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NAMS Position Statement

The 2022 hormone therapy position statement of The North American Menopause Society

Abstract

"The 2022 Hormone Therapy Position Statement of The North American Menopause Society" (NAMS) updates "The 2017 Hormone Therapy Position Statement of The North American Menopause Society" and identifies future research needs. An Advisory Panel of clinicians and researchers expert in the field of women's health and menopause was recruited by NAMS to review the 2017 Position Statement, evaluate new literature, assess the evidence, and reach consensus on recommendations, using the level of evidence to identify the strength of recommendations and the quality of the evidence. The Advisory Panel's recommendations were reviewed and approved by the NAMS Board of Trustees.

Hormone therapy remains the most effective treatment for vasomotor symptoms (VMS) and the genitourinary syndrome of menopause and has been shown to prevent bone loss and fracture. The risks of hormone therapy differ depending on type, dose, duration of use, route of administration, timing of initiation, and whether a progestogen is used. Treatment should be individualized using the best available evidence to maximize benefits and minimize risks, with periodic reevaluation of the benefits and risks of continuing therapy.

For women aged younger than 60 years or who are within 10 years of menopause onset and have no contraindications, the benefit-risk ratio is favorable for treatment of bothersome VMS and prevention of bone loss. For women who initiate hormone therapy more than 10 years from menopause onset or who are aged older than 60 years, the benefit-risk ratio appears less favorable because of the greater absolute risks of coronary heart disease, stroke, venous thromboembolism, and dementia. Longer durations of therapy should be for documented indications such as persistent VMS, with shared decision-making and periodic reevaluation. For bothersome genitourinary syndrome of menopause symptoms not relieved with over-the-counter therapies in women without indications for use of systemic hormone therapy, low-dose vaginal estrogen therapy or other therapies (eg, vaginal dehydroepiandrosterone or oral ospemifene) are recommended.

Key Words: Breast cancer – Cardiovascular disease – Cognition – Genitourinary syndrome of menopause – Hormone therapy – Menopause – Vasomotor symptoms.

This Position Statement uses gender-specific language as reflected in the referenced publications. However, The North American Menopause Society recognizes that some persons experiencing menopause may identify differently than with the gender and pronouns used in the statement.

This NAMS Position Statement has been endorsed by the American Association of Clinical Endocrinologists; the American Association of Nurse Practitioners; the American Medical Women's Association; the American Society for Reproductive Medicine; the Asociacion Argentina para el Estudio del Climacterio; the Asociacion Mexicana para el Estudio del Climaterio; the Australasian Menopause Society; the Canadian Menopause Society; the Chilean Climacteric Society; the Chinese Menopause Society; the Colombian Association of Menopause; the Czech Menopause and Andropause Society; the Dutch Menopause Society; the European Menopause and Andropause Society; the German Menopause Society; HealthyWomen; the Indian Menopause Society; the International Osteoporosis Foundation; the International Society for the Study of Women's Sexual Health; the Japan Society of Menopause and Women's Health; the Korean Society of Menopause; the Mexican College of Specialists in Gynecology and Obstetrics; the National Association of Nurse

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Practitioners in Women's Health; the Philippine Society of Climacteric Medicine; the Society of Obstetricians and Gynaecologists of Canada; the Spanish Menopause Society; the Taiwanese Menopause Society; and the Thai Menopause Society.

METHODS

An Advisory Panel of clinicians and research experts in the field of women's health and menopause were enlisted to review "The 2017 Hormone Therapy Position Statement of The North American Menopause Society," evaluate the literature published subsequently, and conduct an evidence-based analysis, with the goal of reaching consensus recommendations.

NAMS acknowledges that no single trial's findings can be extrapolated to all women. The Women's Health Initiative (WHI) is the largest, randomized, controlled trial (RCT) of hormone therapy in women aged 50 to 79 years, and its findings were therefore given prominent consideration. However, it is important to note that the WHI employed just one route of administration (oral), one formulation of estrogen (conjugated equine estrogens [CEE] 0.625 mg), and only one progestogen (medroxyprogesterone acetate [MPA] 2.5 mg), with limited enrollment of women with bothersome vasomotor symptoms (VMS; hot flashes, night sweats) who were aged younger than 60 years or who were fewer than 10 years from menopause onset—the group of women for whom hormone therapy is currently primarily indicated. In addition, the WHI trials did not include women with early or premature menopause. In achieving consensus, the panel took into consideration the level of evidence (RCTs>longitudinal studies>cross-sectional studies), sample sizes, risk of bias, data from meta-analyses and systematic reviews, and expert opinion from guidelines from other major medical societies, when appropriate.

"The 2022 Hormone Therapy Position Statement of The North American Menopause Society" was written after this extensive review of the pertinent literature and includes key points identified during the review process. The resulting manuscript was submitted to and reviewed and approved by the NAMS Board of Trustees.

When recommendations are provided, they are graded according to these categories:

- Level I: Based on good and consistent scientific evidence.
- Level II: Based on limited or inconsistent scientific evidence.
- Level III: Based primarily on consensus and expert opinion.

EXPLAINING HORMONE THERAPY RISK

Healthcare professionals caring for menopausal women should understand the basic concepts of relative risk and absolute risk to communicate the potential benefits and risks of hormone therapy and other therapies. Relative risk (risk ratio) is the ratio of event rates in two groups, whereas absolute risk (risk difference) is the absolute difference in the event rates between two groups.[1] Absolute risks are more useful to convey risks and benefits in the clinical setting.

Findings on hormone therapy from RCTs are generally considered to provide stronger evidence, and those from observational studies should be interpreted with greater caution, given the potential for confounding. Very small effect sizes may have more limited clinical or public health importance, especially if outcomes are rare (Table 1).[2]

Key points

- Findings from RCTs of hormone therapy can be interpreted with greater confidence than observational studies. (Level I)
- Smaller effect sizes may be less clinically relevant, particularly for rare outcomes. (Level I)

FORMULATION, DOSING, ROUTES OF ADMINISTRATION, AND SAFETY

Formulation

Estrogens

Available estrogen preparations include CEE, synthetic conjugated estrogens (CE), micronized 17β-estradiol, and ethinyl estradiol. Conjugated equine estrogens, used in the WHI trials, contain a mixture of CE purified from the urine of pregnant mares, including estrone sulfate. In postmenopausal women, estrone sulfate is a naturally occurring estrogen that serves as a precursor and intermediate for the formation of estrone (a weak estrogen) and estradiol (a more potent estrogen and the predominant estrogen in premenopausal and perimenopausal women). Synthetic CE is a blend of synthetic estrogen substances including estrone sulfate, equilin sulfate, and estradiol sulfate. Prescription formulations of micronized 17β-estradiol are identical to the structure of estradiol that is produced by the ovaries. Estradiol is reversibly converted to estrone. Ethinyl estradiol is a synthetic estrogen primarily used in combination with a progestin in hormone contraceptives.

Progestogens administered with estrogen

Progestogens (general category that includes synthetic progestins and progesterone) commonly coadministered with estrogen in women with a uterus include MPA, norethindrone acetate (NETA), and micronized progesterone (MP). Medroxyprogesterone acetate, levonorgestrel, and NETA are synthetic progestins, whereas MP is structurally identical to the progesterone produced by the corpus luteum.

Progestogen indication: need for endometrial protection

Chronic unopposed endometrial exposure to estrogen increases the risk for endometrial hyperplasia or cancer.[3,4] The menopause-related indication for progestogen use is to prevent endometrial overgrowth and the increased risk of endometrial cancer during estrogen therapy (ET) use. Women with an intact uterus using systemic ET should receive adequate progestogen, unless they are taking CEE combined with bazedoxifene (BZA).[5-7]

TABLE 1. *Frequency of adverse drug reactions*

Very common	≥1/10
Common (frequent)	≥1/100 and < 1/10
Uncommon (infrequent)	≥1/1,000 and < 1/100
Rare	≥1/10,000 and < 1/1,000 (≤10/10,000/y)
Very rare	<1/10,000

Council for International Organizations of Medical Sciences (CIOMS).[2]

Progestogen dose *and* duration of use are important to ensuring endometrial protection. When adequate progestogen is combined with systemic estrogen, the risk of endometrial neoplasia is not higher than in untreated women. In the WHI, use of continuous oral CEE plus MPA daily was associated with a risk of endometrial cancer similar to placebo (hazard ratio [HR], 0.81; 95% confidence interval [CI], 0.48-1.36),[8] with significant reduction of risk after a median 13 years' cumulative follow-up (HR, 0.67; 95% CI, 0.49-0.91).[9] A systematic review suggested an increased risk of endometrial hyperplasia with MP containing estrogen plus progestogen therapy (EPT).[4] A meta-analysis suggested increased risk of endometrial cancer (relative risk [RR], 1.2) with noncontinuous combined EPT (type of progestogen not specified) but not with continuous EPT.[10] Oral MP should be adequately dosed for prevention of endometrial hyperplasia (eg, 200 mg/d for 12-14 d/mo).[11,12] Off-label use of a levonorgestrel-containing intrauterine device to prevent endometrial hyperplasia may avoid adverse systemic effects of progestogens and can protect against unwanted pregnancy in women initiating hormone therapy for symptom management before their final menstrual period. There are limited clinical trial data to support this use.[13] In women using EPT, unscheduled bleeding occurring more than 6 months after initiation should be investigated.

Tissue-selective estrogen complex

Bazedoxifene, a selective estrogen-receptor modulator (SERM; estrogen agonist or antagonist), has been combined with CEE to form a tissue-selective estrogen complex (TSEC). Studies of up to 2 years in duration suggest that the combination of BZA plus CEE provides endometrial protection without the need for a progestogen.[7,14-16] In women using BZA plus CEE, unscheduled bleeding occurring more than 6 months after initiation should be investigated.

Dosing

Estrogen therapy

The therapeutic goal should be to use the most appropriate, often lowest, effective dose of systemic ET consistent with treatment goals. The appropriate dose of progestogen is added to provide endometrial protection if a woman has a uterus, unless CEE is combined with BZA.

Progestogen therapy

Progestogen dosing-regimen options that provide for endometrial safety are dependent on the potency of the progestogen and vary with the estrogen dose. Different types and doses of progestogens, routes of administration, and types of regimen (sequential or continuous-combined) may have different associations with health outcomes, and patient preference can and should be considered because many women will opt for regimens that avoid periodic menstrual bleeding.[17]

Routes of administration

For treating VMS, systemic estrogens can be prescribed as oral drugs; transdermal patches, sprays, and gels; or as vaginal rings. Meta-analysis of estrogen preparations found no evidence of a significant difference between transdermal EPT and oral EPT for alleviating VMS.[18] Transdermal estradiol and oral CEE are similarly effective in alleviating VMS[19]; however, clinical trials directly comparing risk of myocardial infarction (MI), stroke, breast cancer, and venous thromboembolism (VTE) associated with various estrogen routes and doses are lacking. Progestogens are available as oral drugs or combination patches with estrogen.

Nonoral routes of administration (eg, transdermal, vaginal) may offer potential advantages because nonoral routes bypass the first-pass hepatic effect; however, it is unknown whether nonoral routes of ET or EPT are associated with lower risk (vs oral routes) of VTE, breast cancer, and cardiovascular (CV) events because clinical trials have not been designed to examine those outcomes.

Safety

During the active treatment phase of the WHI, a higher incidence of breast cancer (risk is considered rare; Table 1) was seen in women assigned to CEE plus MPA compared with placebo but a reduced incidence in women assigned to CEE alone compared with placebo.[20] After a median of 20 years' follow-up (including intervention and postintervention follow-up), the lower incidence of breast cancer in women assigned to CEE alone versus placebo and the higher incidence of breast cancer in women assigned to CEE plus MPA persisted.[21] In contrast to findings of the WHI, observational data have shown that breast cancer risk was increased in women using either systemic ET or EPT and was duration-dependent.[22]

Meta-analysis of studies in which most participants (70%) were aged older than 60 years and had some degree of comorbidity shows that EPT is associated with small increases in the risk of a coronary event (after 1 y), VTE (after 1 y), stroke (after 3 y), breast cancer (after 5 y), and gallbladder disease (after 5 y); ET (included oral, transdermal, subcutaneous, and intranasal preparations without disaggregation of data by route of administration) increases the risk of VTE (after 1-2 y), stroke (after 7 y), and gallbladder disease (after 7 y). One trial examined outcomes in women aged 50 to 59 years who were relatively healthy and found that the only significantly increased risk was of VTE in women on EPT.[23] Although comparative RCT data are lacking, there may be less VTE risk associated with lower doses of oral ET than with higher doses.[24,25] Observational studies have not demonstrated an increased risk of VTE with transdermal ET, and limited observational data suggest less risk with transdermal versus oral ET, but comparative RCT data again are lacking.[26-28] The choice of progestogen may also affect risk for VTE, with MP potentially being less thrombogenic than other progestins.[26,28]

The WHI provided information on the rare risks of CEE combined with MPA. It is unknown whether oral MP-containing EPT similarly increases the risk of breast cancer, stroke, gallbladder disease, MI, or VTE because clinical trials have not yet been designed to examine these outcomes. Clinical trials are needed to establish the effect of different types of progestogens and different estrogen doses and administration routes on VTE risk.[29] Overall, ET and EPT are each associated with rare increased risk of gallbladder disease, stroke, VTE, and urinary incontinence; EPT also is associated with increased risk of breast cancer.[22,30] Studies

were not designed to determine whether the combination of BZA plus CEE further increases the risk of VTE beyond the increased risk conferred by CEE alone.

In women in the WHI aged 50 to 59 years, CEE plus MPA (average, 5.6 y of use) or CEE alone (average, 7.2 y of use in women with previous hysterectomy) did not increase cancer mortality or CV mortality after a median of 18 years' follow-up compared with placebo. In women aged 50 to 59 years at randomization, all-cause mortality was significantly reduced in the pooled trials versus placebo (HR, 0.69; 95% CI, 0.51-0.94). With age groups combined, breast cancer mortality was reduced in women using CEE alone (HR 0.55; 95% CI, 0.33-0.92), and Alzheimer disease or dementia mortality was reduced in women using CEE alone (HR, 0.74; 95% CI, 0.59-0.94) and in the pooled trials (HR, 0.85; 95% CI, 0.74-0.98) after a median of 18 years' follow-up.[31] After a median of 20 years' follow-up (including intervention and postintervention follow-up), the lower breast cancer mortality in women assigned to CEE alone versus placebo persisted, whereas breast cancer mortality was not significantly different in women assigned to CEE plus MPA versus placebo.[21]

Contraindications for oral and transdermal hormone therapy include unexplained vaginal bleeding; liver disease; prior estrogen-sensitive cancer (including breast cancer); prior coronary heart disease (CHD), stroke, MI, or VTE; or personal history or inherited high risk of thromboembolic disease.

Potential risks of hormone therapy for women aged younger than 60 years include the rare risk of breast cancer with EPT; endometrial hyperplasia and endometrial cancer with inadequately opposed estrogen; VTE; and gallbladder disease (Figure 1).[9]

More common adverse events (AEs) include nausea, bloating, weight gain, fluid retention, mood swings (progestogen related), breakthrough bleeding, headaches, and breast tenderness.

Key points

- The appropriate, often lowest, effective dose of systemic ET consistent with treatment goals that provides benefits and minimizes risks for the individual woman should be the therapeutic goal. (Level III)
- The various formulations, doses, and routes of prescription hormone therapy preparations have comparable high efficacy for relieving VMS. (Level I)
- Formulation, dose, and route of administration for hormone therapy should be determined individually and reassessed periodically. (Level III)
- Different hormone therapy doses, formulations, and routes of administration may have different effects on target organs, potentially allowing options to minimize risk. (Level II)
- The appropriate formulation, dose, and route of administration of progestogen is needed to counter the proliferative effects of systemic estrogen on the endometrium. (Level I)
- Overall, the increased absolute risks associated with EPT and ET are rare (<10/10,000/y) and include increased risk for VTE and gallbladder disease. In addition, EPT carries a rare increased risk for stroke and breast cancer, and if estrogen is inadequately opposed, an increased risk of endometrial hyperplasia and endometrial cancer. (Level I)
- The absolute risks are reduced for all-cause mortality, fracture, diabetes mellitus (EPT and ET), and breast cancer (ET) in women aged younger than 60 years (Figure 1).[9] (Level I)

FDA-APPROVED INDICATIONS

Vasomotor symptoms

Hormone therapy has been shown in double-blind RCTs to relieve VMS[32] and is FDA approved as first-line therapy for relief of moderate to severe VMS because of menopause.

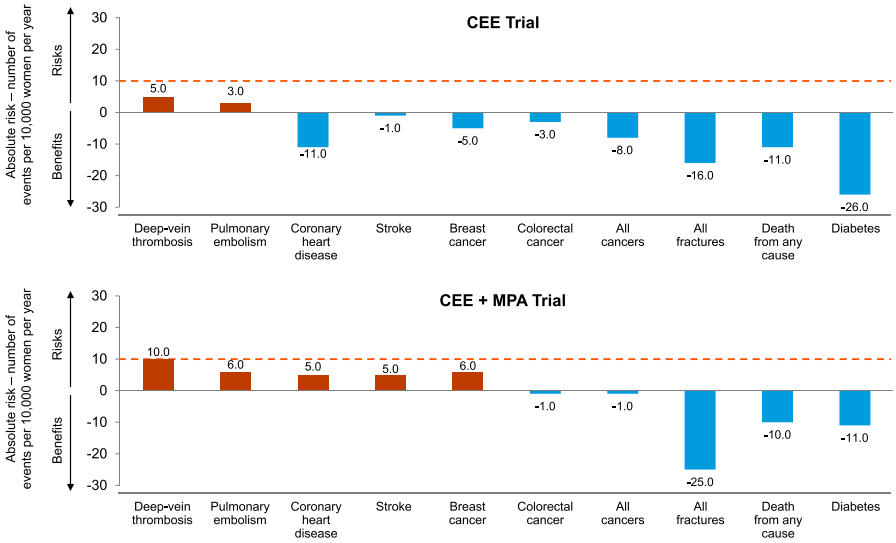

FIG. 1. Benefits and risks of the two hormone therapy formulations, conjugated equine estrogens (CEE) alone or in combination with medroxyprogesterone acetate (MPA), evaluated in the Women's Health Initiative for women aged 50 to 59 years. Risks and benefits are expressed as the difference in number of events (number in the hormone therapy group minus the number in the placebo group) per 10,000 women per year, with <10 per 10,000 per year representing a rare event (dashed red line). Adapted from Manson JE, et al.[9]

Prevention of bone loss

Hormone therapy has been shown in double-blind RCTs to prevent bone loss, and in the WHI, to reduce fractures in postmenopausal women without osteoporosis.[33,34] The FDA indication includes prevention, but not treatment, of postmenopausal osteoporosis. Nonestrogen medications are preferred for treatment of existing osteoporosis.

Premature hypoestrogenism

Hormone therapy is FDA approved for women with hypoestrogenism resulting from hypogonadism, bilateral oophorectomy (BO), or primary ovarian insufficiency (POI). Health benefits have been shown, with greater evidence for women with BO, for menopause symptoms and for prevention of bone loss and in observational studies, heart disease and cognitive decline or dementia.[35-44]

Genitourinary symptoms

Hormone therapy has been shown in RCTs to effectively treat symptoms of vulvovaginal atrophy (VVA).[45,46] Hormone therapy is FDA approved to treat moderate to severe symptoms of VVA and dyspareunia because of menopause but with the preference for low-dose vaginal therapy if solely prescribed for vulvar or vaginal symptoms.

Two vaginal therapies, vaginal ET and vaginal dehydroepiandrosterone (DHEA), have been FDA approved for treatment of moderate to severe dyspareunia, a symptom of VVA resulting from menopause. One oral therapy (a SERM) has FDA approval as well.

Key point

- Hormone therapy is FDA approved for four indications: moderate to severe VMS; prevention of osteoporosis in postmenopausal women; treatment of hypoestrogenism caused by hypogonadism, BO, or POI; and treatment of moderate to severe vulvovaginal symptoms. FDA guidance for treatment of genitourinary symptoms related to menopause in the absence of indications for systemic ET suggests the use of low-dose topical vaginal ET. (Level I)

COMPOUNDED BIOIDENTICAL HORMONES

The term *bioidentical hormone therapy* (similar to endogenous) can be misleading because there are both government-approved and compounded bioidentical hormone therapies. Government-approved (in the United States, FDA-approved) bioidentical hormones include estradiol, estrone, and MP, which are regulated and monitored for purity and efficacy. These are dispensed with package inserts containing extensive product information (based on RCTs) and may include black-box warnings for AEs. In contrast, compounded bioidentical hormone therapies are prepared by a compounding pharmacist using a provider's prescription. These therapies may combine multiple hormones (estradiol, estrone, estriol, DHEA, testosterone, progesterone) and use untested, unapproved combinations or formulations or are administered in nonstandard or untested routes such as subdermal implants, pellets, or troches.[47-50]

Compounded bioidentical hormone therapy has been prescribed or dosed on the basis of serum, salivary, or urine hormone testing; however, the use of such testing to guide hormone therapy dosing is considered unreliable because of differences in hormone pharmacokinetics and absorption, diurnal variation, and interindividual and intraindividual variability.[51-54]

There is a dearth of safety and efficacy data with little or no high-quality pharmacokinetic data to provide evidence of safety and efficacy of compounded bioidentical hormone therapy and insufficient evidence to support overall clinical use of compounded bioidentical hormone therapy for treatment of menopause symptoms. Compounded bioidentical hormone therapy presents safety concerns, such as minimal government regulation and monitoring, overdosing and underdosing, presence of impurities and lack of sterility, lack of scientific efficacy and safety data, and lack of a label outlining risks.[55]

Patient preference for compounded bioidentical hormone therapy should be discussed.[56] Prescribers should only consider compounded hormone therapy if women cannot tolerate a government-approved therapy for reasons such as allergies to ingredients in a government-approved hormone therapy formulation or for a dose or formulation not currently available in government-approved therapies. Patient preference alone should not be used to justify use of compounded bioidentical hormone therapy. Prescribers of compounded bioidentical hormone therapy should document the medical indication for a compounded bioidentical hormone over government-approved therapies.[55] In addition to including financial disclosures of prescribers, pharmacists, and pharmacies, compounding pharmacists should provide standardized content information, include warnings for potential AEs, note that the preparation is not government approved, and provide guidance on reporting AEs.

Key points

- Compounded bioidentical hormone therapy presents safety concerns, such as minimal government regulation and monitoring, overdosing and underdosing, presence of impurities and lack of sterility, lack of scientific efficacy and safety data, and lack of a label outlining risks. (Level I)
- Salivary and urine hormone testing to determine dosing are unreliable and not recommended. Serum hormone testing is rarely needed. (Level II/III)
- Shared decision-making is important, but patient preference alone should not be used to justify the use of compounded bioidentical hormone preparations, particularly when government-regulated bioidentical hormone preparations are available. (Level III)
- Situations in which compounded bioidentical hormones could be considered include allergies to ingredients in a government-approved formulation or dosages not available in government-approved products. (Level III)

MENOPAUSE SYMPTOMS

Vasomotor symptoms

Vasomotor symptoms are associated with diminished sleep quality, irritability, difficulty concentrating, reduced quality of

life,[57] and poorer health status.[58] Frequent VMS persisted on average 7.4 years in the Study of Women's Health Across the Nation[59] and appear to be linked to CV, bone, and cognitive risks.[60-65] Compared with placebo, ET alone or EPT was found to reduce weekly symptom frequency by 75% (95% CI, 64.3-82.3) and significantly reduce symptom severity (odds ratio [OR], 0.13; 95% CI, 0.07-0.23),[34] with no other pharmacologic or alternative therapy found to provide more relief. Considering the dose, there are no appreciable differences in the efficacy of oral versus nonoral formulations, but EPT appears slightly more effective than ET alone.

Lower doses of hormone therapy (oral CEE 0.3 mg; oral 17β-estradiol ≤0.5 mg; or estradiol patch 0.025 mg) may take 6 to 8 weeks to provide adequate symptom relief. Although the lowest dose-approved estradiol weekly patch (0.014 mg/d) appears effective in treating VMS,[66] it is FDA approved only for prevention of osteoporosis.

Progestogen-only formulations have been found to be effective in treating VMS,[67,68] including MPA 10 mg,[69] oral megestrol acetate 20 mg,[70] and MP 300 mg.[68] No long-term studies have addressed the safety of progestogen-only treatment of menopause symptoms.

Vasomotor symptoms return in approximately 50% of women when hormone therapy is discontinued.[71,72] There is no consensus about whether stopping abruptly or gradually tapering the dose is preferable.

Sleep disturbances

Sleep disturbances are common after menopause and begin in perimenopause. Sleep disruptions are strongly associated with VMS and a decreased quality of life. Poorer sleep quality has been associated with mood fluctuations, memory problems, metabolic syndrome, obesity, and other CV risk factors. Short (or very long) sleep duration, poor sleep quality, and insomnia have been associated with greater cardiovascular disease (CVD) risk.[73-76]

Hormone therapy in the form of low-dose estrogen or progestogen may improve chronic insomnia in menopausal women, with 14 of 23 studies reviewed showing positive results.[77] There is some evidence that transdermal ET may benefit sleep in perimenopausal women, independent of VMS.[78]

Oral MP has mildly sedating effects, reducing wakefulness without affecting daytime cognitive functions, possibly through a GABA-agonistic effect,[79] and should therefore be administered at night. A systematic review and meta-analysis concluded that MP improved sleep-onset latency but not sleep duration or sleep efficiency in RCTs in postmenopausal women.[80]

Genitourinary symptoms

The genitourinary syndrome of menopause (GSM) includes the signs and symptoms associated with menopause-related estrogen deficiency involving changes to the labia, vagina, urethra, and bladder and includes VVA.[81] Symptoms may include genital dryness, burning, and irritation; sexual symptoms of diminished lubrication and pain with sexual activity; and urinary symptoms of urgency, dysuria, and recurrent urinary tract infections (UTI). Estrogen therapy, specifically vaginal ET, is an effective treatment for GSM, with no evidence to suggest a difference in safety or efficacy between the various vaginal ET preparations.[45,82,83]

Low-dose vaginal ET preparations include creams, tablets, rings, and a softgel vaginal insert. The different preparations all contain estradiol, and one cream preparation contains CEE. One ring is available for long-term (3 mo) delivery of low-dose estradiol to the vagina, but another is aimed at providing systemic levels of estradiol. The low-dose vaginal estradiol products available result in minimal systemic absorption.[84-86] It is preferred to insert vaginal products (except for the vaginal ring) in the proximal, lower third of the vagina rather than in the upper third. This improves efficacy for genitourinary symptoms and attenuates estradiol absorption.[86]

Because of the potential risk of small increases in circulating estrogens,[87] the decision to use low-dose vaginal ET in women with breast cancer should be made in conjunction with their oncologists.[88,89] This is particularly important for women on aromatase inhibitors (AIs) with suppressed plasma levels of estradiol,[90] although no increased risk was seen in an observational trial of survivors of breast cancer on tamoxifen or aromatase therapy with low-dose vaginal ET during 3.5 years' mean follow-up.[91]

A progestogen is generally not indicated when ET is administered vaginally for GSM at the recommended low doses, although clinical trial data supporting endometrial safety beyond 1 year are lacking.[85] Vaginal bleeding in a postmenopausal woman requires thorough evaluation. Long-term follow up of women in the WHI observational study and in the Nurses' Health Study who used vaginal ET indicated no increased risk of adverse CV or cancer outcomes.[92,93]

Nonestrogen therapies that improve genitourinary symptoms and are approved for relief of dyspareunia in postmenopausal women include ospemifene[94] and intravaginal DHEA.[95]

Urinary tract symptoms (including pelvic floor disorders)

Vaginal ET increases the number of vessels around the periurethral and bladder neck region[96] and has been shown to reduce the frequency and amplitude of detrusor contractions to promote detrusor muscle relaxation.[97,98] Estrogen therapy, along with pelvic floor training, pessaries, or surgery, may improve synthesis of collagen and improve vaginal epithelium, but evidence for effectiveness for pelvic organ prolapse is lacking.[99]

Two large trials found that users of systemic hormone therapy (CEE 0.625 mg plus MPA 2.5 mg) had an increased incidence of stress incontinence.[100,101] Increased incontinence was found in women using oral ET alone (relative risk [RR], 1.32; 95% CI, 1.17-1.48) and in those using EPT (RR, 1.11; 95% CI, 1.04-1.18).[102] Vaginal estrogen use showed a decreased incidence of incontinence (RR, 0.74; 95% CI, 0.64-0.86) and overactive bladder, with one to two fewer voids in 24 hours and reduced frequency and urgency. A reduced risk of recurrent UTIs with vaginal but not oral estrogen has been shown in RCTs.[103,104]

Sexual function

Systemic hormone therapy and low-dose vaginal ET provide effective treatment of GSM, improving sexual problems by increasing lubrication, blood flow, and sensation in vaginal tissues.[105] Studies have not found a significant effect of ET on

sexual interest, arousal, and orgasmic response independent from its role in treating menopause symptoms.[106-108]

If systemic hormone therapy is indicated in women with low libido, transdermal ET formulations may be preferred to oral, given increased sex hormone-binding globulin and reduced bioavailability of testosterone with oral ET.[105,109,110]

Conjugated equine estrogens combined with BZA relieves dyspareunia and improves some aspects of sexual function in postmenopausal women.[111-114]

Key points

Vasomotor symptoms

- Vasomotor symptoms may begin during perimenopause, and frequent VMS may persist on average 7.4 years or longer. They affect quality of life and may be associated with CV, bone, and brain health. (Level I/II)
- Hormone therapy remains the gold standard for relief of VMS.
  - Estrogen-alone therapy can be used for symptomatic women without a uterus. (Level I)
  - For symptomatic women with a uterus, EPT or a TSEC protects against endometrial neoplasia. (Level I)
- Shared decision-making should be used when considering formulation, route of administration, and dose of hormone therapy for menopause symptom management, with adjustment tailored to symptom relief, AEs, and patient preferences. (Level III)
- Periodic assessment of the need for ongoing use of hormone therapy should be individualized on the basis of a woman's menopause symptoms, general health and underlying medical conditions, risks, treatment goals, and personal preferences. (Level III)
- Micronized progesterone 300 mg nightly significantly decreases VMS (hot flashes and night sweats) compared with placebo and improves sleep. Synthetic progestins have also shown benefit for VMS in some studies. No long-term study results are available, and use of progestogens without estrogen for either indication is off-label. (Level II)

Sleep disturbances

- During the menopause transition, women with VMS are more likely to report disrupted sleep. (Level I)
- Hormone therapy improves sleep in women with bothersome nighttime VMS by reducing nighttime awakenings. Estrogen may have some effect on sleep, independent of VMS. (Level II)

Genitourinary symptoms

- Low-dose vaginal ET preparations are effective and generally safe for the treatment of GSM, with minimal systemic absorption, and are preferred over systemic therapies when ET is used only for genitourinary symptoms. (Level I)
- For women with breast cancer, low-dose vaginal ET should be prescribed in consultation with their oncologists. (Level III)
- Progestogen therapy is not required with low-dose vaginal estrogen, but RCT data are lacking beyond 1 year. (Level II)
- Nonestrogen prescription FDA-approved therapies that improve VVA in postmenopausal women include ospemifene and intravaginal DHEA. (Level I)
- Vaginal bleeding in a postmenopausal woman requires thorough evaluation. (Level I)

Urinary tract symptoms (including pelvic floor disorders)

- Systemic hormone therapy does not improve urinary incontinence and may increase the incidence of stress urinary incontinence. (Level I)
- Low-dose vaginal ET may provide benefit for urinary symptoms, including prevention of recurrent UTIs, overactive bladder, and urge incontinence. (Level II)
- Hormone therapy does not have FDA approval for any urinary health indication. (Level I)

Sexual function

- Both systemic hormone therapy and low-dose vaginal ET increase lubrication, blood flow, and sensation of vaginal tissues. (Level I)
- Systemic hormone therapy generally does not improve sexual function, sexual interest, arousal, or orgasmic response independent of its effect on GSM. (Level I)
- If sexual function or libido are concerns in women with menopause symptoms, transdermal ET may be preferable over oral ET because of minimal effect on sex hormone-binding globulin and free testosterone levels. (Level II)
- Low-dose vaginal ET improves sexual function in postmenopausal women with GSM. (Level I)
- Nonestrogen alternatives FDA approved for dyspareunia include ospemifene and intravaginal DHEA. (Level I)

PRIMARY OVARIAN INSUFFICIENCY

Women with loss of ovarian function at a young age experience an extended period without ovarian hormones compared with women experiencing menopause at the typical age. Premature menopause is defined as menopause before age 40 years, and early menopause is defined as menopause that occurs between the ages of 40 and 45 years. Whereas menopause implies the permanent cessation of menses, POI describes the loss of ovarian function before age 40 years but with the potential for intermittent, transient return of hormone production and menstrual cycles. Women with early or premature loss of ovarian function at any age are at increased risk for AEs related to ovarian hormone deficiency. Causes of early or premature loss of ovarian function may be genetic, autoimmune, toxic, metabolic, and iatrogenic, including chemotherapy, radiation, and surgery.

Health risks of POI and premature menopause are well documented.[40,41] The strongest evidence from meta-analyses and systematic reviews links early loss of ovarian function to decreased quality of life and increased risk of fracture, CVD, heart failure, diabetes mellitus (DM), and overall mortality.[115-121] Other significant issues may include persistent VMS, loss of fertility, bone loss, genitourinary symptoms, sexual dysfunction, cognitive and mood changes, and increased risk of dementia, ophthalmic conditions, and depression.[40,41,122-124] Although these risks are generally because of estrogen deficiency, some of these risks may be reflective of premature aging, as evidenced in some studies by shortened telomere length.[125]

In addition to an increased risk of incident CVD, POI and premature menopause are associated with an increased risk of aortic stenosis, VTE, ischemic stroke, coronary artery disease, atrial fibrillation, and hypertension.[123,126] Early menopause is also associated with a decreased risk of breast cancer.[127]

The surgical removal of both ovaries leads to a much more abrupt loss of the ovarian steroids estrogen and progesterone than does natural menopause and includes a significant decrease in testosterone that does not occur with natural menopause.[128] Vasomotor symptoms as well as a variety of estrogen deficiency-related symptoms and diseases are more frequent and more severe after oophorectomy and can have a major effect on quality of life.[129,130] In meta-analyses, oophorectomy is associated with an increased risk of CVD,[131] cognitive dysfunction and dementia,[132] metabolic syndrome,[133] low bone mineral density (BMD),[134] and sleep disturbance,[135] with some evidence for elevated fracture risk.[136] Bilateral oophorectomy before age 40 is associated with elevated rates of incident CVD as well as mitral regurgitation, VTE, heart failure, coronary artery disease, and hypertension.[123] Other risks may include depression, anxiety, sexual dysfunction, bone loss, parkinsonism, DM, ophthalmologic conditions, and stroke, some of which have been shown in observational studies to be reduced by ET.[35]

Effective management of POI and premature or early menopause may include appropriate doses of hormone therapy, calcium with vitamin D, exercise, and screening to detect medical issues, as well as fertility counseling and mental health services.[40] Hormone therapy is recommended at least until the average age of menopause, approximately 52 years.[35,40,41] Oral contraceptives may be an alternative form of hormone therapy with contraceptive benefits, because spontaneous pregnancy may occur in about 5% of women with POI.[137] Higher doses of hormone therapy may provide better bone protection than oral contraceptives, but this is uncertain.[36,37,138]

Unless contraindications are present, ET is indicated for women who have had BO before the average age of menopause to treat VMS, improve BMD, and reduce the risk for osteoporosis.[139] Younger women may require higher doses to relieve symptoms and protect against bone loss.[41,140] Observational data reveal potential benefits of ET in reducing risk of cognitive impairment or dementia and CV mortality in women with early oophorectomy.[35,141] Estrogen therapy may improve aspects of sexual function and GSM, particularly in women with VMS who have had BO.[107] Vaginal estrogens are effective in treating symptoms of GSM. [45,46,142] Ovarian conservation is recommended, if possible, when hysterectomy for benign indications is performed in premenopausal women at average risk for ovarian cancer.[143]

Key points

- Women with POI and premature or early menopause may be at increased risk for fracture, CVD, heart failure, DM, overall mortality, persistent VMS, loss of fertility, bone loss, genitourinary symptoms, sexual dysfunction, cognitive and mood changes, increased risk of dementia, open-angle glaucoma, depression, and poor quality of life. (Level II)
- In the absence of contraindications, hormone therapy is recommended at least until the average age of menopause (approximately age 52 y), with an option for use of oral contraceptives in healthy younger women. (Level II)
- Results of the WHI trials in older women do not apply to women with POI or premature or early menopause. (Level II)
- In women with BO before the average age of menopause, early initiation of ET, with endometrial protection if the uterus is preserved, reduces VMS, genitourinary symptoms, risk for osteoporosis and related fractures, and likely CVD and overall mortality, with benefit seen in observational studies for CV mortality and cognitive impairment or dementia. (Level II)
- Fertility preservation and counseling should be explored for young women at risk for POI. (Level III)
- Ovarian conservation is recommended when hysterectomy is performed for benign indications in premenopausal women at average risk for ovarian cancer. (Level II)

SKIN, HAIR, AND SPECIAL SENSES

Estrogen therapy may benefit wound healing through modifying inflammation, stimulating granulation tissue formation, and accelerating re-epithelialization. Estrogen therapy increased epidermal and dermal thickness, increased collagen and elastin content, and improved skin moisture, with fewer wrinkles.[144] Although menopause is associated with a decrease in hair density and female pattern hair loss, research on the role of hormone therapy in mitigating these changes is lacking.[145]

In the WHI, ET reduced intraocular pressure in postmenopausal women and mitigated the risk for open-angle glaucoma in Black women.[146,147] Similar effects were not seen for EPT.[148] Further, hormone therapy decreased the risk of neovascular and soft drusen age-related macular degeneration but not early or late-stage macular degeneration.[149] Evidence on the effect of hormone therapy on cataract, dry eye disease, and optic nerve disorders is mixed, and good-quality RCTs are lacking.[150-152] Observational data linking hormone therapy to hearing loss is mixed.[153,154]

Little is known about olfactory changes and hormone therapy.[155] In small trials, hormone therapy appears to decrease dizziness or vertigo and improve postural balance.[156,157]

Key points

- Estrogen therapy appears to have beneficial effects on skin thickness and elasticity and collagen when given at menopause. (Level II)
- Changes in hair density and female pattern hair loss worsen after menopause, but research is lacking regarding a role for hormone therapy in mitigating these changes. (Level II)
- Hormone therapy appears to decrease the risk of neovascular and soft drusen age-related macular degeneration but not early or late-stage macular degeneration. (Level II)
- Estrogen therapy appears to reduce intraocular pressure and mitigate the risk for open-angle glaucoma in Black women. (Level II)
- Evidence of hormone therapy effects on cataracts, optic nerve disease, dry-eye disease, and hearing loss is mixed. (Level II)

- Little is known about hormone therapy effects on olfactory changes. (Level II)
- In small trials, hormone therapy appears to decrease dizziness or vertigo and improve postural balance. (Level II)

HORMONE THERAPY AND QUALITY OF LIFE

Quality of life is defined as an overall assessment of one's life in relation to one's goals and expectations. Quality of life can be applied to one's mental and physical health, which is termed health-related quality of life, or specifically to menopause, or menopause-specific quality of life, which emphasizes the bother and interference of menopause symptoms. Clinical trials indicate that in women with menopause symptoms, such as VMS, systemic hormone therapy (ET, EPT, TSECs) can improve menopause-specific quality of life.[158-160] These effects appear to be explained largely by the effect of hormone therapy on the frequency of these symptoms.

Key points

- Menopause symptoms are associated with poorer health-related and menopause-specific quality of life. (Level II)
- Systemic hormone therapy can improve menopause-specific quality of life in women experiencing menopause symptoms. (Level II)

OSTEOPOROSIS

Menopause is associated with increased bone resorption, and ET decreases bone resorption.[161] For osteoporosis treatment, hormone therapy has not been demonstrated in RCTs to reduce fractures in postmenopausal women with established osteoporosis; therefore, hormone therapy does not carry an FDA indication for treatment of osteoporosis.[162,163]

In women who have osteoporosis, hormone therapy has not been demonstrated in RCTs to decrease fracture risk. In the WHI, for women aged 50 to 79 years (N = 16,608), enrolled without regard to bone density or fracture risk, EPT (0.625 mg CEE plus 2.5 mg MPA) significantly increased lumbar spine and total hip BMD by 4.5% and 3.7%, respectively, relative to placebo and reduced fracture risk.[34] The BMD benefits of preventing bone loss persist as long as therapy is continued but abate rapidly when treatment is discontinued. Within a few months, markers of bone turnover returned to pretreatment values, whereas BMD fell to pretreatment levels within 1 to 2 years of stopping therapy.[164]

Women with POI experience long-term AEs on bone density, in addition to other health risks.[35,140] Higher-than-standard doses of hormone therapy may be needed to provide protection against bone-density loss in younger women, particularly those aged younger than 40 years and thus lower future osteoporotic fracture risk.[140,165]

In the setting of prevention, RCTs show that hormone therapy decreases fracture risk.[162,163] Various oral and transdermal estrogen preparations, alone or in combination with progestogens or BZA, have government approval for prevention of osteoporosis. A meta-analysis and a systematic review, based primarily on the WHI, demonstrated that 5 to 7 years of hormone therapy significantly reduced risk of spine, hip, and nonvertebral fractures.[166,167] During the WHI intervention phase in women of all ages, the CEE plus MPA group had six fewer hip fractures per 10,000 women and six fewer vertebral fractures per 10,000 women compared with the placebo group.[9] The CEE-alone group had six fewer hip fractures per 10,000 women and six fewer vertebral fractures per 10,000 women compared with the placebo group. However, in the subset of women aged 50 to 59 years at the time of treatment initiation, neither CEE plus MPA nor CEE alone was associated with decreased risk of hip fracture.

The reason that hormone therapy was not shown to reduce hip fracture in the subset of women aged 50 to 59 years in the WHI may be partly because of the lower baseline absolute risk of fracture in women aged between 50 and 59 years who did not have established osteoporosis.[9,168]

In the WHI hormone therapy trials, after hormone therapy discontinuation, there was a return of fracture risk to levels seen in women who had received placebo, with no excess fracture risk observed after discontinuation of hormone therapy.[169,170] There are no prospective fracture studies directly comparing the efficacy of hormone therapy in preventing fractures with other approved pharmacologic therapies.

Key points

- Hormone therapy prevents bone loss in healthy postmenopausal women, with dose-related effects on bone density. (Level I)
- Hormone therapy reduces fracture risk in healthy postmenopausal women. (Level I)
- Discontinuing hormone therapy results in rapid bone loss; however, no excess in fractures was seen in the WHI after discontinuation. (Level I)
- Hormone therapy is FDA approved for prevention of bone loss, but not for treatment of osteoporosis. (Level I)
- In the absence of contraindications, in women aged younger than 60 years or within 10 years of menopause onset, systemic hormone therapy is an appropriate therapy to protect against bone loss. (Level I)
- Unless contraindicated, women with premature menopause without prior fragility fracture or osteoporosis are best served with hormone therapy or oral contraceptives to prevent bone density loss and reduce fracture risk, rather than other bone-specific treatments, until the average age of menopause, when treatment may be reassessed. (Level II)
- Decisions regarding initiation and discontinuation of hormone therapy should be made primarily on the basis of extraskeletal benefits (ie, reduction of VMS) and risks. (Level III)

JOINT PAIN

Direct binding of estrogen to estrogen receptors acts on joint tissues, protecting their biomechanical structure and function and maintaining overall joint health, but the exact effect of estrogen on osteoarthritis remains controversial.[171-173] There is no clearly observed association between hormone therapy use and osteoarthritis.[171]

Meta-analyses of clinical trials of ET have reported inconsistent results. Thus, there is insufficient evidence to form strong conclusions regarding the effects of estrogen on osteoarthritis.[173]

In the WHI, women on CEE plus MPA had less joint pain or stiffness compared with those on placebo (47.1% vs 38.4%; OR, 1.43; 95% CI, 1.24-1.64) and more joint discomfort after stopping.[174] In the CEE-alone arm, women randomized to CEE had a statistically significant reduction in joint pain frequency after 1 year compared with the placebo group (76.3% vs 79.2%; $P = .001$).[175]

In the WHI, using arthroplasty as a clinical indicator of severely symptomatic osteoarthritis, the association of CEE alone with any arthroplasty was borderline significant (HR, 0.84; 95% CI, 0.70-1.00; $P = .05$), but CEE alone did not significantly reduce the risk of hip or knee arthroplasty. The EPT trial showed no relationship between hormone use and arthroplasty risk.[176]

Key points

- Women in the WHI and other studies have less joint pain or stiffness with hormone therapy compared with placebo. (Level I)
- There is a need for further understanding of estrogen's potential effect on joint health. (Level III)

SARCOPENIA

Frailty is associated with AEs such as falls, hospitalization, disability, and death.[177] Skeletal muscle has been shown to have estrogen receptors,[178] but there is a paucity of studies evaluating the interplay between estrogen and muscle. The regulation of energy intake and expenditure by estrogens in women has not been well studied, with limited basic and preclinical evidence supporting the concept that the loss of estrogen with menopause or oophorectomy disrupts energy balance through decreases in resting energy expenditure and physical activity.[179]

Reviews of preclinical studies and limited clinical studies of hormone therapy in postmenopausal women suggest a benefit on maintaining or increasing muscle mass and related connective tissue and improving strength and posttraumatic or postatrophy muscle recovery when combined with exercise.[180-182]

In the WHI hormone therapy trials, women assigned to ET or EPT (vs placebo) had early preservation of lean body mass after 3 years, but hormone therapy did not ameliorate long-term loss in lean body mass associated with aging.[183] Similarly, low-dose oral estradiol 0.25 mg per day plus cyclical MP did not significantly change skeletal muscle mass or lean body mass.[184]

Systematic reviews find that hormone therapy had neither a beneficial nor harmful association with muscle mass[185,186]; therefore, it is likely that interventions other than hormone therapy will have to be developed to aid in the retention of muscle in aging women.

Key points

- Development of frailty with aging is a health risk. (Level I)
- Sarcopenia and osteoporosis are related to aging, estrogen depletion, and the menopause transition. (Level II)
- Intervention to improve bioenergetics and prevent loss of muscle mass, strength, and performance is needed. (Level III)
- Preclinical studies suggest a possible benefit of ET when combined with exercise to prevent the loss of muscle mass, strength, and performance, but this has not been shown in clinical trials. (Level II)

GALLBLADDER AND LIVER

Estrogens increase biliary cholesterol secretion and saturation, promote precipitation of cholesterol in the bile, and reduce gallbladder motility, with increased bile crystallization.[187,188] Postmenopause use of estrogen is associated with an increased risk of cholelithiasis, cholecystitis, and cholecystectomy.[23] However, no associated risk of biliary cancer has been demonstrated.[189] The transdermal route of administration, which bypasses first-pass metabolism of the liver, has been associated with less risk of gallbladder disease in observational studies.[190] The attributable risk for gallbladder disease as self-reported in the WHI was an additional 47 cases per 10,000 women per year for CEE plus MPA and 58 cases per 10,000 women per year for CEE, both statistically significant ($P < .001$).[9]

Nonalcoholic fatty liver disease is more common after the menopause transition when the prevalence surpasses men.[191] Older women also have higher rates of severe hepatic fibrosis and greater mortality compared with men. Animal models have demonstrated a causal relationship between the loss of estrogen and increase in fatty liver and steatohepatitis, whereas observational studies show dietary factors also may exacerbate liver disease. Preclinical and observational studies suggest possible benefits of hormone therapy on liver fibrosis and fatty liver,[192] but more research is needed before definitive recommendations can be made.

Key points

- Risk of gallstones, cholecystitis, and cholecystectomy is increased with ET and EPT. (Level I)
- Observational studies report lower risk of gallstones with transdermal hormone therapy than with oral, and with oral estradiol compared with CEE, but neither observation is confirmed in RCTs. (Level II)
- In women with hepatitis C and with fatty liver, a slower fibrosis progression has been observed with use of hormone therapy, but RCTs are needed to establish the potential benefits and risks with liver disease. (Level II)

DIABETES MELLITUS, METABOLIC SYNDROME, AND BODY COMPOSITION

Metabolic syndrome and diabetes

In the WHI, women receiving continuous-combined CEE plus MPA had a statistically significant 19% reduction (HR, 0.81; 95% CI, 0.70-0.94; $P = .005$) in the incidence of type 2 DM, translating to 16 fewer cases per 10,000 person-years of therapy.[9] In the CEE-alone cohort, there was a reduction of 14% in new diagnoses of type 2 DM (HR, 0.86; 95% CI, 0.76-0.98), translating to 21 fewer cases per 10,000 person-years. A meta-analysis of published studies found that EPT reduced multiple components of the metabolic syndrome; incidence of type 2 DM was decreased by 30%.[193] A second, smaller meta-analysis confirmed these findings and reported that women with type 2 DM using ET or EPT had better glycemic control.[194] The benefit reverses when hormone therapy is discontinued. For these reasons, hormone therapy can be considered for symptomatic menopausal women with type 2 DM.

Weight and body composition

The menopause transition is associated with an increase in body fat and a decrease in lean body mass, which results in an increase in the fat-to-lean ratio and decreased basal metabolic rate. After controlling for body size and ethnicity, the average weight gain during midlife and the menopause transition is 1.5 lb per year.[195,196] Central fat distribution (gynoid-to-android pattern) also occurs after menopause after adjustment for aging, total body fat, and physical activity level.[196] By about 2 years after the final menstrual period, weight changes flatten.[197] Women who used hormone therapy did not have observable differences in the trajectory of weight or body fat gain compared with those who did not take hormones, although numbers are relatively small.

Estrogen-progestogen therapy either has no effect on weight or is associated with less weight gain in women who are using it than in women who are not.[198-202] In the WHI, women randomized to hormone therapy with CEE with or without MPA had no statistically significant difference in slowing of weight gain and a lesser increase in waist circumference over the first 3 years of use compared with those randomized to placebo. Increasing physical activity was independently associated with less weight gain over time.[195]

Key points

- Hormone therapy significantly reduces the diagnosis of new-onset type 2 DM, but it is not government approved for this indication. (Level I)
- Hormone therapy is not contraindicated in otherwise healthy women with preexisting type 2 DM and may be beneficial in terms of glycemic control when used for menopause symptom management. (Level II)
- Although hormone therapy may help attenuate abdominal adipose accumulation and weight gain associated with the menopause transition, the effect is small. (Level II)

COGNITION

Small clinical trials support the use of ET for cognitive benefits when initiated immediately after hysterectomy with bilateral oophorectomy.[203,204] Three large RCTs demonstrated neutral effects of hormone therapy on cognitive function when used early in the postmenopause period.[205-207]

Two hypotheses—the *critical window* or *timing* hypothesis and the *healthy-cell bias* hypothesis—provide a framework for understanding the scientific literature on hormone therapy and cognition, but neither has been definitively supported in RCTs of postmenopausal women. The critical window or timing hypothesis[208,209] holds that estrogen can confer cognitive benefits if given early in the menopause transition but that later use is neutral or detrimental. The healthy-cell bias hypothesis[210] holds that estrogen confers cognitive benefits when the neural substrate is "healthy" but not diseased, for example in a woman with DM.

Later initiation of hormone therapy

Several large clinical trials indicate that hormone therapy does not improve memory or other cognitive abilities and that CEE plus MPA may be harmful for memory when initiated in women aged older than 65 years.[211-213]

Alzheimer disease

Four observational studies provide support for the opinion that the timing of hormone therapy initiation is a significant determinant of Alzheimer disease risk, with early initiation lowering risk and later initiation associated with increased risk.[214-217] However, long-term effects may differ from short-term effects. Eighteen-year follow-up data from the WHI showed a reduction in Alzheimer disease mortality in women randomized to hormone therapy; this effect was significant for CEE alone but not for CEE plus MPA and was driven by women aged in their 70s at the time of enrollment.[31] Two nested case-control studies investigated the risk of dementia associated with hormone therapy use and showed no increased risk overall but did suggest an increased risk of Alzheimer disease, specifically, with the use of EPT for more than 5 years.[218]

All-cause dementia

In the WHI Memory Study, CEE plus MPA doubled the risk of all-cause dementia (23 cases/10,000 women) when initiated in women aged older than 65 years,[213] whereas CEE alone did not significantly increase the risk of dementia.[219] The effect of hormone therapy may be modified by baseline cognitive function, with more favorable effects in women with normal cognitive function before hormone therapy initiation.[220,221]

Key points

- In the absence of more definitive findings, hormone therapy is not recommended at any age to prevent or treat a decline in cognitive function or dementia. (Level I)
- Initiating hormone therapy in women aged older than 65 years increased the risk for dementia, with an additional 23 cases per 10,000 person-years seen in women randomized to CEE plus MPA in the WHI Memory Study. (Level I)
- The effect of hormone therapy may be modified by baseline cognitive function, with more favorable effects in women with normal cognitive function before hormone therapy initiation. (Level II)
- Estrogen therapy may have cognitive benefits when initiated immediately after hysterectomy with bilateral oophorectomy, but hormone therapy in the early natural postmenopause period has neutral effects on cognitive function. (Level II)

DEPRESSION

Depressive symptoms worsen as women transition through menopause, although evidence is mixed as to whether depressive disorders are more common during the menopause transition relative to premenopause. Most women who present with depressive disorders during the menopause transition are women with a history of depression before the menopause transition, and women with a history of depression are at high risk for recurrence during the menopause transition.[222]

For that reason, clinical guidelines recommend that clinicians screen for depression in women with a history of depression and use antidepressants or proven psychotherapies (eg, cognitive-behavior therapy, interpersonal therapy, mindfulness-based cognitive therapy) as the primary treatment for recurrent major depressive episodes.[223] Use of hormone therapy to treat menopause symptoms such as

VMS in midlife women with depression should be considered. Vasomotor symptoms increase the risk for elevated depressive symptoms, in part because of nocturnal VMS and sleep interruption,[224] and on a day-to-day basis, VMS co-occur with negative mood and predict negative mood the next day.[225] Vasomotor symptoms appear to be more strongly associated with the onset of depressive symptoms than depressive disorders.[226]

Estrogen therapy shows some efficacy in the management of depression in midlife women, but its effect varies by menopause stage. For perimenopausal women with depression, there is evidence that ET improves depressive symptoms to a degree similar to antidepressant medications.[227] This antidepressant effect of ET applies to perimenopausal women with and without VMS. In women with major depression treated with ET, depressive symptoms improve in relation to improvements in sleep but not VMS.[228] Estrogen therapy does not appear to be effective in treating depressive disorders in postmenopausal women, suggesting a window of opportunity in the perimenopause.[229] Little is known about the effects of EPT in treating depressive disorders at any menopause stage.

There is some evidence that ET enhances mood and improves well-being in nondepressed postmenopausal women.[205] Initial evidence suggests that hormone therapy (specifically transdermal estradiol with intermittent MP) may prevent the onset of depressive symptoms in euthymic perimenopausal women.[230]

Estrogen therapy may augment clinical response to antidepressants in midlife and older women, preferably when also indicated for other concurrent menopause-related symptoms such as VMS.[231]

Key points

- There is some evidence that ET has antidepressant effects of similar magnitude to that observed with antidepressant agents when administered to depressed perimenopausal women with or without concomitant VMS. (Level II)
- Estrogen therapy is ineffective as a treatment for depressive disorders in postmenopausal women. Such evidence suggests a possible window of opportunity for the effective use of ET for the management of depressive disorders during the perimenopause. (Level II)
- There is some evidence that ET enhances mood and improves well-being in nondepressed perimenopausal women. (Level II)
- Transdermal estradiol with intermittent MP may prevent the onset of depressive symptoms in euthymic perimenopausal women, but the evidence is not sufficient to recommend estrogen-based therapies for preventing depression in asymptomatic perimenopausal or postmenopausal women, and the risks and benefits must be weighed. (Level II)
- Estrogen-based therapies may augment clinical response to antidepressants in midlife and older women, preferably when also indicated for other menopause symptoms such as VMS. (Level III)
- Most studies on hormone therapy for the treatment of depression examined the effects of unopposed estrogen. Data on EPT or for different progestogens are sparse and inconclusive. (Level II)
- Estrogen is not government approved to treat mood disturbance. (Level I)

CARDIOVASCULAR DISEASE AND ALL-CAUSE MORTALITY

Observational data and reanalysis of older studies by age or time since menopause, including the WHI, suggest that for healthy women who are within 10 years of the menopause transition and who have bothersome menopause symptoms, the benefits of hormone therapy (ET or EPT) outweigh its risks, with fewer CVD events in younger versus older women.[9,31,219,232-242]

Initiation of hormone therapy fewer than 10 years after menopause onset

Surrogate markers of coronary heart disease

Surrogate markers of CHD are intermediate measures that have been associated with the development of CVD and events such as coronary artery calcification (CAC) and subclinical atherosclerosis. Some studies have suggested that initiating hormone therapy in symptomatic women within 10 years of menopause may have benefit in reduction of atherosclerosis progression as measured by CAC,[243-245] whereas RCTs in younger, recently postmenopausal women have not.[246,247] In the Early Versus Late Intervention Trial With Estradiol, hormone therapy (oral 17β-estradiol 1 mg/d plus progesterone vaginal gel 45 mg administered sequentially for women with a uterus) reduced subclinical atherosclerosis progression measured by carotid artery intima-media thickness after a median of 5 years when initiated within 6 years (median, 3.5 y) of menopause onset but not when initiated 10 or more years (median, 14.3 y) afterward.[246] The Kronos Early Estrogen Prevention Study in healthy postmenopausal women aged 42 to 58 years who received hormone therapy (oral CEE 0.45 mg/d; transdermal estradiol patch 50 μg/wk; each with sequential oral MP 200 mg for 12 d/mo) showed no effect on subclinical atherosclerosis progression.[247]

Meta-analyses of clinical outcomes

A 2015 *Cochrane* review of RCT data found that hormone therapy initiated fewer than 10 years after menopause onset lowered CHD in postmenopausal women (RR, 0.52; 95% CI, 0.29-0.96).[236] It also found a reduction in all-cause mortality (RR, 0.70; 95%, 0.52-0.95) and no increased risk of stroke but an increased risk of VTE (RR, 1.74; 95% CI, 1.11-2.73).

A 2020 systematic review and meta-analysis of RCTs published from 2000 to 2019 showed null effects of hormone therapy initiated fewer than 10 years after menopause or at an age younger than 60 years on all-cause mortality, stroke, and VTE.[248]

A 2019 systematic review and meta-regression analysis of RCTs that examined the timing hypothesis of hormone therapy compared with controls or nonusers of hormone therapy found that younger hormone therapy initiation (participants aged <60 y) was associated with lower odds of CHD (OR, 0.61; 95% CI, 0.37-1.00), all-cause mortality (OR, 0.72; 95% CI, 0.57-0.91), and cardiac mortality (OR, 0.61; 95% CI, 0.37-1.00) but with higher odds of a composite measure of incidence stroke, transient ischemic attack, and systemic embolism (OR, 1.40; 95% CI, 1.10-1.78).[249] However, the results for CHD, cardiac mortality, and all-cause mortality were all attenuated after excluding open-label trials in which the knowledge of active treatment may affect treatment options and outcomes. Direct comparisons

across these meta-analyses may not be applicable, given differences in inclusion/exclusion criteria and analytical methods that were applied in each analysis.

Cardiovascular outcomes in the Women's Health Initiative

Intervention phase

For CEE alone, CHD, MI, and coronary artery bypass grafting or *percutaneous coronary intervention* showed a lowered HR in women aged younger than 60 years and fewer than 10 years since menopause onset, including in intention-to-treat analyses.[9] In the 50- to 59-year-old age group, the HR for CHD was elevated but not statistically significant at 1.34 (95% CI, 0.82-2.19) for CEE plus MPA. When data from the two WHI trials were combined and analyzed, a reduction in all-cause mortality was shown in younger but not in older women; HRs in women aged 50 to 59 years, 60 to 69 years, and 70 to 79 years were 0.69 (95% CI, 0.51-0.94), 1.04 (95% CI, 0.87-1.25), and 1.13 (95% CI, 0.94-1.36), respectively ($P_{\text{for trend}} = .01$).[31]

Cumulative follow-up

For CEE alone, in the 13-year cumulative intervention and postintervention follow-up, significant age-treatment interaction was shown for MI such that only in the 50- to 59-year-old age group a reduction in MI risk was significant (HR, 0.60; 95% CI, 0.39-0.91).[9] Although a similar interaction was not significant for CHD and all-cause mortality, there was a significant reduction in CHD risk (HR, 0.65; 95% CI, 0.44-0.96) in this age group. In the 18-year intervention and postintervention cumulative follow-up, the reduction in all-cause mortality was shown to be statistically significant for the 50- to 59-year-old age group (HR, 0.79; 95% CI, 0.64-0.96),[31] although interaction between age and treatment was not significant. Additional analysis focusing on oophorectomy status in the CEE-alone trial revealed a significant age-treatment interaction for all-cause mortality; younger women with BO assigned to CEE alone showed a significant reduction in all-cause mortality compared with placebo (HR, 0.68; 95% CI, 0.48-0.96).[242]

Initiation of hormone therapy more than 10 years from menopause onset or in women aged older than 60 years

For women who initiated hormone therapy more than 10 years from menopause onset or aged older than 60 years, a 2015 *Cochrane* meta-analysis found no evidence that hormone therapy had an effect on CHD (RR, 1.07; 95% CI, 0.96-1.20) or all-cause mortality (RR, 1.06; 95% CI, 0.95-1.18), with an average follow-up of 3.8 years.[236] There was an increased risk of stroke (RR, 1.21; 95% CI, 1.06-1.38) and VTE (RR, 1.96; 95% CI, 1.37-2.80).

A 2020 systematic review and meta-analysis of RCTs showed similar results as the 2015 *Cochrane* analysis for older women who initiated hormone therapy.[248] Compared with placebo or nonusers of hormone therapy, initiating hormone therapy in women aged 60 years or older or after 10 years since menopause had a null effect on CHD (summary estimate, 1.00; 95% CI, 0.87-1.14) and all-cause mortality (summary estimate, 1.00; 95% CI 0.96-1.05) but was associated with higher risk of stroke (summary estimate, 1.17; 95% CI, 1.01-1.37) and VTE (summary estimate, 1.79; 95% CI, 1.39-2.29).

Similarly, in a 2019 systematic review and meta-regression analysis of RCTs testing the timing hypothesis, women who initiated hormone therapy relative to placebo or nonusers of hormone therapy aged 60 years or older showed a null effect on CHD and all-cause mortality but was associated with higher risk of a composite measure of incidence stroke, transient ischemic attack, and systemic embolism (OR, 1.52; 95% CI, 1.39-1.71).[249]

Attributable risk of stroke in women aged younger than 60 years or within 10 years of menopause onset

The 2015 *Cochrane* meta-analysis found no increased risk of stroke in women who initiated hormone therapy aged younger than 60 years or fewer than 10 years from menopause onset.[236] In subgroup analysis, the attributable risk of stroke in the WHI for women who initiated hormone therapy aged younger than 60 years or within 10 years of menopause onset was rare (<10/10,000 person-years) and statistically nonsignificant for CEE plus MPA, with an absolute risk of 5 per 10,000 person-years,[9,240] similar to other studies.[232]

Findings were inconsistent for CEE-alone in the WHI. For women aged 50 to 59 years at randomization, a decrease of 1 per 10,000 person-years was seen for stroke; whereas for women fewer than 10 years from menopause onset, an increase in 13 strokes per 10,000 person-years was seen.[9]

On the basis of only observational studies, lower doses of either oral[250] or transdermal[251] estrogen may confer less risk of stroke; no clear association with age has been found. No head-to-head data comparing oral to transdermal hormone therapy are available.

Venous thromboembolism

Women who began hormone therapy fewer than 10 years after menopause onset or who were aged younger than 60 years have higher risk of VTE compared with placebo (RR, 1.74; 95% CI, 1.11-2.73), according to the 2015 *Cochrane* meta-analysis.[236] In a 2020 systematic review and meta-analysis of RCTs published between 2000 and 2019, risk of VTE was elevated in women who initiated hormone therapy aged older than 60 years or after 10 years since menopause (summary estimate, 1.79; 95% CI, 1.39-2.29) and a null effect in women who initiated hormone therapy aged younger than 60 years or within 10 years of menopause (summary estimate, 0.69; 95% CI 0.25-1.93).[248] Lower doses of oral ET may confer less risk of VTE than higher doses,[24,25] but comparative RCT data are lacking. Micronized progesterone may be less thrombogenic than other progestins.[26] Transdermal hormone therapy has not been associated with VTE risk in observational studies, limited observational data and a systematic review suggest less risk with transdermal hormone therapy than oral[26,27,29]; however, comparative RCT data are lacking.

Areas of scientific uncertainty and need for randomized, controlled trial data

Although observational studies, meta-analyses of RCTs, and smaller RCTs with surrogate CVD risk markers suggest that hormone therapy may reduce CVD risk when initiated in women aged younger than 60 years and/or who are within 10 years of menopause onset, significant research gaps remain regarding dose, formulation, route of delivery, and duration of use. Furthermore,

because most RCTs are performed on North American and European women, future studies should also evaluate the role of ethnicity with respect to hormone therapy and CVD. Data are insufficient for risk related to long-term hormone therapy use in perimenopausal women and in postmenopausal women aged younger than 50 years.[23,252] Hormone therapy is not government approved for prevention of CVD.

Key points

- For healthy symptomatic women aged younger than 60 years or within 10 years of menopause onset, the favorable effects of hormone therapy on CHD and all-cause mortality should be considered against potential rare increases in risks of breast cancer, VTE, and stroke. (Level I)
- Hormone therapy is not government approved for primary or secondary cardioprotection. (Level I)
- Personal and familial risk of CVD, stroke, VTE, and breast cancer should be considered when initiating hormone therapy. (Level III)
- The effects of hormone therapy on CHD may vary depending on when hormone therapy is initiated in relation to a woman's age or time since menopause onset. (Level I)
- Initiation of hormone therapy in recently postmenopausal women reduced or had no effect on subclinical atherosclerosis progression and coronary artery calcification in randomized, controlled trials. (Level I)
- Observational data and meta-analyses show reduced risk of CHD in women who initiate hormone therapy when aged younger than 60 years or within 10 years of menopause onset. Meta-analyses show a null effect of hormone therapy on CHD after excluding open-label trials. (Level II)
- Women who initiate hormone therapy aged older than 60 years or more than 10 or 20 years from menopause onset are at higher absolute risks of CHD, VTE, and stroke than women initiating hormone therapy in early menopause. (Level I)

BREAST CANCER

Breast cancer affects approximately one in eight US women, so an understanding of the potential effect of hormone therapy on breast cancer risk is of considerable importance. Potential differences of the effects of ET, EPT, and CEE plus BZA on breast tissue may exist. Different types of estrogen or progestogen, as well as different formulations, timing of initiation, duration of therapy, and patient characteristics, may play a role in the effects of hormone therapy on the breast.

Estrogen-progestogen therapy

In the WHI, daily continuous-combined CEE plus MPA resulted in an increased risk of breast cancer, with nine additional breast cancer cases per 10,000 person-years of therapy.[9] The HR remained elevated at a median of 20 years' cumulative follow-up in the unblended, postintervention phase (HR, 1.28; 95% CI, 1.13-1.45).[21]

Estrogen-alone therapy

Compared with women who received placebo, women who received CEE alone in the WHI showed a nonsignificant reduction in breast cancer risk after an average of 7.2 years of randomization, with seven fewer cases of invasive breast cancer per 10,000 person-years of CEE (HR, 0.79; 95% CI, 0.61-1.02).[9] A significant reduction in breast cancer became evident in the postintervention phase, with a median 20 years' cumulative follow-up (HR, 0.78; 95% CI, 0.65-0.93).[21]

Longer duration of hormone therapy use

No large RCTs have assessed the effect of long duration of hormone therapy use. Both the ET and the EPT components of the WHI reported data for finite intervals because both were terminated early because of predefined safety considerations, with a median of 7.2 years for ET and 5.6 for EPT. Notably, although long-term follow-up at 13 and 20 years provided information about use for 5 to 7 years, no data were available regarding longer-term use. The recent pooled analysis of observational data in the Collaborative Group Study included information on duration of hormone therapy use in women starting hormone therapy when aged 45 to 54 years.[22] In each age category, the risk of breast cancer increased with duration of use. Specifically, for ET, the HRs increased from 1.23 (95% CI, 1.11-1.35) for 1 to 4 years of use, to 1.29 (95% CI, 1.21-1.37) for 5 to 9 years, to 1.44 (95% CI, 1.35-1.53) for 10 to 14 years, and to 1.61 (95% CI, 1.49-1.74) for 15 or more years. For EPT, increases for similar periods were 1.66 (95% CI, 1.55-1.78) for 1 to 4 years of use, 1.96 (95% CI, 1.87-2.05) for 5 to 9 years, 2.31 (95% CI, 2.18-2.44) for 10 to 14 years, and 2.68 (95% CI, 2.44-2.95) for 15 or more years.

Attributable risk of breast cancer

The attributable risk of breast cancer in women (mean age, 63 y) randomized to CEE plus MPA in the WHI is less than one additional case of breast cancer diagnosed per 1,000 users annually,[9] a risk slightly greater than that observed with one daily glass of wine, less than with two daily glasses, and similar to the risk reported with obesity and low physical activity.[253,254] Compared with placebo or nonusers of hormone therapy, there appears to be no additive effect of hormone therapy with age or elevated personal breast cancer risk factors on breast cancer incidence.[21,22,255-259] Although the relative risk of breast cancer associated with hormone therapy use is similar in women at average or high risk, the actual number of cases or attributable risk will be greater in women with an increased underlying risk.[86]

Use of hormone therapy in women with genetic risk factors for breast cancer

Observational evidence suggests that hormone therapy use does not further increase the relative risk of breast cancer in women with a family history of breast cancer, in women after oophorectomy for *BRCA 1* or *2* genetic variants, or in women having undergone a benign breast biopsy.[255-258,260-266] A prospective longitudinal cohort study of *BRCA 1* genetic variant carriers without prior history of breast cancer who underwent BO (mean age, 43.4 y) showed no increased risk of developing breast cancer associated with any use of hormone therapy after a mean follow-up of 7.6 years; however, there was a difference between ET and EPT, with a nonsignificant increase in breast

cancer risk associated with the latter.[266] Similarly, the Two Sister Study of 1,419 sister-matched cases of breast cancer in women aged younger than 50 years and 1,665 controls showed no increased risk of young-onset breast cancer with use of EPT (OR, 0.80; 95% CI, 0.41-1.59), and unopposed estrogen use was associated with a reduced diagnosis of young-onset breast cancer (OR, 0.58; 95% CI, 0.34-0.99).[267] The absolute risk of breast cancer is low in women with genetic variants who undergo risk-reducing BO at a young age, and use of hormone therapy is considered acceptable.

Role of type of hormone use, dose, and route of administration

Some but not all observational data suggest that MP and dydrogesterone may have a lesser association with breast cancer, whereas other synthetic progestogens such as MPA may have a more adverse effect.[268] Randomized trials are needed to confirm these findings. Preclinical data suggest that CEE may have lesser effects on occult breast cancer growth than estradiol,[269] but clinical data from observational studies, such as the Collaborative Group study, do not report a difference.[22] Regarding route, both oral and transdermal estrogens appear to have similar effects on number of breast cancers diagnosed, whereas vaginal estrogens have no effect. Insufficient clinical data on newer therapies such as TSECs, including CEE plus BZA, are available to assess their breast cancer risk,[270] although preclinical data suggest greater safety.[271]

Mammographic breast density and hormone therapy

Different hormone therapy regimens may be associated with increased breast density, which may obscure mammographic interpretation.[272] More mammograms and breast biopsies were performed in women receiving CEE plus MPA than placebo in the WHI.[273] In trials up to 2-years' duration, breast cancer, breast density, and breast tenderness showed no difference between oral CEE plus BZA and placebo.[274-276]

Hormone therapy after breast cancer

Two RCTs reported conflicting outcomes of breast cancer recurrence with hormone therapy. One study ("Hormonal Replacement Therapy After Breast Cancer—Is It Safe?") showed an elevated risk of breast cancer recurrence in hormone therapy users relative to nonusers after a median follow-up of 2.1 years (HR, 3.5; 95% CI, 1.5-8.1)[277] and 4 years, (HR, 2.4; 95% CI, 1.3-4.2),[278] whereas another trial (Stockholm Breast Cancer Study) showed no effect on breast cancer recurrence in hormone therapy users relative to nonusers after median follow-up of 4.1 years (HR, 0.82; 95% CI, 0.35-1.9)[279] and 10.8 years (HR, 1.3; 95% CI, 0.9-1.9) but did show an increased risk of breast cancer in the contralateral breast (HR, 3.6; 95% CI, 1.2-10.9).[280]

Although systemic use of hormone therapy in survivors of breast cancer is generally not advised, if symptoms of estrogen deficiency are severe and unresponsive to nonhormone options, women, in consultation with their oncologists, may choose hormone therapy after being fully informed about the risks and benefits. Several observational studies in women with a history of breast cancer have shown a decreased risk of recurrent breast cancer or neutral effects compared with nonusers.[281-286] In addition, mortality was reported to be reduced in breast cancer survivors who used hormone therapy relative to those who did not.[282,284] Four meta-analyses reported similar findings.[281,284-286] A confounding factor in all of these observational studies is that women at low risk of breast cancer recurrence are more likely to elect hormone therapy use than women at high risk.

Low-dose vaginal ET remains an effective treatment option for GSM in survivors of breast cancer, with minimal systemic absorption. Treatment with low-dose vaginal ET or DHEA may be considered if symptoms persist after an initial trial of nonhormone therapies and in consultation with an oncologist, with more concern for women on AIs.[88,90]

Breast cancer mortality and hormone therapy

Only one randomized trial, the WHI, examined breast cancer-specific mortality. After 20 years of median cumulative follow-up, CEE alone was associated with significantly lower breast cancer incidence (HR, 0.78; 95% CI, 0.65-0.93) and breast cancer mortality (HR, 0.60; 95% CI, 0.37-0.97) compared with placebo. In contrast, CEE plus MPA was associated with significantly higher breast cancer incidence (HR, 1.28; 95% CI, 1.13-1.45) but no significant difference in breast cancer mortality (HR, 1.35; 95% CI, 0.94-1.95) compared with placebo.[21]

The mortality risk of breast cancer in hormone therapy users has been reported to be reduced in many but not all observational studies.[287-295] The breast cancers in hormone therapy users (ET and EPT) appear in most (but not all) studies to have more benign histologic features (localized, smaller, better differentiated, lower mean tumor proliferation rate) than in hormone therapy nonusers. The most recent study, using a large data registry in Finland and comparing populations rates, reported a reduction in breast cancer mortality in users of both ET and EPT.[296] A confounding factor in all these studies is that hormone therapy users undergo more frequent mammograms and diagnostic examinations, especially with occurrence of signs or symptoms.[297-301] This is likely to result in earlier diagnosis and therefore more benign histologic features and lower mortality.

Key points

- The risk of breast cancer related to hormone therapy use is low, with estimates indicating a rare occurrence (less than one additional case per 1,000 women per year of hormone therapy use or three additional cases per 1,000 women when used for 5 years with CEE plus MPA). (Level I)
- Women should be counseled about the risk of breast cancer with hormone therapy, putting the data into perspective, with risk similar to that of modifiable risk factors such as two daily alcoholic beverages, obesity, and low physical activity. (Level III)
- The effect of hormone therapy on breast cancer risk may depend on the type of hormone therapy, duration of use, regimen, prior exposure, and individual characteristics. (Level II)
- Different hormone therapy regimens may be associated with increased breast density, which may obscure mammographic interpretation, leading to more mammograms or more breast biopsies and a potential delay in breast cancer diagnosis. (Level II)

- A preponderance of data does not show an additive effect of underlying breast cancer risk (age, family history of breast cancer, genetic risk of breast cancer, benign breast disease, personal breast cancer risk factors) and hormone therapy use on breast cancer incidence. (Level II)
- Insufficient data are available to assess the risk of breast cancer with newer therapies such as TSECs, including BZA plus CEE. (Level II)
- Observational evidence suggests that hormone therapy use does not further increase risk of breast cancer in women at high risk because of a family history of breast cancer or after bilateral salpingo-oophorectomy (BSO) for *BRCA 1* or *2* genetic variants. (Level II)
- Systemic hormone therapy is generally not advised for survivors of breast cancer, although hormone therapy use may be considered in women with severe VMS unresponsive to nonhormone options, with shared decision-making in conjunction with their oncologists. (Level III)
- For survivors of breast cancer with GSM, low-dose vaginal ET or DHEA may be considered in consultation with their oncologists if bothersome symptoms persist after a trial of nonhormone therapy. There is increased concern with low-dose vaginal ET for women on AIs. (Level III)
- Regular breast cancer surveillance is advised for all postmenopausal women per current breast cancer screening guidelines, including those who use hormone therapy. (Level I)

ENDOMETRIAL CANCER

Endometrial cancer is the most common gynecologic malignancy in the United States. Unopposed systemic ET in a postmenopausal woman with an intact uterus increases the risk of endometrial cancer, which is dose- and duration-related. Greater risk is seen with higher estrogen doses used for longer duration, and risk persists after discontinuation. Progestogen used continuously or cyclically for 10 to 14 days monthly significantly reduces this risk. With long-duration hormone therapy use, observational studies suggest a potentially increased risk of endometrial cancer with cyclic progestogen regimens compared with continuous progestogen use and with the use of MP compared with other progestogens.[3,4,302] In the WHI, women with a uterus receiving EPT had a lower risk of endometrial cancer than women randomized to placebo after 13 years of cumulative follow-up because of the baseline risk of endometrial cancer in postmenopausal women from endogenous estrogen production.[9] Adequate concomitant progestogen is recommended for a woman with an intact uterus when using systemic ET.

Low-dose vaginal ET does not appear to increase endometrial cancer risk,[92,93] although trials with endometrial biopsy end points are limited to 1 year in duration. Progestogen is not advised in women using low-dose vaginal ET for the treatment of GSM, although intermittent use may be considered in women at increased risk of endometrial cancer. Postmenopausal bleeding must be evaluated thoroughly in any woman, whether she is using hormone therapy or not, because this may be a sign of endometrial hyperplasia or cancer.

Hormone therapy after endometrial cancer

Although hormone therapy is generally contraindicated in women with estrogen-responsive cancers, hormone therapy may be used to treat bothersome menopause symptoms in women with low-grade, Stage I endometrial cancer after hysterectomy. Meta-analyses of retrospective studies, with one RCT, do not identify an AE on the risk of recurrence or survival in these cases.[303-306] A woman's oncologist should be included in shared decision-making. Systemic hormone therapy is not advised with high-grade, advanced-stage endometrial cancers or with endometrial stromal sarcomas or leiomyosarcomas, because there are insufficient studies assessing safety.[307,308]

Key points

- Unopposed systemic ET in a postmenopausal woman with an intact uterus increases the risk of endometrial cancer, so adequate progestogen is recommended. (Level I)
- Low-dose vaginal ET does not appear to increase endometrial cancer risk, although trials with endometrial biopsy end points are limited to 1 year in duration. (Level II)
- Use of hormone therapy is an option for the treatment of bothersome menopause symptoms in women with surgically treated, early stage, low-grade endometrial cancer in consultation with a woman's oncologist if nonhormone therapies are ineffective. (Level II)
- Systemic hormone therapy is not advised with high-grade, advanced-stage endometrial cancers or with endometrial stromal sarcomas or leiomyosarcomas. (Level II)

OVARIAN CANCER

Ovarian cancer causes more deaths than any other gynecologic malignancy. Use of oral contraceptives is associated with a significant reduction in ovarian cancer risk. Risk declines with longer duration of use, with risk reduction seen after 1 to 4 years of use, which persists for up to 30 years after oral contraceptive discontinuation.[309] Current and recent use of hormone therapy is associated with statistically significant but small increased risk of ovarian cancer in observational studies, principally for serous type, with an estimate of one additional ovarian cancer death in 1,700 to 3,300 hormone therapy users.[310,311] This risk is seen with combined EPT and ET alone and dissipates within 5 years of discontinuing hormone therapy. In the WHI, there was no significant increase in ovarian cancer risk with EPT.[9]

Hormone therapy after ovarian cancer

The use of hormone therapy after a diagnosis of epithelial ovarian cancer does not appear to affect recurrence risk or survival.[312,313] Although most studies are observational, this finding also is supported by two RCTs. Several studies identify improved survival in women with ovarian cancer who use hormone therapy, but this likely represents selection bias.[307] Use of hormone therapy is not advised in women with hormone-dependent ovarian cancers, including granulosa-cell tumors and serous carcinomas.[306,314] Tumors of low malignant potential (borderline) often affect younger women, with excellent survival rates. Limited data are available, but hormone therapy may be considered in women with completely resected disease, especially given the benefits of

hormone therapy in the setting of early menopause.[315] Short-term hormone therapy use appears safe in women with *BRCA1* and *BRCA2* genetic variants who undergo risk-reducing BSO before the average age of menopause.[308]

Key points

- Use of oral contraceptives is associated with a significant reduction in ovarian cancer risk. (Level I)
- Current and recent use of hormone therapy is associated with a small but statistically significant risk of ovarian cancer in observational studies, principally for serous type, although there was no increase in ovarian cancer risk in women randomized to EPT in the WHI. (Level II)
- In women with a history of ovarian cancer, benefits of hormone therapy use generally outweighs risks, especially with bothersome VMS or early menopause; use of hormone therapy is not advised in women with hormone-dependent ovarian cancers, including granulosa-cell tumors and low-grade serous carcinoma. (Level II)
- Short-term hormone therapy use appears safe in women with *BRCA1* and *BRCA2* genetic variants who undergo risk-reducing BSO before the average age of menopause. (Level II)

COLORECTAL CANCER

Colorectal cancer is the third most common cancer and the third leading cause of cancer death in US women.[309] Risk factors include physical inactivity, obesity, smoking, and decreased use of screening strategies, which may be more likely in hormone therapy nonusers. Observational studies generally support a reduced risk of colorectal cancer in current hormone therapy users compared with never users (HR, 0.6-0.8), with no benefit associated with past hormone therapy use.[310-312] In observational studies, both EPT and ET alone are associated with reduced colorectal cancer risk[313,314] and mortality.[315] Although confounding may contribute to the reduced risk of colorectal cancer seen in hormone therapy users, there is also biologic plausibility, because estrogen receptors are present in colonic epithelium,[316] and estrogen reduces colon cancer cell growth in vitro.[317]

In the WHI trials, use of CEE plus MPA, but not CEE alone, was associated with a reduced risk of colorectal cancer compared with placebo (HR, 0.62; 95% CI, 0.43-0.89).[9] Although EPT reduced the risk of colorectal cancer, the cancers that were detected in EPT users were more likely to be diagnosed at an advanced stage, with positive lymph nodes.[318] The reduced risk of colorectal cancer in EPT users was no longer seen during the postintervention phase of the WHI at 13 years, and there was no difference in colorectal cancer mortality with either EPT or ET alone.[31] The reason for disparate findings between observational studies and the WHI with regard to colorectal cancer risk and mortality is unclear.

Key points

- Observational studies suggest a reduced incidence of colorectal cancer in current hormone therapy users, with reduced mortality. (Level II)
- In the WHI, EPT, but not ET alone, reduced colorectal cancer risk, although cancers diagnosed in EPT users were diagnosed at a more advanced stage. There was no difference in colorectal cancer mortality with either EPT or ET. (Level I)

LUNG CANCER

Lung cancer is the second most common cancer and the leading cause of cancer death in US women.[309] Smoking is the principal risk factor. An interaction between hormone therapy and lung cancer is biologically plausible because estrogen receptors (α and β) and aromatase are identified in both healthy lung tissue and lung cancers.[319,320] Non-small cell lung cancer, including adenocarcinoma and squamous cell carcinoma, is the most common type and the type affected by hormone therapy in observational studies and RCTs. Observational studies, including several large meta-analyses, are conflicting and in aggregate identify no consistent association between hormone therapy use and lung cancer risk.[321-327] Smoking may influence the association between hormone therapy use and lung cancer risk.[326] For women with lung cancer, the effect of hormone therapy use on survival is unclear, with studies showing improved, worsened, or no difference in risk of death.

In the WHI, in the intervention phase or after a median of 13 years' cumulative follow-up, the incidence of lung cancer did not differ significantly between placebo and treatment with CEE plus MPA or CEE alone.[9] In a post hoc analysis of the intervention phase of the WHI, women treated with CEE plus MPA had more deaths from lung cancer compared with placebo (HR, 1.71; 95% CI, 1.16-2.52).[328] Cancers were more likely to be poorly differentiated, with distant metastasis. This increase in lung cancer deaths was not seen with treatment with CEE alone[329] and dissipated over time after stopping hormone therapy.[330]

Key points

- There appears to be an overall neutral effect of hormone therapy on lung cancer incidence and survival. (Level II)
- Smoking cessation should be encouraged, with increased lung cancer surveillance for older smokers, including current or past users of hormone therapy. (Level I)

DURATION OF USE, INITIATION AFTER AGE 60 YEARS, AND DISCONTINUATION OF HORMONE THERAPY

Benefits of hormone therapy use generally outweigh risks for healthy women with bothersome menopause symptoms who are aged younger than 60 years or within 10 years of menopause onset. Because increasing risk is observed with advancing age and extended duration of use,[9,22] women are advised to use the appropriate dose for the time needed to manage their symptoms. Because many women will experience bothersome VMS for many years, long-duration hormone therapy use may be needed, and an arbitrary age-based stopping rule is not clinically appropriate. Frequent VMS persist on average 7.4 years and for many more than 10 years.[59,331] In a study of Swedish women aged older than 85 years, 16% reported hot flashes at least several times per week,[332] and up to 8% of women continue to have hot flashes for 20 years or longer after menopause.[333]

There are important questions related to long-duration hormone therapy use and discontinuation that are unanswered by

available data, because the WHI, the longest adequately powered blinded RCT, was limited to 5 to 7 years of therapy. In the WHI, initiating hormone therapy in women aged older than 60 years or more than 10 years beyond the onset of menopause was associated with greater risk, and initiating hormones in women aged older than 70 years was associated with the highest risk.[9] It is not known whether women who initiate hormone therapy at the time of menopause and continue use at older ages will incur the same risks as women initiating hormones later in life. The WHI studied only one formulation of oral hormones (CEE with or without MPA). Observational data suggest lower CVD risk, including VTE and stroke, with other hormone formulations and routes of administration, including transdermal estradiol, lower-dose estrogens, and different progestogens.[25,251,334-336] Mitigation of risk through the appropriate choice of dosing, formulation, and route of administration becomes increasingly important as women age and with longer duration of therapy. Factors that should be considered include severity of symptoms, effectiveness of alternative nonhormone and lifestyle interventions, and underlying risk for osteoporosis, CHD, cerebrovascular accident, VTE, and breast cancer. The decision regarding duration of treatment and when to stop hormone therapy must be considered in the context of the individualized risk-benefit profile, as well as the woman's personal preferences.[337,338]

Initiation after age 60 years

Initiation of hormone therapy in women aged older than 60 years or more than 10 years from menopause onset has complex risks and requires careful consideration, recognizing that there may be well-counseled women aged older than 60 years who choose to initiate or restart hormone therapy. For women requesting to initiate hormone therapy because of VMS appearing many years after menopause onset, further evaluation is needed. Although new-onset VMS in an older woman could be caused by estrogen-deficiency, hot flashes or night sweats may be related to an underlying medical problem (eg, obstructive sleep apnea, hyperthyroidism, carcinoid, lymphoma, Lyme disease, tuberculosis, HIV) or medication or substance use (eg, antidepressants, hypoglycemic agents, or withdrawal from alcohol or opioids).

Extended use after age 65 years

There is no general rule for stopping systemic hormone therapy in a woman aged 65 years. The Beers criteria from the American Geriatrics Society[339] has warnings against the use of hormone therapy in women aged older than 65 years. However, the recommendation to routinely discontinue systemic hormone therapy in women aged 65 years and older is neither cited or supported by evidence nor is it recommended by the American College of Obstetricians and Gynecologists or The North American Menopause Society.[340,341] Of note, the continued use of hormone therapy in healthy women aged older than 65 years at low risk for breast cancer and CVD is limited by insufficient evidence regarding safety, risks, and benefits.

For otherwise healthy women with persistent VMS, continuing hormone therapy beyond age 65 years is a reasonable option with appropriate counseling, regular assessment of risks and benefits, and shared decision-making. Hormone therapy also may be considered for prevention of fracture in healthy older women at elevated fracture risk when bothersome VMS persist or when hormone therapy remains the best choice because of lack of efficacy or intolerance of other fracture-prevention therapies.[23,340] Long-duration hormone therapy use and use in older women is not appropriate for reduction in the risk of CHD or dementia.[23,236,342] When providing hormone therapy to older women, clinicians must remain vigilant about risk stratification and potential mitigation strategies, such as switching from oral to transdermal hormone therapy, choice of progestogen, and lowering of dose.[337,338]

Discontinuation of hormone therapy

Controversy exists regarding how long hormone therapy may safely be used and when it should be discontinued. Based on findings from the WHI, breast cancer risk becomes detectable after 3 to 5 years in women using EPT. For women without a uterus using ET alone, breast cancer risk did not increase after 7 years, so a longer duration of hormone therapy use may be acceptable. There are few studies to guide the optimal way for women to stop hormone therapy, and VMS will recur in approximately 50% of women after discontinuation.[71] Data directly comparing the effects of abrupt discontinuation with those of slowly tapering are lacking,[343] although clinical experts generally advise gradually decreasing hormone therapy doses over time.[338,343] If hormone therapy is being used for prevention of osteoporosis, it is important to remember that protection against bone density loss and fracture prevention is lost rapidly with discontinuation.[164] Although VMS generally improve with time, GSM worsens with prolonged estrogen deficiency, so women should be provided with treatment options on discontinuation of systemic hormone therapy. Observational studies confirm the long-term safety of low-dose vaginal ET,[92,93] a highly effective treatment for GSM. In the absence of contraindications, a woman should determine her preferred hormone therapy formulation, dose, and duration of use, with ongoing assessment and shared decision-making with her healthcare professional.[337,338]

Key points

- The safety profile of hormone therapy is most favorable when initiated in healthy women aged younger than 60 years or within 10 years of menopause onset, so initiation of hormone therapy by menopausal women aged older than 60 years requires careful consideration of individual benefits and risks. (Level I)
- Long-term use of hormone therapy, including for women aged older than 60 years, may be considered in healthy women at low risk of CVD and breast cancer with persistent VMS or at elevated risk of fracture for whom other therapies are not appropriate. (Level III)
- Factors that should be considered include severity of symptoms, effectiveness of alternative nonhormone interventions, and underlying risk for osteoporosis, CHD, cerebrovascular accident, VTE, and breast cancer. (Level III)
- Hormone therapy does not need to be routinely discontinued in women aged older than 60 or 65 years. (Level III)

- Mitigation of risk through use of the lowest effective dose and potentially with a nonoral route of administration becomes increasingly important as women age and with longer duration of therapy. (Level III)
- Longer durations or extended use beyond age 65 should include periodic reevaluation of comorbidities with consideration of periodic trials of lowering or discontinuing hormone therapy. (Level III)
- For women with GSM, low-dose vaginal ET may be considered for use at any age and for extended duration, if needed. (Level III)
- In the absence of contraindications, a woman should determine her preferred hormone therapy formulation, dose, and duration of use, with ongoing assessment and shared decision-making with her healthcare professional. (Level III)

SUMMARY

Hormone therapy formulation, dose, regimen, route of administration, and the timing of initiation of therapy likely produce different effects, although these have yet to be evaluated in head-to-head RCTs. There is a significant difference in the benefits and risks of ET alone compared with EPT. Decision-making surrounding the use of hormone therapy should be individualized, with recommendations for the use of the appropriate dose, duration, regimen, and route of administration required to manage a woman's symptoms and to meet treatment goals. Given the more favorable safety profile of ET alone, longer durations may be more appropriate. Risk stratification by age and time since menopause is recommended. Transdermal routes of administration and lower doses of hormone therapy may decrease risk of VTE and stroke; however, comparative RCT data are lacking.

Personalization with shared decision-making remains key, with periodic reevaluation to determine an individual woman's benefit-risk profile. Benefits may include relief of bothersome VMS, prevention of bone loss and reduction of fracture, treatment of GSM, and improved sleep, well-being, and quality of life. Absolute attributable risks for women in the 50- to 59-year-old age group or within 10 years of menopause onset are low, whereas the risks of initiation of hormone therapy for women aged 60 years and older or who are further than 10 years from menopause onset appear greater, particularly for those aged 70 years and older or more than 20 years from menopause onset, with more research needed on potential risks of longer durations of use.

Women with POI and premature or early menopause have higher risks of bone loss, heart disease, and cognitive or affective disorders associated with estrogen deficiency. In observational studies, these risks appear to be mitigated if ET is given until the average age of menopause, at which time treatment decisions should be reevaluated. In limited observational studies, women who are *BRCA*-positive and have undergone risk-reducing BO appear to receive similar benefits from receiving hormone therapy, with minimal to no increased risk of breast cancer. There is a paucity of RCT data about the risks of extended duration of hormone therapy in women aged older than 60 or 65 years, although observational studies suggest a potential rare risk of breast cancer with increased duration of hormone therapy. It remains an individual decision in select, well-counseled women aged older than 60 or 65 years to continue therapy. There are no data to support routine discontinuation in women aged 65 years.

For select survivors of breast and endometrial cancer, observational data show that use of low-dose vaginal ET for those who fail nonhormone therapy for treatment of GSM appears safe and greatly improves quality of life for many. The use of systemic hormone therapy needs careful consideration for survivors of estrogen-sensitive cancers and should only be used for compelling reasons in collaboration with a woman's oncologist after failure of nonhormone therapies.

Additional research is needed on the thrombotic risk (VTE, pulmonary embolism, and stroke) of oral versus transdermal therapies (including different formulations, doses, and durations of therapy). More clinical trial data are needed to confirm or refute the potential beneficial effects of hormone therapy on CHD and all-cause mortality when initiated in perimenopause or early postmenopause. Additional areas for research include the breast effects of different estrogen preparations, including the role for SERM and TSEC therapies; optimal progestogen or SERM regimens to prevent endometrial hyperplasia; the relationship between VMS and the risk for heart disease and cognitive changes; and the risks of POI. Studies are needed on the effects of longer use of low-dose vaginal ET after breast or endometrial cancer; extended use of hormone therapy in women who are early initiators; improved tools to personalize or individualize benefits and risks of hormone therapy; the role of aging and genetics; and the long-term benefits and risks on women's health of lifestyle modification or complementary or nonhormone therapies if chosen in addition to or over hormone therapy for VMS, bone health, and CVD risk reduction.

CONCLUSIONS

- Hormone therapy is the most effective treatment for VMS and GSM and has been shown to prevent bone loss and fracture.
- Risks of hormone therapy differ for women, depending on type, dose, duration of use, route of administration, timing of initiation, and whether a progestogen is needed. Treatment should be individualized using the best available evidence to maximize benefits and minimize risks, with periodic reevaluation.
- For women aged younger than 60 years or within 10 years of menopause onset and without contraindications, the benefit-risk ratio appears favorable for treatment of bothersome VMS and for the prevention of bone loss and reduction of fracture. Based on the WHI RCTs, longer duration may be more favorable for ET than for EPT.
- For women who initiate hormone therapy more than 10 or 20 years from menopause onset or when aged 60 years or older, the benefit-risk ratio appears less favorable than for younger women because of greater absolute risks of CHD, stroke, VTE, and dementia.
- For GSM symptoms not relieved with nonhormone therapies, low-dose vaginal ET or other government-approved therapies (eg, vaginal DHEA or oral ospemifene) are recommended.

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