonable options. However, custom-compounded bioidentical hormone therapy does not have the same level of regulation for dose consistency and purity; the quality may be substandard (58), and the safety (59) and efficacy of these products have not been well established. Such concerns apply to the prescribing of individualized doses of steroid hormones such as estradiol, estrone, estriol, progesterone, testosterone, and dehydroepiandrosterone, compounded as pills, gels, sublingual tablets, or suppositories (59). The FDA has begun enforcement action against seven compounding pharmacies, stating that the claims made by these pharmacies about safety and efficacy of compounded bioidentical hormones are false and misleading, with no credible scientific evidence to support them (60).

Transdermal vs. *oral estrogen*

FDA-approved oral and transdermal estrogen preparations appear to be equally effective for hot flashes and bone mineral density, but they have different metabolic profiles. Potential advantages of oral estrogen include its ease of administration and favorable effects on lipoprotein profiles (high-density lipoprotein and low-density lipoprotein), whereas potential disadvantages of oral estrogen include unfavorable changes in serum triglycerides, C-reactive protein, fibrinogen, factor VII, and plasminogen activator inhibitor type 1 (61). Also, oral estrogen is more likely to increase SHBG and reduce free testosterone levels; thus, it may be more likely than transdermal estrogen to have adverse effects on libido. Similar effects on T_4 binding globulin and bioavailable T_4 have been identified (62). It is uncertain whether effects on endothelial function and glucose tolerance vary by route of estrogen delivery. Epidemiological data and a metaanalysis of clinical trials suggest a higher risk of venous thromboembolic events with oral rather than transdermal estrogen preparations (63). Clinical trial data that address the effect of transdermal estrogen on CHD and stroke risk are limited. Other nonoral estrogen preparations available for the treatment of hot flashes include a topical estrogen gel, lotion, spray, and a vaginal ring.

Choice of progestin regimen

In the WHI, combined estrogen-progestin therapy was associated with increased risk of CHD and breast cancer, whereas unopposed estrogen was not, suggesting that progestins contribute to both risks. Therefore, there is considerable interest in minimizing progestin dose and duration. Progestins are typically given for 12–14 d (cyclic regimens) or daily with continuous regimens. The progestin dose for continuous regimens is typically half of that used for cyclic regimens. Endometrial protection with long-cycle progestins (*e.g.* 14 d every 3 months) may not be as reliable (64). A levonorgestrel-containing intrauterine device that releases 20 μg of levonorgestrel per day is available for contraceptive use; it has also been used off label for endometrial protection in perimenopausal and postmenopausal women using estrogen therapy and appears to prevent endometrial hyperplasia (65). A lower-dose levonorgestrel-intrauterine device that releases 14 μg/d is approved in Europe for postmenopausal hormone therapy. There are theoretical reasons to believe that natural micronized progesterone might be safer for the cardiovascular system (less adverse effect on lipids) (66), and limited data suggest that it may be associated with a lower breast cancer risk than synthetic progestins (67), but these potential advantages are not well established.

Vaginal estrogen

Both systemic and vaginal estrogens are effective for genitourinary atrophy symptoms, but vaginal estrogen is the preferred therapy for isolated vaginal symptoms, given its potent local effect and minimal degree of systemic absorption (68). For women with mild urogenital atrophy symptoms, vaginal moisturizing agents (polycarbophil-based, bioadhesive polymers) on a regular basis and lubricants during intercourse are a reasonable first step. However, for women with moderate to severe symptoms, low-dose vaginal estrogen should be tried (21). Low-dose vaginal estradiol tablets and rings result in lower serum estradiol concentrations when compared with standard doses of vaginal estrogen cream (69). In the United States, effective low-dose preparations include a vaginal estradiol tablet (25 μg administered daily for 2 wk, followed by twice weekly) and a vaginal ring that delivers approximately 8–9 μg/d. A lower-dose vaginal tablet (10 μg) is available in Europe. Caution should be used when considering the use of vaginal estrogen in women with breast cancer, particularly in women taking aromatase inhibitors (70).

Nonestrogen therapies

A number of other therapies for hot flashes have been used off label for women who cannot or choose not to take estrogen. In a metaanalysis of 43 trials of nonestrogen therapies, SSRIs, SNRIs, clonidine, and gabapentin were all more effective than

placebo (71). Although all reduced the number of hot flashes per day, the mean difference compared with placebo for SSRIs/SNRIs and clonidine was approximately one hot flash per day and for gabapentin, two hot flashes per day. These effects are less than what has been observed with estrogen, and these drugs are all associated with significant side effects that may limit their use in some women. In the same metaanalysis, red clover extracts were ineffective, and the results for soy isoflavone extracts were mixed. Effective doses for hot flashes include paroxetine 10–20 mg/d, paroxetine controlled release 12.5–25 mg/d, venlafaxine 75 mg/d, and gabapentin 900 mg at bedtime. Fluoxetine may have a modest effect on hot flashes (72), but sertraline does not appear to be effective (71). Desvenlafaxine, a new SNRI, appears to be more effective than placebo at a dose of 100 mg/d (73). SSRIs, in particular paroxetine, reduce the metabolism of tamoxifen to its most active metabolite, endoxifen (74). Therefore, paroxetine use should be avoided in women with breast cancer receiving adjuvant tamoxifen therapy.

Black cohosh, one of the most commonly used complementary therapies by menopausal women, was no more effective than placebo in a high-quality, randomized, controlled trial (75). High-dose progestins are effective but are infrequently used in women because of side effects and concerns about breast cancer risk (76). Tibolone, a synthetic steroid whose metabolites have estrogenic, androgenic, and progestagenic properties, reduces vasomotor symptoms, fracture risk, and possibly breast cancer risk (77, 78). However, there are significant concerns about excess stroke risk with tibolone (78, 79). Tibolone is available in many countries, but not the United States.

Returning to the patient

This patient has symptoms that are attributable to the menopause: hot flashes, sleep disturbances, and vaginal dryness, which are severe enough to interfere with her quality of life. Because it has been less than 5 yr since her final menstrual period and she is at low risk for cardiovascular disease, short-term hormone therapy is a reasonable option. Transdermal rather than oral estrogen would be preferred because oral estrogen is associated with an increase in serum thyroxine-binding globulin concentrations, which might necessitate adjustments in her levothyroxine dose. In addition, oral estrogen is more likely than transdermal estrogen to increase the risk of venous thromboembolism (63).

She was initially started on a low dose of transdermal estradiol (0.025 mg), but the dose was increased to 0.0375 mg after 1 month because of persistent bothersome symptoms. The higher dose was associated with significant reduction in all of her symptoms. A progestogen was added because the patient has an intact uterus. She was initially started on micronized progesterone 200 mg for 14 d each month. However, she noticed bothersome mood symptoms on the days of progesterone therapy, which resolved when she was switched to a continuous progesterone regimen (micronized progesterone 100 mg daily). She initially had intermittent spotting on the continuous regimen but developed amenorrhea after 3 months. After 2 yr of therapy, her dose of estrogen was decreased to 0.025 mg without recurrent symptoms. After 3 yr, the patient stopped estrogen on her own because of concerns about breast cancer. Her vasomotor symptoms returned as did her vaginal dryness. Gabapentin therapy (900 mg at bedtime) and vaginal estrogen (25 μg vaginal tablets) were both started. She experienced a significant reduction in hot flash frequency and severity, and the vaginal dryness resolved. For prevention of bone loss and CHD, she was counseled on the importance of continuing her calcium and vitamin D supplements, regular exercise, and maintaining her current weight.

Conclusions

Clinical decision making for women interested in hormone therapy involves balancing the potential benefits of hormone therapy against its potential risks. Accumulating data suggest that initiation of estrogen many years after menopause is associated with excess CHD risk, whereas initiation soon after menopause is not. Therefore, most now agree that short-term estrogen therapy, using the lowest effective estrogen dose, is a reasonable option for recently menopausal women who have moderate to severe symptoms and no previous history of, or at elevated risk of, CHD, stroke, breast cancer, or venous thromboembolism. Women are generally treated for 2–3 yr but rarely more than 5 yr because symptoms diminish after several years, whereas the risk of breast cancer increases with longer duration of hormone therapy. A minority of women may need long-term therapy for severe, persistent symptoms after stopping hormone therapy. However, these women should first undergo trials of nonhormonal options such as gabapentin or SSRIs/SNRIs, returning to estrogen only if these alternatives are ineffective or cause significant side effects. Low-dose vaginal estrogens are a highly effective therapy for isolated genitourinary atrophy symptoms, with minimal systemic absorption and endometrial effects.

Acknowledgments

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