

Estrogen and progestogen therapy in postmenopausal women

The Practice Committee of the American Society for Reproductive Medicine

Hormone therapy (HT) can be used to treat or prevent problems associated with the decline in estrogen production by the ovaries after menopause. Menopause occurs naturally when the ovarian follicles are depleted or following surgical removal of both ovaries. The resulting hypogestrogenic state may adversely affect estrogen target tissues, which include the brain, skeleton and skin, as well as the cardiovascular and genitourinary systems. The concentration and function of hormone receptors varies in these organs and systems; differences in genetics, body mass index, and body habitus also may influence the levels of endogenous estrogen and androgen in postmenopausal women. Significant variability among women exists with regard to their development of menopausal symptoms, the reaction of their target tissues to estrogen deficiency, and in their response to HT.

GOALS OF THERAPY

There are two broad categories of menopausal hormone therapy: estrogen alone therapy (ET) and estrogen combined with progestogen therapy (E/PT). For the purposes of this document, progestogen refers to natural progesterone as well as synthetic congeners of progesterone (progestins).

The goals of menopausal hormone therapies are to:

- a. reduce symptoms resulting from estrogen depletion, including hot flushes, sleeplessness, lethargy, depressed mood, and vaginal dryness;
- b. treat urogenital atrophy; and
- c. prevent osteoporosis.

Although ET and E/PT may improve a woman's quality of life, each woman has a unique risk profile which might lead to more, or less,

benefit from HT. Patient preferences as well as evidence from medical research influence management decisions. As a result, an unwavering policy applied to all menopausal women will not meet the individual needs of many women. Health care providers should therefore consider how the benefits and risks may affect each patient before drawing conclusions or recommending HT. In addition, the balance between risks and benefits, compliance with therapy, and side effects needs to be periodically reassessed, and newly published research findings must be incorporated into patient care decisions.

ESTROGEN DEFICIENCY SYMPTOMS

The principal symptom of the early menopausal years is the vasomotor (hot) flush. Hot flushes and night sweats are experienced by 50% to 85% of postmenopausal women and cause significant distress to approximately 25%. Sleep disturbances caused by nocturnal hot flushes and sweating can lead to lethargy and depressed mood, although depression is equally common in premenopausal and postmenopausal women. Vasomotor symptoms are more common and more severe after a surgical menopause. The frequency of hot flushes decreases with time: in the Postmenopausal Estrogen/Progestin Interventions (PEPI) trial, the percentage of women taking placebo who experienced vasomotor symptoms declined from 56% at baseline to 30% in year three (1). Only a small percentage of women continue to suffer from vasomotor flushes 10 years after their menopause. Fifteen years after menopause approximately 3% of women report very frequent hot flushes and 12% report moderate to severe hot flushes (2, 3).

HT is the most effective treatment for hot flushes and also decreases sleep disturbances,

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thereby improving quality of life. The value of such treatment has been demonstrated in numerous randomized controlled trials (RCTs). One of these, the three-year PEPI trial, involved 875 menopausal women who were randomly allocated to one of five treatments. The treatments were placebo, estrogen alone (conjugated equine estrogens [CEE]), estrogen plus cyclic progestogen (either medroxyprogesterone acetate [MPA] or micronized progesterone) or estrogen plus continuous progestin (medroxyprogesterone acetate). All hormone treatments were more effective than placebo in reducing hot flashes. There were no significant differences between the treatments, and the size of the treatment effect became smaller after the first year. For instance, the likelihood of having severe vasomotor symptoms was approximately 78% lower in the four active treatment groups compared with the placebo group during the first year of treatment (summary RR = 0.22, 95% CI, 0.17–0.30), and approximately 60% lower during the third year of treatment (summary RR = 0.40, 95% CI, 0.30–0.53). For every two patients treated during the first year, one reported fewer severe vasomotor symptoms, but during the third year when the placebo group was experiencing fewer symptoms, the number needed to treat (NNT) rose to six patients. In summary, HT reduces vasomotor symptoms, the benefit compared to placebo is more dramatic during the first year of treatment, and cyclic or continuous progestogen does not add to or subtract from the estrogen effect to an extent that can be measured. RCTs in younger postmenopausal women have demonstrated similar improvement in the severity and frequency of hot flashes and an improvement in the quality of life (4, 5).

In earlier trials, estrogen increased feelings of well-being, while combinations with progestin attenuated the impact of estrogen on behavioral effects (6, 7). In the PEPI trial, however, cognitive-affective symptoms such as forgetfulness (present in 34% of subjects at baseline), feeling easily distracted (25%), and difficulty concentrating (24%) were not changed with ET or E/PT after one year or three years of treatment. Symptoms of anxiety were present in only 5% at baseline and were unchanged over three years in each arm of the PEPI trial.

The Women's Health Initiative (WHI) primary prevention trial of continuous combined E/PT was not designed to evaluate management of menopausal symptoms. Nevertheless, quality-of-life measures were collected at baseline and at one year in all women and at three years in a subgroup of 1,511 of the 16,608 women randomized to receive placebo or E/PT. In a post-hoc subgroup analysis, randomization to E/PT resulted in no significant effects on general health, vitality, mental health, depressive symptoms, or sexual satisfaction, and a small but significant benefit for sleep disturbance, physical functioning, and bodily pain after one year. At three years, there were no significant benefits in any quality-of-life outcomes. Among women 50 to 54 years of

age with moderate-to-severe vasomotor symptoms at baseline, E/PT improved vasomotor symptoms and resulted in a small benefit in terms of sleep disturbance but no benefit in terms of the other quality-of-life outcomes (3).

Results observed in the Heart and Estrogen/progestin Replacement Study (HERS), a secondary prevention trial comparing E/PT with placebo, contrast with those from the WHI. HERS demonstrated that the effect of HT on health-related quality of life measures depended upon the presence or absence of menopausal symptoms at baseline. Study participants were on average 18 years postmenopausal, with a mean age of 67 years. HT reduced hot flashes, trouble sleeping, and vaginal dryness more than placebo, and the benefit was more marked in younger women who were symptomatic at study entry (2).

An important knowledge gap in this area concerns the differential risk of cardiovascular disease, osteoporosis, and cancer for women who have estrogen deficiency symptoms compared with those who do not experience such symptoms, because women with severe hot flashes were largely excluded from participation in the WHI. Women who experience significant vasomotor symptoms tend to be thinner and have lower endogenous estrogen levels. In a single large cohort study of elderly postmenopausal women, cardioprotective effects were limited to women who had a lower body mass index (8). Most studies, however, have insufficient power to perform comprehensive subgroup analyses.

UROGENITAL SYMPTOMS

Estrogen is an effective treatment for symptoms of urogenital atrophy, such as vaginal dryness and sexual discomfort. A meta-analysis of 10 randomized placebo-controlled trials found significant improvement in all outcomes evaluated: dyspareunia, related symptoms, and the physician's assessment (9). The vaginal route of administration achieved better symptomatic relief than oral, transdermal, or parenteral routes of administration. Few of the studies included in the analysis evaluated whether treatment benefits continued after six months.

Estrogen also has been recommended for the treatment of urinary incontinence, a problem that affects 5% to 14% of women age 60 years or older. The presence of estrogen receptors in urethral mucosa and smooth muscle suggests that estrogen alone might improve symptoms of urinary incontinence. In a meta-analysis including five RCTs involving a total of 117 subjects, subjective improvement in symptoms of urinary incontinence was significantly greater with ET compared to placebo treatment (10). However, HERS reported contrasting results from a considerably larger trial; among 1,525 participants who reported at least one episode of urinary incontinence per week, E/PT was associated with a worsening of incontinence symptoms compared to the placebo group (11). After an average follow-up of 4.1 years,

incontinence had worsened in 38.4% of the hormone-treated group and 28.4% of the placebo group. The WHI trial involving E/PT did not report on an evaluation of urogenital symptoms. There is a need for studies of the possible mechanisms by which HT might affect stress and/or urgency incontinence and for trials having incontinence as a primary outcome and sufficient power to address effectiveness in clinically important endpoints.

EFFECTS ON BONE

Although RCTs uniformly indicate that HT maintains or improves bone mineral density in the spine, proximal femur and radius (12), results have not been as consistent with respect to prevention of clinical fractures. The HERS involved 2,763 American women with established heart disease (average age 66.7 years). The interventions were 0.625 mg of conjugated equine estrogens plus 2.5 mg of medroxyprogesterone acetate daily (E/PT) or placebo. After a mean 4.1 years of follow-up, E/PT did not alter significantly the likelihood of hip fracture (RR = 1.09, 95% CI, 0.48–2.46) or other type of fracture (RR = 0.93, 95% CI, 0.73–1.20) (13). Between 55% and 57% of each group had a body mass index >27 kg/m². On average, patients enrolled in HERS were 18 ± 8 years postmenopausal and fracture incidence was not a primary outcome measure. In contrast, a Finnish RCT involving 464 postmenopausal women (average age 52.7 years) with fracture risk as the primary outcome measure yielded different results. Patients were randomly allocated to one of four groups: E/PT alone (estradiol and cyproterone), vitamin D alone, E/PT plus vitamin D, or placebo. After a mean 4.3 years follow-up, and adjusting for baseline bone density and fracture history, the two HT groups had significantly fewer non-vertebral fractures than the two groups not receiving HT (RR = 0.43, 95% CI, 0.20–0.91) (14). The trial is vulnerable to small sample errors, as there were only three hip fracture events, all in the non-HT groups.

In a Swedish case-control study involving 1,327 women (average age 72.5 years) with hip fractures and 3,262 population controls, the odds ratio for hip fracture among current HT users was 0.35 (95% CI, 0.24, 0.53) and 0.76 (95% CI, 0.57–1.01) for past users. Transdermal formulations of estrogen were as effective as oral estrogens (15). Since the incidence of hip fracture is less than five per 100,000 women years in women under age 70, studies with a mean age at enrollment below 70 years may have insufficient power to demonstrate a significant benefit. The greater benefit from current use provides a justification for HT use after age 70 when hip fracture incidence is meaningful and if other osteoporosis preventive agents cannot be used or tolerated. Summing up, the bone density outcome trials, the epidemiological data, and the smaller of two fracture outcome trials all suggest that current HT use may prevent clinical fractures.

In the WHI trial there were 10 and 15 hip fractures in the E/PT and placebo groups, respectively, and the relative hazard was 0.66 (adjusted 95% confidence interval 0.33–1.33). Because hip fracture was a secondary outcome, the 95% confidence interval was adjusted for the number of statistical comparisons that were made. The WHI was the first large clinical trial to show a significant overall reduction in osteoporotic fractures (hip, vertebral, and other osteoporotic fractures, including all fractures except those of the ribs, chest/sternum, skull/face, fingers, toes, and cervical vertebrae). Even after adjustment, the hazard ratio for any osteoporotic fracture was significantly reduced in the E/PT group (HR 0.76, 95% CI, 0.63–0.92). The mean age of subjects enrolled in the WHI was 63.3 years. Approximately 85% of osteoporotic fractures observed in the WHI trial were non-vertebral and non-hip fractures.

Because the effect on hip fracture is small, HT treatment is not warranted solely for prevention of hip fractures. Although osteopenia and osteoporosis may be prevented and treated with HT, alternative agents may have a better risk-benefit ratio. Trials are needed to compare other strategies with protocols that include HT treatment.

SENILE DEMENTIA AND COGNITION

More than 33% of women 65 years or older will develop dementia during their lifetime (16). In a meta-analysis which included two cohort studies and 10 case-control studies, HT was associated with a 34% reduction in the risk of dementia (summary OR = 0.66, 95% CI, 0.53–0.82) (17). There was insufficient information in the studies to assess the effect of estrogen or progestogen in formulation, dosage, duration or recency of use. Results of three subsequent epidemiological studies are conflicting but do not change the overall estimate of risk reduction in a meaningful way (18–20).

Memory loss is the first process to be affected in Alzheimer's disease, but it has been difficult to demonstrate an effect of HT on memory, both in normal women and in women with early dementia. A meta-analysis including nine RCTs and eight cohort studies which employed a variety of cognitive tests in women free of dementia, found that HT was associated with improved verbal memory, vigilance to task, reasoning and motor speed; generally, benefits were limited to symptomatic women and were unlikely to be detected in asymptomatic women (17). Not included in the meta-analysis was a recent report on cognitive function among healthy older women in the Nurses' Health Study cohort (21); HT users scored higher in only one of four cognitive tests. The estimated risk of hormone users having a low score on the test of verbal fluency was reduced by 30% (RR = 0.70, 95% CI, 0.45–1.09); results were similar for ET and E/PT. In addition, a three-year prospective study reported that prior HT use and current use of greater than 10 years was associated with a reduced risk of Alzheimer's disease (RR = 0.59, 95% CI, 0.36–0.96) (22).

In the Women's Health Initiative Memory Study (WHIMS), E/PT increased the risk of dementia among women 65 years and older, and it did not prevent mild cognitive impairment (23, 24). Compared to placebo, the hazard ratio for probable dementia was 2.05 (95% CI, 1.21–3.48) in women who received E/PT. Approximately 50% of cases were classified as Alzheimer's disease in each group. Approximately 12.5% of cases were classified as vascular dementia in the E/PT group compared to 5% in the placebo group. There were 45 and 22 cases of probable dementia observed per 10,000 woman-years in the E/PT and placebo groups, respectively. Annual assessments of global cognitive function showed no difference between groups. Most women receiving E/PT did not experience clinically relevant declines in cognitive function compared to placebo.

In the WHIMS, cases of probable dementia appeared in the first year of intervention in both the E/PT and placebo groups, suggesting that some subjects had cognitive decline at baseline. E/PT did not improve cognitive function or slow the progression of symptoms and actually appeared to increase progression to probable dementia. The ET arm of the WHIMS continues. Other trials are needed to evaluate effects on memory and cognition among asymptomatic women.

EFFECTS ON CORONARY HEART DISEASE

Cardiovascular disease is the leading cause of death in postmenopausal women. The association between HT and coronary heart disease (CHD) has been evaluated in three types of studies: epidemiological studies (the most common), RCTs evaluating intermediate outcomes, and RCTs evaluating definitive coronary heart disease outcomes, usually nonfatal myocardial infarction (MI) and CHD death.

A summary of epidemiological studies that appeared in a 1996 World Health Organization (WHO) Technical Report published in 1996 suggested that HT use reduced the risk of nonfatal MI or coronary artery disease (CAD) death by 44% (summary RR = 0.56, 95% CI, 0.51–0.61) compared to no use (25). In the most recent analysis from the Nurses' Health Study, the relative risk of a major coronary event (nonfatal MI or CHD mortality) was lower among current users of HT compared to never-users. After adjustment for cardiovascular risk factors, the relative risk was 0.61 (95% CI, 0.52–0.71) (26). Among women taking oral conjugated estrogens, the reduction in risk for 0.3 mg and 0.625 mg daily dosages and for conjugated estrogens plus progesterin was similar.

The results of RCTs that have evaluated intermediate outcomes are less consistent than those observed in epidemiologic studies, but favorable effects of HT on lipid profiles, including lipoprotein (a), have been observed (12, 27–29). HT does not slow the progression of coronary artery atherosclerosis, as estimated by angiographic measurements

of coronary artery diameter. In the Estrogen Replacement and Atherosclerosis (ERA) Trial (27), angiographic endpoints were used to determine the effect of ET and E/PT on the progression of atherosclerosis in 309 postmenopausal women with documented CAD. Neither conjugated estrogens alone (0.625 mg per day) nor continuous combined HT (0.625 mg conjugated estrogens plus 2.5 mg medroxyprogesterone acetate per day) affected the progression of coronary atherosclerosis when compared to placebo treatment, even though lipoprotein profiles were improved in both HT groups. The women in the ERA trial were followed for an average of 3.2 years (27). Identical results were found in the Women's Estrogen-progestin Lipid Lowering Hormone Atherosclerosis Regression Trial (WELL-HART) which examined HT regimens utilizing 17 β -estradiol with or without cyclic medroxyprogesterone acetate (69).

The most valid evidence comes from three large RCTs (HERS, ESPRIT, and WHI) which found no evidence that E/PT (HERS, WHI) or ET (ESPRIT) was effective for primary or secondary prevention of nonfatal MI and CHD deaths (13, 30, 31).

The HERS secondary prevention trial involved 2,763 women with coronary artery disease who were postmenopausal and who had an intact uterus. Women were 55 to 80 years old (mean age 66.7 years) (13). During an average follow-up of 4.1 years, treatment with oral E/PT (0.625 mg of conjugated equine estrogens plus 2.5 mg of medroxyprogesterone acetate) had no effect on MI or CHD death (relative hazard 0.99; 95% CI, 0.80–1.22). There was a pattern of early increase in CHD events with a time trend toward fewer CHD events in years 4 and 5. HERS II, a follow-up open label observational study of 2.7 years' duration, demonstrated that the lower rates of CHD events among women seen in the final years of HERS did not persist during the additional years of observation. After 6.8 years, E/PT did not reduce the risk of cardiovascular events in women with preexisting coronary artery disease. The smaller ESPRIT study randomized 1,017 postmenopausal women aged 50 to 69 years of age (mean age 62.6 years) with a recent first MI to placebo or ET (2 mg of estradiol valerate) for two years. The frequency of nonfatal reinfarction or cardiac death did not differ between the two groups (rate ratio 0.99; 95% CI, 0.70–1.41) (31). The results of HERS and HERS II suggest that E/PT should not be used for secondary prevention of cardiac events in women with CHD. Secondary analysis of HERS identified a substantial underutilization of medications proven effective for secondary prevention by the study participants, such as aspirin, β -blockers, and statins (32). Data from ESPRIT suggest that ET administered soon after recovery from a first MI does not reduce the risk of subsequent cardiac events. A smaller RCT concluded that ET and E/PT do not reduce risk of MI or CHD death in postmenopausal women hospitalized with unstable angina (33).

In the WHI primary prevention trial (30), there were 37 and 30 CHD events per 10,000 woman-years in the E/PT and placebo groups, respectively, yielding a small but significant increase in CHD risk (hazard ratio 1.29, 95% CI, 1.02–1.63). The small increase in CHD occurred despite a significant 12.7% reduction in low-density lipoprotein cholesterol and 7.3% increase in high-density lipoprotein cholesterol with E/PT relative to placebo. Most of the excess CHD risk was nonfatal MI, excluding silent MI (HR 1.30, 95% CI, 1.01–1.67) (70). Deaths due to cardiac disease were not significantly increased (15 and 13 per 10,000 woman-years in E/PT and placebo-treated groups, respectively). In the final analysis of the WHI E/PT trial, the HR was lower and less significant, 1.24 (95% CI, 1.00–1.54). Significantly higher risk was observed only in the first year of E/PT treatment (HR 1.81, 95% CI, 1.09–3.01) and risk did not correlate with age at study entry, body mass index, presence of vasomotor flushes or night sweats, or aspirin or statin use. An excess risk of CHD was observed in E/PT-treated women who were more than 20 years postmenopausal at the time of study entry or had higher baseline levels of LDL-cholesterol (70).

Do the results of the HERS and WHI trials differ from the observational studies because the intervention included progestin? In the epidemiologic studies, ET was the dominant treatment and progestogen diminished some of the intermediate effects of ET on lipids and other heart disease risk factors. However, in the five epidemiological studies which provided information about ET and E/PT exposure, the average risk reduction was 39% (95% CI, 27%–49%) with ET and 31% (95% CI, 13–45%) with E/PT (26, 34, 36, 71).

Level I evidence indicates that HT is not indicated for the primary or secondary prevention of coronary artery disease events. Alternative health strategies and pharmaceutical agents with established value should be used for primary prevention of CHD. Women with established CHD are at high risk for MI and cardiac death and frequently do not receive adequate treatment for secondary prevention (32).

The WHI study results are relevant to long-term use of E/PT among women aged 50 to 79 years who are predominantly healthy and free from estrogen deficiency symptoms. Risks may vary with lower doses, different formulations, and non-oral routes of HT administration. The estrogen only-arm of the WHI is ongoing and may add insight concerning the relative impact of progestogen on risk modification.

STROKE

The incidence of stroke among otherwise healthy postmenopausal women is approximately two per 1,000 per year, and approximately 75% of strokes are ischemic (30, 37, 38). In 29 different epidemiological studies, stroke endpoints and HT definitions were inconsistent and there was no conclusive evidence for a beneficial or harmful effect of HT on stroke risk (35). The Nurses' Health Study reported a trend

toward increased risk with combined continuous E/PT. Only a small non-significant increase in risk was observed for ET (relative risk 1.18, 95% CI, 0.95–1.46), but for E/PT the risk was 1.45-fold higher (95% CI, 1.10–1.92) for any type of stroke, compared with never users (37).

Stroke risk associated with E/PT has now been addressed in two RCTs, HERS, and WHI. In HERS and HERS II combined continuous E/PT was not associated with an increased risk for transient ischemic attack (TIA) (relative hazard [RH] 0.90, 95% CI, 0.84–1.43) or ischemic stroke (RH 1.18, 95% CI, 0.84–1.43), compared with placebo, but HERS lacked the necessary power to evaluate these small relative changes in risk (38). Overall, the RH for any stroke or TIA was 1.09, a non-significant increase (11).

In the WHI study of E/PT, 151 women (1.8%) in the E/PT group and 107 (1.3%) in the placebo group had strokes (39), 80% of which were ischemic. The hazard ratios were 1.44 (95% CI, 1.09–1.90) for ischemic stroke and 0.82 (95% CI, 0.43–1.56) for hemorrhagic stroke. There were 26 and 18 ischemic strokes per 10,000 woman-years in the E/PT and placebo groups, respectively.

Stroke risk with ET has also been addressed in two RCTs. One involving 664 postmenopausal women with a recent stroke or TIA found that ET (1 mg estradiol valerate per day) did not reduce the risk of subsequent stroke or mortality over the 2.8 years of follow-up (40). Similarly, ESPRIT did not demonstrate an increased risk of stroke or TIA (31).

Presently available data show that HT does not provide protection against stroke and may increase the risk of ischemic stroke. Little is known about the characteristics of the patients who are at greatest risk of stroke while using E/PT.

VENOUS THROMBOEMBOLISM (VTE)

VTE is a rare but important risk for women receiving HT. Data from epidemiologic studies, HERS, and WHI consistently demonstrate an increased risk of VTE events in postmenopausal women who use ET or E/PT (13, 30, 41). In five epidemiological studies published between 1992 and 1997 involving 592 cases of VTE of which 130 (22%) were in current HT users, the risk of VTE was increased by approximately two-fold (typical OR = 2.3, 95% CI, 1.7–3.0) (42–46). In the HERS trial the relative risk of VTE was similar in magnitude: 2.66 (95% CI, 1.4–5.0) (47). The excess risk was 3.9 per 1,000 woman-years and the NNT to cause harm in one additional woman with established heart disease (average age 66.7 years) was 256 (95% CI, 157, 692). VTE is not confined to the first year of HT use, but risk declines from approximately four-fold in the first year to less than two-fold after the third year of use (13, 42, 45, 46). In HERS II, the 2.7-year unblinded follow-up study of women with existing CHD receiving E/PT, VTE was not significantly increased (RH 1.40, 95% CI, 0.6–3.0).

The WHI study confirmed the magnitude and timing of the VTE risk estimates from previous studies. There were 34 and 16 VTE events per 10,000 woman-years in the E/PT and placebo groups, respectively, an increase that was significant after adjusting for multiple statistical testing (HR 2.11, adjusted 95% CI, 1.26–3.55). The relative hazard for pulmonary embolism (2.13) and deep venous thrombosis (2.07) were similar. VTE events decreased over time during the study (z for trend = -2.46 , $P = 0.014$).

Continuing research on the prevalence and effects of procoagulation factors and the genetics of VTE risk may identify screening procedures to reduce overall risk among women using HT. At present, routine screening of women for thrombophilias is not indicated prior to initiating HT. VTE risks may vary according to the route of administration of HT, since oral estrogens are associated with greater impact on coagulation factors than transdermal or vaginal routes of administration (72).

ENDOMETRIAL CANCER

Epidemiologic studies since 1975 have consistently shown that unopposed estrogen increases the risk of endometrial cancer among women having a uterus. Data from 30 case-control studies and seven cohort studies suggest that risk among ever users of ET is increased approximately 2.8-fold (95% CI, 2.6–3.0) over that in never users (48). Moreover, there is a significant trend toward increasing risk of endometrial cancer with increasing duration of ET; risk is 2.0-fold higher (95% CI, 1.8–2.2) with less than five years of use and 6.7-fold higher (95% CI, 5.9–7.6) with longer durations of ET. After discontinuation of ET, the relative risk remains elevated; risk is still 3.5 times higher (95% CI, 3.0, 4.0) for up to five years after treatment ends, and 2.5 times higher (95% CI, 1.9–3.2) five and more years after discontinuing ET. The ET-associated endometrial cancer risk is similar for different estrogen preparations and higher doses are associated with a small additional increase in risk (48).

Treatment with progestogens appears to reduce the risk of endometrial cancer associated with ET in a duration dependent manner. Endometrial cancer risk is decreased with either cyclic or continuous E/PT. Cyclic regimens including more than 10 days of progestogen exposure per month appear to provide maximum protection. Morphological and biochemical studies suggest that shorter durations of cyclic progestogen treatment may not prevent development of endometrial hyperplasia. The risk of endometrial cancer associated with less than five years of continuous E/PT was 1.01 (95% CI, 0.76–1.35) and 0.86 (95% CI, 0.53–1.42) for five or more years of use.

Both the HERS and the WHI E/PT trials confirmed that continuous E/PT has no effect on risk for developing endometrial cancer. In the WHI trial, five and six cases of endometrial cancer were observed per 10,000 woman-years

in the E/PT and placebo groups, respectively, yielding a small but insignificant decrease in risk (RH 0.83, adjusted 95% CI, 0.29–2.32).

HT AND BREAST CANCER

Estimates of HT-associated breast cancer risks vary widely, mainly because studies involving fewer than 200 HT-exposed breast cancer cases are too small to estimate risk with precision. The WHO Collaborative Group report attempted to overcome the limitations of small sample size by combining data from 90% of the published epidemiological studies, which together included 52,705 women with breast cancer (49). For current users of HT and those who stopped using HT one to four years before, breast cancer risk increased 2.3% per year of use, an effect comparable to that of delayed menopause (2.8% increase in risk per year of delay). For short-term HT use (one to four years), the increase in risk was not significant (1.05, 95% CI, 0.99–1.12). After five years of current use, risk increased significantly by 12% (RR = 1.12). For current users of HT for five years or longer, the relative risk was 1.35 (95% CI, 1.21–1.49). Overall, the increase in breast cancer risk was most evident in women having a BMI <25 kg/m² and risk of localized, but not metastatic, disease was increased. Within five years after discontinuing HT, the increased risk associated with HT use virtually disappeared (49). Both the combined report and subsequent separate studies indicated that dose and type of estrogen did not affect breast cancer risk (49–51).

Combined estrogen-progestin therapy increases the point estimates for breast cancer risk compared with estrogen alone, but there were relatively few cases exposed to combined therapy in the collaborative analysis (49). Several studies subsequent to the collaborative analysis include subjects with combined estrogen-progestin HT exposure. In the Breast Cancer Detection Demonstration Project (BCDDP), the per annum breast cancer risk was 1.01-fold higher (95% CI, 1.002, 1.03) with ET alone and 1.08-fold higher (95% CI, 1.02, 1.06) with combined E/PT. Only 12 cases used a progestogen for 15 days or more per month, so this estimate reflects cyclic use of progestogens (51). Current and recent use of ET was associated with a nonsignificant RR of 1.2 (95% CI, 1.0–1.4), and similar use of E/PT was associated with a significant RR of 1.4 (95% CI, 1.1–1.8). In a case control study, the per annum relative risks calculated from the data for unopposed estrogen, cyclic combined estrogen-progestin and continuous combined estrogen-progestin were 1.015, 1.076, and 1.018, respectively (50). Per five years of use, the relative risk for developing breast cancer was 1.06 (95% CI, 0.97–1.15) for ET, 1.38 (95% CI, 1.13, 1.68) for cyclic progestin plus estrogen, and 1.08 (95% CI, 0.88, 1.35) for continuous combined estrogen-progestin. A recent multicenter, population based case control study demonstrated a significantly increased odds ratio (OR) with five or more years of current use of continuous combined HT (1.54, 95%

CI, 1.10–2.17) but no increased risk with either cyclic progestin HT (OR = 1.07) or ET (OR = 0.81). As with other studies (52), the increased risk dissipated very quickly after discontinuing therapy (53). Most recently, a population-based case-control study that confirmed the increased risk associated with long-term therapy (>5 years), found no difference regardless whether the progestin component of HT was administered cyclically or continuously, and suggested an increase in lobular carcinoma as well as invasive ductal carcinoma (73). The data remain inconclusive but suggest that cyclic and combined E/PT may present a slightly higher breast cancer risk than ET. In all of the studies, however, risk was minimal with less than five years' duration of use. Increased risk appears to be limited to current use of at least five years and recent users of long-term therapy.

A key analysis in the collaborative study showed that the breast cancer risk associated with current or recent HT use for five years or more and a positive family history for breast cancer was lower than the HT-associated risk with a negative family history (49). A subsequent cohort study found a higher ratio of HT-associated breast cancer risk with a positive family history (54), but the combined results of the cohort study and the collaborative analysis indicate that the relative risk of breast cancer associated with five years or more of HT use currently or within five years was 1.13 (95% CI, 0.82, 1.57) with a positive family history and 1.32 (95% CI, 1.20, 1.46) with a negative family history of breast cancer. Therefore HT does not appear to further magnify the higher breast cancer risk associated with a family history of breast cancer.

During the three years of the HERS trial, breast cancer risk was not elevated. There were 34 and 25 new invasive breast cancer cases in the HT and placebo groups, respectively, a nonsignificant increase (relative hazard 1.38, 95% CI, 0.82, 2.31) (47). During the average 5.2 years of exposure during the WHI trial, there were 38 and 30 new invasive breast cancer cases per 10,000 woman-years in the HT and placebo groups. The relative hazard of 1.26 (95% CI, 1.00, 1.59), although not statistically significant, was associated with a highly significant trend analysis that demonstrated increasing risk with increasing duration of use (30). Frequency of surveillance by mammography was equivalent in both WHI study groups.

To better understand the relationship between breast cancer and HT, the WHI performed a detailed analysis of the breast cancers that developed during the study and extended the mean follow-up period to 5.6 years. The unweighted hazard ratio (HR) was 1.24 for total breast cancer (95% CI, 1.02–1.50), 1.24 for invasive breast cancer (95% CI, 1.01–1.54), and 1.18 for in situ cancer (95% CI, 0.77–1.82). Invasive breast cancers were of similar histology and grade in HT and placebo groups, but HT was associated with slightly larger tumor size, 1.7 cm vs. 1.5 cm ($P=0.4$) and

cancers in the HT group were more likely to be lymph node positive, 25.9% vs. 15.8% ($P=0.3$) (74, 56). In addition, the WHI data suggest that women taking E/PT are more likely to require additional diagnostic studies for equivocal mammographic findings than non-HT users.

The invasive breast cancer risk with HT in both RCTs is small and similar in magnitude to the breast cancer risks indicated by the Collaborative analysis. Also, the timing of the risk was similar: breast cancer risk was the same in HT and placebo groups for four years in the WHI study, while in the Collaborative study, breast cancer was not significantly elevated until after five years of use.

The absolute effect (eight and 17 cases per 10,000 women per year in the WHI and HERS trials, respectively) is low and in the range of the increased breast cancer risk from two glasses of wine per day. The Collaborative analysis estimate of the absolute risk of breast cancers among users of estrogen plus progestin HT was based on incidence rates intermediate between the United Kingdom and the United States. Among 1,000 non-HT users aged 50 years, 20 breast cancer cases would be diagnosed in 10 years. With five and 10 years of HT use, there would be two and six additional breast cancer cases, respectively. An absolute risk of this magnitude has public health significance, but for the average woman it is generally below the level which affects decisions about HT. Moreover, most studies published to date suggest that breast cancer survival is not adversely affected, and may be improved, in women who were taking HT at the time of diagnosis (55). The Million Women Study, in contrast, demonstrated an increased risk of fatal breast cancer in current users of HT (RR = 1.22, 95% CI, 1.05–1.41) but not past users (RR = 1.05, 95% CI, 0.85–1.29) (75).

The increased risk of invasive breast cancer seen in the WHI is similar to that reported in prior studies. The WHI found that in situ breast cancer incidence was not significantly different among HT and placebo users. Breast cancer mortality tends to be lower in observational studies among patients who were HT users (55). The mortality data that will continue to come from the WHI study may indicate whether the estrogen plus progestin HT-breast cancer link is causal or due to HT-mediated facilitation of early diagnosis. Our knowledge gap concerning the risks of ET should be answered when the estrogen-only arm of the WHI reports its data. A knowledge gap still exists regarding the safety of administering HT to symptomatic women who survive disease-free after treatment for localized breast cancer.

COLON CANCER

An important but as yet unproven benefit of long-term HT may be a reduction in the risk of colon cancer, an observation in numerous epidemiological studies. One possible biological rationale is a reduction in the concentrations of bile acids which are potentially tumor-promoting, a hypothesis

associated with the lower risk among women who have been pregnant or taking HT. Another possibility is linked to the dominant estrogen receptor subtype in the colonic mucosa, which is ER β . Evidence has emerged that this subtype is significantly decreased in colonic tumors from females. The epidemiological evidence was summarized in a meta-analysis which included 25 epidemiological studies and distinguished between risk of colon cancer and risk of rectal cancer (56). Rectal cancer incidence was not affected by HT use. For colon cancer, however, recent use of HT was associated with a 33% reduction in the risk (RR = 0.67, 95% CI, 0.59, 0.77). In a second meta-analysis, current users of HT demonstrated a 34% reduction in colon cancer (RR = 0.66; 95% CI, 0.59–0.74) (57).

This promising benefit was consistent with the WHI RCT results, in which there were 10 and 16 new colorectal cases per 10,000 woman-years in the estrogen-progestin HT and placebo groups, respectively. This small benefit of HT was not significant, however, after adjusting for multiple statistical testing (relative hazard, 0.63, adjusted 95% CI, 0.32–1.24). Time trend analysis showed a benefit for colorectal cancer after three years of HT use.

More research is needed into the mechanisms by which estrogen with or without progestin might influence the development of colon cancer. Results might guide focused trials to evaluate whether the observed reduced incidence is due to hormone use or alternative actions.

EPITHELIAL OVARIAN CANCER

Epithelial ovarian cancer shares certain reproductive and hormonal risk factors with endometrial cancer: it is less common in parous women and in those who have used oral contraceptives or had an early menopause (58, 59). Ovarian cancer incidence also is higher among well-educated women and those in the highest social classes who are most able to pay for HT (60). One meta-analysis of 15 case-control studies found heterogeneous risk estimates and the summary odds ratio was not significant (OR = 1.1, 95% CI, 0.9–1.3) (61). In a pooled analysis of data from four European case-control studies, the ovarian cancer risk was 1.7-fold higher (95% CI, 1.3–2.3) for ever users of HT compared with never users.

In a Swedish case-control study reported in 2002, epithelial ovarian cancer risk was increased with ever use of unopposed estrogen (adjusted OR = 1.43, 95% CI, 1.02–2.00) or estrogen with sequential progestin (OR = 1.54, 95% CI, 1.15–2.05) (62). Ever use of estrogen with continuous progestin, however, was not associated with increased risk (OR = 1.02, 95% CI, 0.73–1.43). Another 2002 report of an analysis of ovarian cancer incidence during 19 years of follow-up in the Breast Cancer Detection Demonstration Project estimated that ovarian cancer risk was 1.6-fold higher (95% CI, 1.2–2.0) in users of estrogen only, but not

increased in users of estrogen-progestin (adjusted RR = 1.1, 95% CI, 0.64–1.7) (63). Short-term use of ET for less than four years, or four to nine years, was associated with a small but nonsignificant increased risk. Increased duration of ET use for 10 or more years was associated with a significantly increased risk of ovarian cancer (RR = 1.8, 95% CI, 1.1–3.0). Overall, the results of the two 2002 epidemiologic studies, as well as an earlier prospective study of 944 fatal cancers (64), are consistent in finding an increased risk with long term unopposed estrogen use but not when estrogen is combined with progestin. Ovarian cancer mortality, unlike breast cancer mortality, may be increased among users of ET, but the reported 1.5-fold higher risk (95% CI, 1.2, 2.0) among long-term ever users did not include exposure information after 1982 (64). Although epithelial ovarian cancer is an uncommon disease, the mortality ratio is high.

At the present time, it is uncertain whether the observed effects of HT on epithelial ovarian cancer reflect bias, chance, or reality. Further studies are needed involving current patterns of HT usage to determine whether ovarian cancer is an important risk associated with use of combined estrogen-progestin. Further studies on long-term ET and E/PT will need to address the impact of dose, duration, and prescription schedule.

SYMPTOMS AND SIDE EFFECTS DUE TO HT USE

Irregular or withdrawal bleeding with HT is a frequent reason for early discontinuation of treatment (65). Factors in favor of continuation are those associated with less likelihood of bleeding: hysterectomy, an older age when initiating treatment, age greater than 60 years, use of continuous combined rather than sequential combined HT, and a sufficient dose of progestin in continuous combined HT (66–68). In a multicenter RCT involving 1,724 postmenopausal women, bleeding was reported in 15% of the estrogen only cycles, 18% of the continuous combined HT cycles, and 74% of the sequential therapy cycles (67). In ESPRIT, 208 of 373 women who had not had a hysterectomy had vaginal bleeding while taking estradiol valerate (31). In five RCTs involving continuous combined regimens, bleeding rates were approximately 35% at cycle two or three, 24% at cycle six and 16.5% (95% CI, 14.5, 18.9) at cycle 12. Overall, bleeding is least likely with continuous combined estrogen and progestin regimens. Breast pain was present at baseline in 4% of women in the PEPI trial. Compared with placebo treatment, breast symptoms were not worse with unopposed estrogen, but were approximately two-fold more likely with each of the three progestin formulations. For every 21 (95% CI, 12, 90) patients treated with progestin formulations for three years, there would be one more with worse breast symptoms than in 21 placebo-treated women (1).

Musculoskeletal symptoms were commonly reported by subjects before treatment in the PEPI trial, including aches

and pains (48%), joint pain (44%), muscle stiffness (42%), and skull and neck aches (34%) (1). This group of symptoms was significantly improved in the regimens combining conjugated estrogens with cyclic or continuous medroxyprogesterone acetate. The frequency of headache was not significantly changed during treatment. At baseline 32% of the women in the PEPI trial reported concerns about perceived weight gain with hormonal therapy. The proportion reporting this perception was decreased in the hormone treatment groups at 12 and 36 months, and the reduction was significant in the CEE and continuous MPA group (odds ratio 0.61, 95% CI, 0.41, 0.91) (1).

The WHI study has not yet reported on symptomatic side effects of HT use. HERS reported that standard HT dosages in elderly women were associated with increased complaints of vaginal discharge, genital irritation, uterine bleeding, and breast symptoms. Uterine bleeding occurred in 31% and spotting in another 33% of the HT group during the first year of the study. These numbers reduced to 11% and 20%, respectively, during the fourth year. Placebo treatment was associated with bleeding rates of 2% and 13% during year one, and 2.5% and 6% during year four. There was no difference between the HT and placebo groups in reported weight gain (2).

SUMMARY AND CONCLUSIONS

- Hot flushes occur in over 50% of women entering the menopause and the frequency declines to 30% after three years. Symptoms may persist, however, in up to 16% of women at 67 years of age.
- The usual reason for prescribing HT is the treatment of vasomotor symptoms. The average patient is a woman aged 45 to 60 years, and the most common duration of use is less than three years.
- Estrogen with or without progestogen is an effective treatment for urogenital atrophy, but may worsen urinary incontinence.
- Estrogen and progestogen reduce risk of osteoporotic fractures of the hip, vertebrae, and other sites, but the effect on hip fracture is small, and HT treatment is not warranted solely for fracture prevention.
- Although estrogen was associated with a 34% reduction in the risk of senile dementia in epidemiological studies, the WHIMS failed to corroborate these observations.
- HT is not indicated for the primary or secondary prevention of coronary artery disease events. Alternative health strategies and pharmaceutical agents with established value should be used for primary prevention of coronary heart disease.
- Risk of venous thromboembolism is increased among women using E/PT and declines during continuing use. Route of administration may affect the magnitude of risk.
- E/PT treatment has a small but significant effect on breast cancer risk equivalent to eight new cases per annum per 10,000 women. The increased risk is seen after five years of current use and disappears several years after discontinuing therapy.

- Epidemiological studies suggest that there is a small but significant increased risk of epithelial ovarian cancer with unopposed estrogen use that is not observed when estrogen is combined with progestin. The effect is significant in women who take ET for 10 or more years.
- ET and E/PT are associated with side effects that include breast tenderness, vaginal discharge and uterine bleeding. Weight gain is not more common in hormone users.
- The current indications for ET and E/PT include the treatment of moderate to severe vasomotor symptoms, the treatment of vulvar and vaginal atrophy, and the prevention of osteoporosis.

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