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FOR CLINICIANS WHO PROVIDE CARE FOR WOMEN

Should Symptomatic Menopausal Women Be Offered Hormone Therapy?

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Abstract

Many physicians remain uncertain about prescribing hormone therapy for symptomatic women at the onset of menopause. The American Society for Reproductive Medicine (ASRM) convened a multidisciplinary group of healthcare providers to discuss the efficacy and risks of hormone therapy for symptomatic women, and to determine whether it would be appropriate to treat women at the onset of menopause who were complaining of menopausal symptoms.

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Major Findings: Numerous controlled clinical trials consistently demonstrate that hormone therapy, administered via oral, transdermal, or vaginal routes, is the most effective treatment for vasomotor symptoms. Topical vaginal formulations of hormone therapy should be preferred when prescribing solely for the treatment of symptoms of vulvar and vaginal atrophy. Data from the Women's Health Initiative indicate that the overall attributable risk of invasive breast cancer in women receiving estrogen plus progestin was 8 more cases per 10,000 women-years. No increased risk for invasive breast cancer was detected for women who never used hormone therapy in the past or for those receiving estrogen only. Hormone therapy is not effective for the treatment of cardiovascular disease and that the risk of cardiovascular disease with hormone therapy is principally in older women who are considerably postmenopausal.

Conclusions: Healthy symptomatic women should be offered the option of hormone therapy for menopausal symptoms. Symptom relief with hormone therapy for many younger women (at the onset of menopause) with menopausal symptoms outweighs the risks and may provide an overall improvement in quality of life. Hormone therapy should be indi-

FROM THE EDITOR

David F. Archer, M.D.

Menopausal women present to their physician with a variety of symptoms. Many of these symptoms are non-specific, but some are directly related to changing levels of estrogen associated with waning ovarian function. Hormone therapy (HT) has been used extensively to manage these symptoms—specifically hot flashes, and vulvovaginal atrophy. The publications of the Women's Health Initiative (WHI) in 2002 resulted in a significant decline in the use of HT. This reflected the impact of the news media on physician and consumer attitudes toward HT, resulting in an ongoing debate over the appropriate use of hormones in postmenopausal women.

This issue of Menopausal Medicine contains the reports of two ASRM expert panels that addressed the use of HT in postmenopausal women. Both panels reviewed the risks and benefits associated with HT. The ASRM Practice Committee has provided an Educational Bulletin on its effectiveness for relieving vasomotor and urogenital symptoms and on the side-effects associated with such treatment. The risk of osteoporosis and related fractures and the risks of coronary artery disease, dementia, and colorectal cancer are taken into consideration, and the risks of stroke; venous thromboembolism, and cancer of the breast, endometrium, and ovary are evaluated and placed in context.

The second article is the result of a multidisciplinary workshop convened to address the issue of HT in peri- and postmenopausal women. Nineteen North American organizations reviewed the current medical literature and focused on the potential risks and benefits of hormone therapy for the younger symptomatic woman. The group noted that many of the clinical trials were carried out in older women. The bulk of the evidence from smaller prospective clinical trials in younger women does not provide evidence of significant increased risks or adverse outcomes with hormone therapy. Their conclusion is that HT is indicated for the younger symptomatic woman for management of menopausal and urogenital symptoms.

The management of symptoms and bone loss with estrogen is key for the appropriate patient in order to provide symptom relief and prevent bone loss. All therapeutic interventions carry the risk of side effects. The younger woman is not at risk for cardiovascular adverse events as presented in the prospective randomized WHI studies. Individualization of treatment and annual reassessment of the need for HT have become the norm of practice.

Menopausal Medicine

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vidualized for symptomatic women. This involves tailoring the regimen and dose to individual needs.

Background

The use of hormone therapy in menopausal patients underwent a dramatic shift following the published results of the Heart and Estrogen/Progestin Replacement Study (HERS) and the Women's Health Initiative (WHI). Hersh and colleagues^[1] evaluated national trends in hormone therapy use between January 1995 and July 2003 using the National Prescription Audit and the National Disease and Therapeutic Index databases. Prior to the release of the HERS and WHI results, approximately 42% of women aged 50-74 years were taking hormone therapy. Following the publication of HERS and WHI results in 2002, hormone therapy exposure declined to 28% of women in this age group. Further, annual prescriptions fell 38%, from 91.0 million in 2001 to 56.9 million in 2003. The greatest decline in hormone use was among the oral estrogen and oral estrogen/progestin preparations, contrasting that of transdermal and vaginal formulations which remained stable.

HERS showed that in women with pre-existing coronary heart disease (CHD), hormone therapy (conjugated equine estrogens [CEE] 0.625 mg and medroxyprogesterone acetate [MPA] 2.5 mg) was not effective as a means of preventing cardiovascular events and was associated with an increased risk for myocardial infarction in the first year in some women.^[2] Similarly, the attributable risk (per 10,000 person-years) as reported by the WHI was 7 more CHD events, 8 more strokes, and 8 more invasive breast cancers, as well as 5 fewer hip fractures and 6 fewer colorectal cancers.^[3] However, selective reporting from the popular media and some scientific sources have clouded the overall results from WHI by emphasizing results in terms of relative risks. For example, the 29% increase in CHD, 41% increase in stroke, 26% increase in breast cancer, 37% reduction in colorectal cancer, and 34% reduction in hip fractures were presented as a meaningful increase in risk rather than risks which were all less than 1.5 times the placebo rate. In the case of CHD, the final data analysis found that the relative risk decreased from 29% to 24%, and the overall risk of CHD did not achieve statistical significance.^[4]

A number of position papers by major organizations have attempted to clarify the risks and benefits with hormone therapy in the aftermath of the recent clinical trials. However, despite such efforts, the popular media failed to correctly communicate the clinical implications of the results for everyday practice of providing healthcare to the individual patient. The influence of the media on this matter was underscored by a postal survey of 1700 current users of hormone therapy in Sweden. Hoffmann and colleagues^[5] found that women (53-54 years of age) perceived hormone therapy as more risky and less beneficial in 2003 (post HERS II and WHI) compared with 1999. The major sources of information that women relied on were from print media (43.8%) and television/radio (31.7%). Only 18.3% of women received information about hormone therapy from their healthcare providers. Use of hormone therapy decreased from 40.5% to 25.3%, and this decline was significantly correlated with the changes in attitudes towards hormone therapy ($P < .001$).

Many physicians also remain uncertain about prescribing hormone therapy for symptomatic women at the onset of menopause. For example, Williams and colleagues^[6] conducted a postal survey in March 2004 of all primary care physicians in Florida about their understanding of the risks and benefits of hormone therapy. The respondents comprised 600 primary care specialists, including 203 ob/gyns, 145 internists, 219 family practitioners, and 33 "other." They found that respondents overestimated the magnitude of risks and benefits with hormone therapy 67% of the time. The study authors postulated that the lack of understanding regarding attributable risk and relative risk may have contributed to the overestimation of risk (and benefit). These concepts will be discussed later in this article.

The data from Williams and colleagues, as well as others, underscore the need to educate physicians to address perceptions of hormone therapy based on WHI findings and clarify the appropriate use of hormone therapy in symptomatic menopausal women. In October 2004, the American Society for Reproductive Medicine (ASRM) reported the results of an online survey of 556 reproductive health professionals at its annual meeting. Nearly 100% of the reproductive health professionals surveyed agreed that their patients are confused about menopausal treatments,

and 73% said that they spend a considerable amount of time counseling their menopausal patients about the best treatment. On the basis of the survey results and many informal conversations, ASRM concluded that additional guidance and educational tools were needed to assist general gynecologists and primary care practitioners in appropriate decision-making for the treatment of symptomatic menopausal women.

In November 2005, ASRM supported a workshop that convened a multidisciplinary group of healthcare providers to discuss whether it would be appropriate to treat healthy women at the onset of menopause who were complaining of menopausal symptoms. This was not a consensus meeting and there was no intent to duplicate or modify position papers of major organizations such as the American College of Obstetrics and Gynecologists, American Society for Reproductive Medicine, the North American Menopause Society, etc. Eighteen national societies whose members provide primary care for women were invited to send representatives to the workshop. It was predetermined, however, that these member representatives were representing themselves and not the official positions of the societies. Presentations focused on hormone therapy as a therapeutic option for the major symptoms (ie, vasomotor symptoms, vulvovaginal problems, mood/depression, and changes in sleep and sexual function) associated with the onset of menopause. This publication is not a position statement, nor does it represent the official positions of the societies who sent representatives. Rather, this document is a condensed summary of the presentations, discussions, and clinical experience of the group in addressing this important clinical scenario of the symptomatic menopausal woman seeking treatment.

Efficacy of Hormone Therapy Vasomotor Symptoms

Vasomotor symptoms are prevalent and a source of significant quality-of-life issues for many women entering the menopause. The Study of Women's Health across the Nation (SWAN), which was a community-based survey of 16,065 women aged 40-55 years, found that approximately 32% of women (mean range by ethnicity 17.7% to 45.6%) complained of hot flushes or night sweats.^[7] In a cross-sectional

general-population survey of 5213 women aged 39-60 years, Oldenhalve and colleagues^[8] found that the incidence and severity of hot flushes and sweating increased up to and immediately following menopause and negatively affected quality of life. These authors also noted that women who experienced severe flushes and sweating were more likely to also experience a larger number of other symptoms, called "irregular complaints," in particular tenseness and tiredness. In a number of surveys, conducted prior to and after HERS and WHI, menopausal symptoms were the most frequently cited reason by current users of hormone therapy for initiating hormone therapy.^[9,10] For example, Strothmann and colleagues^[10] conducted a cross-sectional survey of US women aged 45-75 years of age. Of the 5002 women surveyed, 17% were currently using hormone therapy, 24% were former users, and 60% had never used hormone therapy. Hormone therapy use was most common among those aged 50-54 (22%) and 55-59 (26%) years of age. The most common reasons for initiating hormone therapy were menopausal symptoms (58%), post surgery (39%), and general well-being (36%). These results are consistent with a previous report from these investigators who conducted a similar survey among European women.^[11]

The primary indication for hormone therapy is the treatment of moderate-to-severe vasomotor symptoms. The average patient is a woman 45-60 years of age and uses hormone therapy for an average of 3 years or less. It should be noted that HERS and WHI were not designed to evaluate the effect of hormone therapy on vasomotor symptoms and included patients who were generally 60 years or older.

There are numerous randomized controlled trials appropriately designed for evaluating the impact of hormone therapy on vasomotor symptoms. The results from these trials consistently demonstrate that hormone therapy, administered via oral, transdermal, or vaginal routes, is the most effective treatment for vasomotor symptoms.^[12-20] In a meta-analysis of 14 clinical trials, conjugated equine estrogens (CEE) and 17beta-estradiol demonstrated comparable effects in significantly reducing the weekly number of hot flushes compared with placebo.^[12] The Women's Health, Osteoporosis, Progestin, Estrogen (HOPE) study evaluated the effect of CEE

alone (0.3, 0.45, and 0.625 mg/day), CEE plus medroxyprogesterone acetate (MPA) (0.3/1.5, 0.45/1.5, 0.45/2.5, and 0.625/2.5 mg/day), and placebo on relief of vasomotor symptoms in 241 women.^[14] After 1 year (13 cycles), all hormone treatments, at each dose level, were significantly more effective than placebo in reducing the number and severity of hot flushes within the first few weeks of the study ($P < .01$). Lower doses of CEE plus MPA were equally effective as standard doses of this combination for the relief of vasomotor symptoms. Standard doses usually were the equivalent of CEE 0.625 mg or micronized estradiol 1 mg. Lower doses are doses smaller than this. The use of MPA with lower doses of CEE (0.45 and 0.3 mg/day) appears to enhance the efficacy of CEE in relieving vasomotor symptoms. Similar results have been shown with both low (ie, ≤ 0.45 mg/day) and standard (≥ 0.625 mg/day) doses of synthetic conjugated estrogens preparations, as well as with oral, transdermal, and vaginal estradiol preparations (with or without the addition of norethindrone acetate).^[13, 16-20] In a recent report, Ettinger^[13] suggested that lower doses may be underused and that by using lower doses for vasomotor symptoms, women may experience fewer side effects.

Lifestyle changes alone or combined with alternative therapies (ie, progestins, selective serotonin receptor inhibitors [eg, venlafaxine, paroxetine, fluoxetine], anti-convulsants [eg, gabapentin], and antihypertensives [eg, clonidine]) may be an option for some women, especially those with mild vasomotor symptoms. Studies have shown that some alternate therapies are more effective than placebo for the treatment of vasomotor symptoms. Many of the trials suffer from too small sample size and for being too short in duration; the strong placebo effect begins to dissipate with time. Results vary from trial to trial and these alternatives are not free of adverse events.^[21-29] To this end, it was the opinion of the group that these alternatives were not as effective as hormone therapy for the treatment of vasomotor symptoms associated with menopause, but may be an option for some women.

Vulvovaginal Problems

Vulvovaginal changes associated with estrogen depletion include loss of collagen and adiposity in the vulva, loss of

protective covering over the glans clitoris, and thinning of the vaginal surface, making it less elastic and more friable. Atrophy and thinning of the vaginal epithelium can lead to vaginitis, dyspareunia, and vaginismus. If untreated, vaginal atrophy progressively worsens over time.

In a longitudinal, population-based study of 438 women aged 45-55 years, Dennerstein and colleagues^[30] found that the percentage of women reporting vaginal dryness increased progressively as women approached and passed through menopause. Among premenopausal women, 3% reported vaginal dryness compared with 25% of women postmenopausal by 1 year and 47% of women postmenopausal by 3 years. In a study of 285 perimenopausal and postmenopausal women, Versi and colleagues^[31] found that the percentage of women showing both superficial dyspareunia and signs of vulvovaginal atrophy increased with menopausal age. Among perimenopausal women, 15% reported superficial dyspareunia, but this number increased to 28% for postmenopausal women. Additionally, 40% of sexually active women reported dyspareunia; however, the increase in vulvovaginal atrophy was more pronounced than that of dyspareunia.

The use of estrogen hormone therapy is indicated for the treatment of vulvar and vaginal atrophy associated with menopause. Topical vaginal formulations, which have been shown to achieve greater symptom relief than oral, transdermal, or parenteral routes of administration, should be considered when prescribing solely for the treatment of symptoms of vulvar and vaginal atrophy.^[32] Estrogen therapy reverses vaginal atrophy, promotes cell growth and maturation in estrogen-sensitive cells, enhances blood flow in vaginal tissue and reduces pH, and reduces urinary tract infections. Outcomes depend on the timing of therapy relative to the severity of vaginal atrophy at the time of initiating therapy.^[33] Improvements in vaginal dryness, genital atrophy, decreased vascularization, and decreased vaginal elasticity with estrogen therapy can have a beneficial effect on sexual functioning in women whose symptoms are suggestive of dyspareunia.^[34] (Note: Hormone therapy is not indicated by the US Food and Drug Administration for the treatment of female sexual dysfunction.)

In the short-term, randomized, controlled trials have shown no evidence of

endometrial proliferation associated with vaginal administration of unopposed estrogen at lower doses in menopausal women with a uterus.^[35] Overall doses below 25 mcg twice weekly of estradiol, or 0.5 mg of estriol weekly, have not been associated with endometrial proliferation in either short (ie, 1-3 weeks) or long (3-12 months) courses of therapy. This finding is irrespective of the pharmaceutical formulation,^[32] tablet, cream, or ring.^[36-43] These data suggest that the risk for endometrial stimulation with vaginal administration of unopposed estrogen in women with an intact uterus is minimal.^[35]

Urinary incontinence affects approximately 5% to 14% of women 60 years of age or older. Recent data on hormone therapy suggest that it increases urinary incontinence in menopausal women.^[44,45] However, trials demonstrating these negative effects were not designed to include urinary incontinence as a primary endpoint. The results were reported for women who did not have incontinence as a primary complaint. Some, but not all, earlier studies have demonstrated a benefit with estrogen formulations administered via the vaginal route for women who were complaining of incontinence.^[44] Local vaginal estrogen therapy may be able to relieve certain urinary complaints because of the presence of estrogen receptors in urethral mucosa and smooth muscle. In addition, data do show that estrogen therapy reduces the frequency of urinary tract infections in menopausal women.^[46]

Mood and Sleep Disorders

The prevalence of mood symptoms varies from 8% to 37% in premenopause, from 11% to 21% in perimenopause, and from 8% to 38% in postmenopause.^[47,48] Over the past 3 decades, the relationship between mood and menopause has been extensively studied.^[49,50] Results from these studies indicate that there is not a specific relationship between natural menopause and mood syndromes.^[50] Nevertheless, although the majority of women do not experience a mood or anxiety disorder, there is a subgroup of women who do, and there are some women who experience symptoms (ie, depression, mood swings, irritability, and anxiety) but no identifiable psychiatric disorder.^[51]

Data from earlier clinical studies have shown that conventional doses of estrogen enhance mood in nondepressed postmenopausal women but not in severely

depressed women.^[52-63] Randomized placebo-controlled trials of estrogen for depression occurring during perimenopause indicate that it also is an effective treatment for affected women.^[51,64] These authors found that 60% to 75% of patients receiving 4-12 weeks of transdermal estradiol (50-100 mcg/day) had partial or total remission of depressive episodes compared with a response rate of 20% to 30% achieved with placebo. Improvements in mood were independent of severity of depressive symptoms and of estrogen's effect on vasomotor symptoms. Data from an open-label study suggest that citalopram and mirtazapine are effective adjuncts to estrogen therapy when depression symptoms do not respond to estrogen alone.^[65] No data are available on the impact of hormone therapy in patients with a diagnosis of depression. It should be noted that hormone therapy is not indicated for the treatment of mood or sleep disorders, although there are some data to support a beneficial effect in some women, as described below.

Sleep disorders are a hallmark of the menopausal transition. The prevalence of sleep disturbance varies from 16% to 42% in premenopause, from 39% to 47% in perimenopause, and from 35% to 60% in postmenopause.^[47] Sleep disorders have a complex etiology, and hormone therapy may be useful if sleep disruption is due to flushing or other vasomotor symptoms that affect sleep patterns. Estrogen has been shown to decrease sleep latency, decrease the number of episodes of awakening, increase total sleep time, decrease the number of cyclic spontaneous arousals, and increase the amount of slow-wave sleep and REM. In a post-hoc subgroup analysis of WHI, Hays and colleagues^[66] found that estrogen plus progestin therapy improved sleep disturbances among menopausal women 50-54 years of age with moderate-to-severe vasomotor symptoms at baseline.

Clinically, the improvement in overall sense of well-being in postmenopausal women receiving hormone therapy probably results from the beneficial effect of estrogen on a number of variables (ie, vasomotor symptoms, vaginal dryness, and sleep). Data from epidemiologic studies, such as the Rancho Bernardo study^[67] and the ARIC study,^[68] found no association between estrogen use (whether current or past) and protection against age-related cognitive decline. In

contrast, results from a growing number of randomized clinical trials indicate that estrogen maintains some aspects of cognitive functioning in the postmenopausal years.^[69-71] Data from Kampen and colleagues^[71] found that estrogen users performed significantly better on tests of immediate and delayed paragraph recall compared with a group of never-users who had been matched for age, number of years of education, and socioeconomic status. This study, however, found no between-group differences in other domains of language and spatial skills. These results suggest that estrogen affects various brain functions differentially, exerting a specific (ie, verbal memory) rather than global effect on cognition.

Dose Considerations

There is considerable evidence supporting the use of lower doses of hormone therapy in symptomatic women.^[13,14, 16-18, 72-77] Low doses of hormone therapy are effective in patients with vasomotor symptoms and vulvovaginal problems.^[14] In addition, low doses of hormone therapy have beneficial effects on bone mineral density, plasma lipids and lipoproteins, coagulation factors, and carbohydrate metabolism in menopausal women as compared with placebo.^[74,75] The use of lower doses of estrogen is associated with 50% lower rates of irregular bleeding or breast tenderness (which is not a surrogate for breast cancer risk) compared with women taking standard doses of hormone therapy.^[78] There are also observational data suggesting a reduced risk for serious thrombosis and no increased risk for stroke.^[79] Low-dose estrogen preparations include oral preparations of CEE (0.3 and 0.45 mg/day), esterified estrogens (0.3 mg/day), and micronized estrogen (0.5 mg/day). Low-dose transdermal preparations include 17beta-estradiol (0.025 and 0.037 mg/day).

Safety

It was not the purpose of this workshop to dwell on adverse symptomatology, such as bleeding, but to focus on major risks such as cancer and cardiovascular disease, which will be covered here. Issues of adverse symptoms may be dealt with somewhat by the use of lower doses of hormones as suggested above.

Risks are a major concern for women who do not accept hormone therapy, and they also influence the prescribing habits

of providers.^[6,10,11] In a cross-sectional survey of 5002 US women (age 45-75 years), cancer, in particular breast cancer, was the major risk of hormone therapy identified by 53% of US women, followed by cardiovascular disease (16%) and stroke (6%).^[10,11] Williams and colleagues^[6] found that the overall perception of hormone therapy differed among primary care specialties (n = 600). Using a scale of 1-5 (1 = negative, 3 = neutral, 5 = positive), perception scores for hormone therapy among ob/gyns was 3.89 compared with 2.71 for internists and 3.08 for family practitioners.

As previously mentioned, Williams and colleagues^[6] postulated that the reason for physicians' overestimation of the magnitude of risks and benefits with hormone therapy was misunderstanding regarding attributable risk and relative risk. Relative risk is different from attributable risk, and relative risk should not be interpreted as attributable risk. Relative risk refers to the likelihood of disease in patients exposed to a potential risk factor compared with those not exposed. Relative risk is independent of the overall incidence of disease in the population. In contrast, attributable risk refers to the disease incidence in patients exposed to a potential risk compared with those unexposed. For clinical decision-making, it is important to know the attributable risk associated with any potential risk factor and the number of individuals who may be affected.

Cancer Risks

Breast Cancer. Data from the WHI showed that the overall relative risk of invasive breast cancer was 1.24 (95% CI 1.01-1.54) in women with standard dosages of estrogen plus progestin (CEE + MPA) who were followed for a mean of 5.6 years (maximum 8.6 years).^[80] The attributable risk was 8 more cases of invasive breast cancer per 10,000 person-years among those receiving estrogen plus progestin. The increase in risk, however, occurred only in those women who were prior users of hormone therapy. This risk was not statistically significant over the period of the trial in those women who had never received hormone therapy. It is important to note that there is uncertainty about whether risk estimates from the WHI can be applied to other types of estrogens and progestins.

The estrogen-only portion of the WHI found no increase in breast cancer risk,

even in those with prior exposure to estrogen. The overall relative risk of total breast cancer and invasive breast cancer with estrogen only was 0.82 (95% CI 0.65-1.04) and 0.80 (95% CI 0.62-1.04), respectively.^[81] An earlier report found a relative risk of invasive breast cancer of 0.72 (95% CI 0.43-1.21) among those aged 50-59 years at the time of initiating estrogen-only therapy.^[82] Although mammographic density increased with estrogen-only and hormone therapy, the increase in density does not appear to correlate with cancer incidence.

The pattern of risk of invasive breast cancer seen in the WHI for both estrogen with or without progestin was similar to that reported in prior studies.^[32] A recent report from the Nurses Health Study of hysterectomized women receiving standard doses of estrogen alone was consistent with the results from the WHI and did not show an increased risk for breast cancer for up to 20 years of use.^[83] It is logical to assume that the use of lower doses of hormone therapy and minimizing progestin exposure would be associated with an even lower risk for breast cancer. However, there are no data at present to validate this assertion.

Endometrial Cancer. With regard to endometrial cancer, data from the WHI were consistent with those of many studies showing that estrogen-plus-progestin therapy does not increase the risk of developing endometrial cancer. Note also that other studies have shown a decreased risk of developing endometrial cancer with estrogen- plus-progestin therapy.^[81] The relative risk in WHI was 0.83 (95% CI 0.29-2.32). The risk for endometrial cancer with unopposed estrogen in women with intact uteri is well documented.^[32] The risk is 2.0-fold higher (95% CI 1.8-2.2) with less than 5 years' exposure and 6.7-fold higher (95% CI 5.9-7.6) with longer durations of exposure. There is no difference among the different estrogen preparations with regard to risk for endometrial cancer.

Colorectal Cancer. Nanda and colleagues^[84] conducted a meta-analysis of 25 epidemiologic studies and found that recent use of hormone therapy was associated with a 33% reduction in the risk for colon cancer (relative risk 0.67; 95% CI 0.59, 0.77). The benefits were limited to recent users of hormone therapy,

and duration of hormone therapy use did not appear to modify reduction in colon cancer risk. The risk for death from colon cancer was also reduced among hormone therapy ever-users (relative risk 0.72; 95% CI 0.64-0.81). The risk for rectal cancer was not associated with hormone therapy. Data from the WHI^[82] were consistent with the findings of Nanda and colleagues. There were 10 new colorectal cases per 10,000 women-years with estrogen-only therapy compared with 16 new cases with placebo (relative risk 0.63; 95% CI 0.32-1.24). The greatest benefit of hormone therapy was seen among those who were 50-59 years of age at the start of the WHI (relative risk 0.59; 95% CI 0.25-1.41) followed by those 60-69 years of age (relative risk 0.88; 95% CI 0.52-1.48).

Ovarian Cancer. Research findings on the impact of hormone therapy on ovarian cancer are inconsistent.^[85-89] If an increase in risk exists, then it is small and difficult to demonstrate from study to study. There is a possible weak association with long-term (greater than 10 years) use of unopposed estrogen, but these data are inconclusive. Overall, the data are not sufficient to offer a clinical recommendation.

Cardiovascular Risks

The results from HERS (women with established CHD) and WHI (women without established CHD) demonstrated an overall increased risk for CHD events within the first year among women taking hormone therapy.^[4,82,90] This phenomenon, often referred to as "early harm," appears to be a characteristic of older women with existing atherosclerosis. Plaque instability caused by hormone therapy is a plausible hypothesis for this circumstance in that in women receiving statin therapy, "early harm" was not witnessed in HERS.^[91] The average age of women participating in both HERS and WHI was greater than 60 years (66.7 and 63 years of age for HERS and WHI, respectively).^[82,90] In addition, women with severe vasomotor symptoms were excluded from WHI because these women would most likely drop out of the trial if randomized to the placebo arm. These distinctions are important because the majority of women who choose to receive hormone therapy do so for symptom relief during the early menopausal years (ie,

younger than 60 years of age). Thus, understanding early CHD risk in this younger menopausal population is important. In the WHI, approximately 32% of women were 50-59 years of age.^[3,82] Subgroup analyses of women receiving CEE plus MPA found no significant increase in CHD events among those who had begun menopause within the past 10 years (hazard ratio 0.89) or who were 50-59 years of age and had hot flashes (hazard ratio 0.95) at baseline.^[4] A recent analysis of these data showed a suggestion of lower CHD risk among women beginning hormone therapy near menopause.^[92] In this study, reanalysis of data from the Nurses' Health Study strongly supports the concept that women who are close to the age of menopause benefit the most, while those 10 or more years after menopause do not have a coronary benefit from hormone therapy. Similarly, in the CEE-only arm of the WHI, the hazard ratio for CHD events among women 50-59 years of age at baseline was 0.56 (95% CI 0.3-1.03) vs 0.92 (95% CI 0.69-1.23) and 1.04 (0.75-1.44) for those 60-69 and 70-79 years of age, respectively. Recent data showed a borderline trend for a reduction in CHD in women ages 50-59, which was statistically significant for coronary revascularization and confirmed angina.^[93] Similar age-related differences in stroke risk was also found with hazard ratios of 1.08 (0.57-2.04), 1.65 (1.16-2.36), and 1.25 (0.85-1.82) for those 50-59, 60-69, and 70-79 years of age, respectively.

The risk for venous thrombotic events (VTE) in the WHI was increased among all age groups of women receiving oral estrogen with or without progestin. However, nonoral formulations of hormone therapy may be safer. Scarabin and colleagues^[94] conducted a hospital-based case-control study of 155 postmenopausal women (1999-2002) with a first documented episode of idiopathic VTE (92 with pulmonary embolisms and 63 with deep venous thrombosis) and 381 matched controls. The adjusted odds ratio for VTE in current users of oral vs that of transdermal estrogen was 4.0 (95% CI 1.9-8.3).

To further evaluate the impact of hormone therapy on CHD risk, Lobo and colleagues^[95] combined evidence from 2 large similar cohorts (Women's HOPE study and Menopause Study Group) that included younger, healthy postmenopausal women (average 53 years, 4.9 years from last menstrual period). A total of 322

women received placebo and 4065 women received CEE with or without MPA. There were no CHD events among women receiving hormone therapy in either trial compared with 1 event in the placebo arms (0 vs 3.01 per 1000 women). The expected CHD rate in the United States for the group 35-64 years of age is 2-3 per 1000 women.

Thus, it appears that the risk for CHD with hormone therapy is principally in those older women distant from menopause who have atherosclerosis. While it should be emphasized clearly that hormone therapy is not effective for the treatment of CHD, younger women may have some benefits, at least with estrogen alone.^[93] This latter point remains to be clarified in future randomized trials.

Conclusions

The November 2005 ASRM workshop focused on symptomatology in the young, healthy, perimenopausal/menopausal woman. We conclude that young, healthy symptomatic women should be offered the option of hormone therapy. There is clear evidence that hormone therapy improves vasomotor and urogenital symptoms and provides benefits to many women with sexual dysfunction and psychological disturbances related to estrogen deficiency. Taken together, the beneficial effects of hormone therapy for many younger women outweigh the risks and provide an overall improvement in quality of life. Thus, the fears of hormonal therapy in this setting do not seem to be justified. All hormonal therapy should be individualized in symptomatic women. This involves prescribing the regimen and dosage according to individual needs.

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A complete list of references for this article is located at www.medscape.com/viewarticle/537095_1.

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Estrogen and Progestogen Therapy in Postmenopausal Women

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Hormone therapy (HT) can be used to manage problems associated with the decline in ovarian estrogen production after menopause. Menopause occurs naturally when the ovarian follicular pool is functionally exhausted or can be induced by surgical removal of both ovaries. The resulting hypoestrogenic 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. The frequency and severity of menopausal symptoms, the reaction of target tissues to estrogen deficiency, and the response to HT varies significantly among women.

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, the term progestogen refers to natural progesterone as well as synthetic congeners of progesterone (progestins).

The goals of menopausal hormone therapies are to [1] reduce symptoms resulting from estrogen depletion, including hot flushes, sleeplessness, lethargy, and depressed mood; [2] treat urogenital atrophy and vaginal dryness; and [3] minimize the risk of disorders that may be more frequent during hormone treatment. 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, a standard treatment applied to all menopausal women will not meet the needs of many individual women. Health care providers should therefore consider the relative balance between the benefits and risks of treatment for each patient before drawing conclusions or recommending HT (Table 1, Table 2). In addition, that judgment, compliance with the prescribed treatment, and any associated side effects should be reassessed periodically, and newly published research findings must be incorporated into patient care decisions.

This Educational Bulletin focuses first on the effectiveness of HT for relieving vasomotor and urogenital symptoms and on the side effects associated with such treatment. Next, it considers the evidence concerning the effects of HT on the risk of osteoporosis and related fractures and on the risks of coronary artery disease, dementia, and colorectal cancer. Finally, it seeks to evaluate the longer-term effects of HT on the risks of stroke; venous thromboembolism; and cancer of the breast, endometrium, and ovary.

Treatment of Estrogen Deficiency Symptoms

Neurovascular Symptoms

The principal symptom of the early menopausal years is the vasomotor (hot) flush. Hot flushes and night sweats are experienced by 50%-85% of postmenopausal women and cause significant distress for 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 3 (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, thereby improving quality of life. The value of such treatment has been

demonstrated in numerous randomized controlled trials (RCTs). A systematic review of 24 RCTs involving 3,329 women who had moderate to severe intensity hot flashes found that HT reduced the frequency of hot flashes by about 18 per week or by about 75% (95%

confidence interval [CI], 64.3-82.3) compared with placebo. The severity of vasomotor symptoms also was reduced significantly (odds ratio [OR] 0.13, 95% CI, 0.07-0.23) (4). One of the trials, the 3-year PEPI trial, involved 875 menopausal women (mean age, 56 years) who were randomly allocated to one of five treatments: placebo, estrogen alone (conjugated equine estrogens [CEE]), estrogen plus cyclic progestogen (either medroxyprogesterone acetate [MPA] or micronized progesterone), and estrogen plus continuous progestin (MPA). 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 than in the placebo group during the first year of treatment (summary relative rate [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). The estimated number needed to treat (NNT) for the first year effect is approximately two: for every two patients treated during the first year, one would report fewer severe vasomotor symptoms. During the third year, because the

placebo group was experiencing fewer symptoms, the NNT would rise to six patients. In the Heart and Estrogen/progestin Replacement Study (HERS), HT reduced hot flashes, trouble sleeping, and vaginal dryness more than placebo among women who were on average 18 years post-

Title	Acronym	Citation
Randomized controlled trials		
Postmenopausal Estrogen/Progestin Interventions Trial	PEPI	Greenbone et al., 1996 (1)
Heart and Estrogen/progestin Replacement Study	HERS	Hulliy et al., 1998 (24)
Women's Health Initiative Hormone Trials	WHI-HT	E/PT Writing Group, 2002 (26); ET; The WHI Steering Committee, 2004 (27)
Observational studies		
The Nurses Health Study	NHS	Grodstein et al., 2004 (38)
The Million Women Study	MWS	Berg et al., 2003 (65)
WHI Observational Study	WHI-OS	Chlebowski et al., 2005 (83)

Note: WHI = Women's Health Initiative.
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menopausal (mean age, 67 years), and the benefit was greatest for younger women who were symptomatic at study entry (2).

The following summarizes existing evidence regarding the effects of HT on vasomotor symptoms:

- HT reduces the number of hot flashes by about 18 per week more than placebo (4).
- The effect is greatest during the first year of treatment (1).
- There are no significant differences between the effects of different types of estrogen or routes of administration (5, 6).
- Any influence of progestogen treatment, in continuous or cyclic forms, cannot be determined from the trial evidence (5, 6).

With respect to secondary benefits, estrogen increased feelings of well-being in several trials (7,8,9). However, in the PEPI trial, cognitive-affective symptoms such as forgetfulness (present in 34% of subjects at baseline), feeling easily distracted (25%), and difficulty concentrating (24%) were not changed by ET or E/PT compared with placebo after one year or three years of treatment (1). Symptoms of anxiety were present in only 5% at base-

line and were unchanged over three years in each arm of the PEPI trial. In the HERS secondary prevention trial that compared E/PT with placebo, HT improved health-related quality of life measures only in those women who had menopausal symptoms at baseline (2).

The Women's Health Initiative (WHI) primary prevention trial of continuous combined E/PT involved women who were mainly symptom free and was not designed to evaluate the effects of treatment on 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. After one year, E/PT had no significant effects on general health, vitality, mental health, depressive symptoms, or sexual satisfaction, but there were small significant improvements in sleep disturbance, physical functioning, and bodily pain. At three years, there were no significant benefits observed 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 sleep disturbance but did not affect other quality-of-life outcomes (3).

Whether women with estrogen deficiency symptoms have a different risk of cardiovascular disease, osteoporosis, and cancer than those who do not have such symptoms is unknown because women with severe hot flashes were largely excluded from participation in the WHI trials, which were

the only studies designed to evaluate all of these endpoints. 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

Outcome	Estrogen and progestin				Unopposed	
	WHI	HERS	WHI	95% CI	RR	95% CI
CHD	1.2	0.97-1.00	0.89	0.80-1.20	0.95	0.79-1.10
Stroke	1.4	0.86-2.31	1.23	0.89-1.70	1.39	0.87-1.99
VTE	2.1	1.26-3.55	2.79	0.89-8.75	1.33	0.88-2.08
Breast Ct	1.2	0.97-1.59	1.30	0.77-2.19	0.77	0.57-1.06
Colon Ca	0.6	0.39-1.24	0.69	0.32-1.48	1.08	0.63-1.80
Hip fracture	0.6	0.35-1.25	1.00	0.48-2.46	0.61	0.33-1.11

Note: WHI = Women's Health Initiative (26, 27, 47, 81); HERS = Heart and Estrogen/progestin Replacement Study (24); RR = adjusted relative hazards; CI = confidence interval; CHD = coronary heart disease; VTE = venous thromboembolism.
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women who had a lower body mass index (10), but most studies were not designed with sufficient power to perform such explanatory analyses.

Urogenital Symptoms

Estrogen is an effective treatment for symptoms of urogenital atrophy, such as vaginal dryness and sexual discomfort. A meta-analysis of ten randomized placebo-controlled trials found significant improvement in all outcomes evaluated: dyspareunia, related symptoms, and the physician's assessment (11). 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 extended beyond 6 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 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 in women who received ET than in those who received placebo (12). However, HERS reported contrasting results from a considerably larger trial involving 2,763 postmenopausal women; among the 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 with the placebo group (13). 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. In the WHI trials, for the one third of women who were continent at baseline, estrogen alone and E/PT increased the incidence of urinary incontinence of all types. Stress incontinence developed in 16%-17% of the hormone groups and 9% of the placebo groups. Hormone treatment also worsened urinary incontinence in women who were incontinent at baseline (14).

Side Effects Associated With Treatment of Symptoms

Irregular or withdrawal bleeding during HT is a frequent reason for early discontinuation of treatment (15). Factors that favor continuation of treatment are those associated with less likelihood of bleeding: hys-

terectomy, an older age when initiating treatment, age greater than 60 years, use of continuous combined rather than sequential E/PT, and a sufficient dose of progestin in continuous combined E/PT (16,17,18). In a multicenter RCT involving 1,724 postmenopausal women, bleeding was reported in 15% of estrogen only cycles, in 18% of continuous combined E/PT cycles, and in 74% of the sequential E/PT cycles (17). In one trial, 208 of 373 women who had not had a hysterectomy had vaginal bleeding during treatment with estradiol valerate (19). In five RCTs involving continuous combined treatment regimens, bleeding rates were approximately 35% at cycle 2 or 3, 24% at cycle 6, and 16.5% (95% CI, 14.5-18.9) at cycle 12. Overall, bleeding is least likely with continuous combined E/PT regimens.

In the subgroup of women in the WHI E/PT trial who had no breast tenderness at baseline, the group receiving E/PT developed breast tenderness more often than the placebo group (9.3% vs. 2.4%) (20). 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). Musculoskeletal symptoms were significantly improved in women receiving treatment with conjugated estrogens and cyclic or continuous MPA. The frequency of headache was not significantly changed during treatment. In the PEPI trial, 32% of women reported concerns about perceived weight gain during HT at baseline. However, the proportion reporting the complaint was decreased in the hormone treatment groups at 12 and 36 months, and the reduction was significant in those who received treatment with CEE and continuous MPA (odds ratio 0.61; 95% CI, 0.41-0.91) (1).

HERS observed 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% of the HT group and spotting in another 33%, during the first year of the study. Those frequencies decreased to 11% and 20%, respectively, during the fourth year. By comparison, uterine bleeding and spotting occurred in 2% and 13% of placebo-treated women during year 1 and in 2.5% and 6% during year 4. There was no difference between the HT and placebo groups in reported weight gain (2). In the WHI E/PT study, 33% of women in the hormone group required evaluation with endometrial biopsy for bleeding compared with 6% of women in the placebo group ($P<.001$) (21).

Hormone Use to Prevent Disease

Osteoporosis and Fractures

Osteoporosis is common in white postmenopausal women and causes 1.5 million fractures per year in the United States (22). Hip fracture is the most severe consequence of osteoporosis, and its incidence in women rises exponentially from approximately 100 to 1,000 per 100,000 women per year from age 60 to age 80 years (22). Osteoporosis is an important risk factor for fracture, but numerous other factors determine fracture incidence. RCTs involving the surrogate outcome of bone mineral density uniformly indicate that HT maintains or improves bone mineral density in the spine, proximal femur and radius (23). Four RCTs have evaluated the effectiveness of HT for prevention of clinical fractures (24,25,26,27) (Table 3).

HERS involved 2,763 American women with established heart disease (average age, 66.7 years) in which fracture incidence was a secondary outcome. The interventions were 0.625 mg of CEEs plus 2.5 mg of MPA daily (continuous 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) (24).

A Finnish RCT with fracture incidence as the primary outcome measure involved 464 postmenopausal women (average age, 52.7 years) who 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 after 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) (25). However, the trial is vulnerable to small sample errors because there were only

three hip fracture events, all occurring in the non-HT groups.

In the WHI trial of E/PT versus placebo, the mean age of the 16,608 women

in the study was 63.3 years (26). Ten and 15 hip fractures per 10,000 woman-years were observed in the E/PT and placebo groups, respectively, yielding a relative hazard of 0.66 (adjusted 95% CI, 0.33-1.33). Because hip fracture was a secondary outcome, the 95% CI for that outcome has been adjusted for the number of statistical comparisons that were made.

In the WHI trial of ET versus placebo, the mean age of the 10,739 women was 63.6 years (27). Eleven and 17 hip fractures per 10,000 woman-years were observed in the ET and placebo groups, respectively, yielding a relative hazard of 0.61 (adjusted 95% CI, 0.33-1.11). For the four RCTs combined, which involved a total of 29,323 women, HT reduced the overall relative likelihood of hip fracture by approximately one third (RR 0.64; 95% CI 0.45-0.92) (Table 3) (24,25,26,27).

The WHI trials were the first to show a significant overall reduction in fractures among women who were not known to be at high risk for osteoporotic fracture. Although the majority of postmenopausal fractures are assumed to relate to osteoporosis, hip and vertebral fractures accounted for only 16% of all osteoporotic fractures and 12% of all fractures in the WHI E/PT trial. Even with adjusted 95% CIs, the hazard ratio (HR) for any fracture in the E/PT group was significantly reduced (HR 0.76; 95% CI, 0.63-0.92) (26). In the WHI ET trial, total fractures were 30% less likely in those receiving ET (HR 0.70; adjusted 95% CI, 0.59-0.83) (26).

The absolute effect of E/PT and ET on hip fracture incidence is small, involving only 5 and 6 fewer hip fractures per 10,000 women per year, respectively. Therefore, HT is not warranted solely for the prevention of hip fractures. Although osteopenia and osteoporosis may be prevented and treated with HT, alternative agents may have a better risk-benefit ratio. Further trials are needed to compare other treatment strategies with those including HT.

Authors	Exposure	Relative Rate	95% CI
Hulley et al., 2002 (52)	Estrogen/progestin	1.09	0.48-2.48
Komulainen et al., 1998 (24)	All hormones	0.43	0.20-0.91
WHI 2002 (25)	Estrogen/progestin	0.68	0.33-1.33
WHI 2004 (26)	Estrogen	0.61	0.33-1.11
Summary		0.64	0.45-0.92

Senile Dementia and Cognitive Impairment

More than 33% of women 65 years or older will develop dementia during their lifetime (28). In a meta-analysis that 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) (29). There was insufficient information in the studies to assess the effect of estrogen or progestogen in formulation, dosage, duration, or time since last use. Results of three subsequent epidemiological studies are conflicting but do not change the overall estimate of risk reduction in a meaningful way (30,31,32).

Memory loss is the first process to be affected in Alzheimer disease, but it has been difficult to demonstrate an effect of HT on memory, either in normal women or in women with early dementia. A meta-analysis including nine RCTs and eight cohort studies that 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 (29). Not included in the meta-analysis was a recent report on cognitive function among healthy older women in the Nurses' Health Study cohort (33); 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 for greater than 10 years was associated with a reduced risk of Alzheimer disease (RR = 0.59; 95% CI, 0.36-0.96) (34).

In the Women's Health Initiative Memory Study (WHIMS), neither ET nor E/PT prevented mild cognitive impairment (MCI) (35,36,37). In the ET trial, 76 participants were diagnosed with MCI in the CEE group compared with 58 in the placebo group (HR 1.34; 95% CI, 0.95-1.89)

(37). In the E/PT trial, 63 participants were diagnosed with MCI in the E/PT group versus 59 in the placebo group (HR, 1.07; 95% CI,

0.74-1.55) (35). When data from both trials were pooled as planned in the original WHIMS protocol, the combined HR was 1.25 (95% CI, 0.97-1.60). Annual assessments of global cognitive function in the WHIMS E/PT trial showed no difference between groups (36).

In the WHI ET trial, 47 participants were diagnosed with probable dementia, of whom 28 were assigned to CEE and 19 to placebo (HR, 1.49; 95% CI, 0.83-2.66) (36). In the E/PT study, the HR for probable dementia was 2.05 (95% CI, 1.21-3.48) in women who received E/PT compared with those who received placebo. There were 45 and 22 cases of probable dementia per 10,000 woman-years in the E/PT and placebo groups, respectively. Approximately 50% of cases were classified as Alzheimer disease in each group. Approximately 12.5% of cases in the E/PT group were classified as vascular dementia compared with 5% in the placebo group (35). Incidence rates for probable dementia in the ET trial were statistically similar to those observed in the E/PT trial ($P=.11$). For both WHIMS trials, the pooled likelihood of probable dementia was 1.76 (95% CI, 1.19-2.60; $P=.005$) in the hormone groups compared with the placebo groups (37). In the WHIMS E/PT study, cases of probable dementia appeared in the first year of treatment in both the E/PT and placebo groups, suggesting that some subjects had cognitive decline at baseline.

The level I evidence does not support a role for ET or E/PT in the prevention of cognitive impairment or dementia and suggests that HT is unlikely to slow the progression of symptoms.

Coronary Heart Disease

Cardiovascular disease is the leading cause of death in postmenopausal women. Coronary heart disease (CHD) rates are lower in premenopausal women than in men of comparable age, but the incidence rises after the menopause to approximately 3 to 5 cases per 1,000 per year in low-risk women (26,27). The association of an

increasing risk with postmenopausal estrogen deficiency motivated trials of HT treatment as a preventive measure. The potential effectiveness of HT in preventing CHD has been evaluated in three types of studies: epidemiological studies (the most common); RCTs evaluating intermediate outcomes; and, finally, the highest level of evidence, RCTs that evaluated primary or secondary prevention of CHD using definitive outcomes such as nonfatal myocardial infarction (MI) and CHD death.

Epidemiological Studies

A summary of epidemiological studies that appeared in a 1996 World Health Organization Technical Report suggested that HT use reduced the risk of nonfatal MI or CHD death by 44% (summary RR 0.56; 95% CI, 0.51-0.61), compared with no use (38). In a subsequent 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 with never users. After adjustment for cardiovascular risk factors, the relative risk was 0.61 (95% CI, 0.52-0.71) (39). 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 progestin was similar. 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 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 (40).

Intermediate Outcome RCTs

The results of RCTs that have evaluated intermediate outcomes are less consistent than those observed in epidemiologic studies, but many studies recorded favorable effects of HT on lipid profiles, including lipoprotein (a) (23,41,42,43,44). However, 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 Trial (41), angiographic endpoints were used to determine the effect of ET and E/PT on the progression of atherosclerosis in 309 postmenopausal women with documented CHD who were followed for an average of 3.2 years. Neither conjugated estrogens alone (0.625 mg/d) nor continuous combined HT (0.625

mg conjugated estrogens plus 2.5 mg MPA per day) affected the progression of coronary atherosclerosis when compared with placebo treatment, even though lipoprotein profiles were improved in both HT groups (41). Corresponding results were found in the Women's Estrogen-progestin Lipid Lowering Hormone Atherosclerosis Regression Trial, which examined HT regimens using 17 β -estradiol with or without cyclic MPA (45).

Primary Prevention RCTs

The most valid evidence about primary prevention of coronary artery disease comes from RCTs with clinical event outcomes, and, in such trials, there is little evidence of benefit from E/PT (26) or ET (46). Only the WHI trials had clinical cardiovascular outcomes as primary endpoints and sufficient power to evaluate benefit or risk.

In the WHI E/PT primary prevention trial (26), there were 37 and 30 CHD events per 10,000 woman-years in the E/PT and placebo groups, respectively, indicating that E/PT was associated with a small but significant increase in CHD risk (HR 1.29; 95% CI, 1.02-1.63). The increased CHD risk 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 in nonfatal MI events, excluding silent MI (HR 1.30; 95% CI, 1.01-1.67) (47). 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). A 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 symptoms, or use of aspirin or statins. 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 low-density lipoprotein cholesterol (47). In the WHI ET primary prevention trial (46), there were similar numbers of CHD events in the ET and placebo groups, 53 and 56 per 10,000 woman-years, respectively, indicating that ET did not cause a significant increase in CHD risk (HR 0.95; 95% CI, 0.79-1.16).

One criticism of the WHI study reports

is that they provided no specific information about cardiovascular risks among women who started to use hormones soon after the menopause, before atherosclerotic heart disease was established. In the ET trial, the risk increased with age, although the trend was not significant ($P=.07$) (Fig. 1).

The HR for CHD associated with ET among women 50-59 years was 0.63 (95% CI, 0.36-1.08) (46). In the E/PT trial, a trend with age was not apparent, but the HRs increased with years since menopause ($P=.33$). For E/PT use within 10 years of the menopause, the HR was 0.89 (27). New data from the Nurses Health Study cohort also support the possibility that initiation of HT soon after onset of menopause or at younger age might influence CHD risk (48). Among women similar to those in the WHI studies starting hormones within four years of menopause, major CHD risk was significantly reduced: the adjusted RR (95% CI) was 0.62, (0.52-0.76) and 0.71 (0.56-0.89) for ET and E/PT, respectively. Risks were not significantly reduced when treatment began 10 or more years after menopause: RR was 0.87 (0.69-1.10) and 0.90 (0.62-1.29) for ET and E/PT, respectively.

The findings of a meta-analysis of pooled data from 30 trials involving a total of 26,708 participants are pertinent to issues concerning age and years after menopause (49). HT reduced total mortality in trials among younger women (mean age <60 years) (OR 0.61; CI, 0.3-0.95) but not in those among older women (mean age >60 years) (OR 1.03; CI, 0.90-1.18). In the trials with younger women, there were 14 deaths per 10,000 women, and in the trials with older women, there were 175 deaths per 10,000 women.

The absolute beneficial effects among younger women are small. Among women aged 50-59 years in the ET trial, there were 17 and 27 CHD events per 10,000 per year in the ET and placebo groups, respectively (46). If this were not a subgroup analysis, and if the finding were significant, the NNT would be 1,000; that is, 1,000 women treated for one year would have one less CHD event than 1,000 women treated with placebo. Thus, it is unlikely that hormonal effects would make a large contribution to cardiovascular mortality in younger women.

Secondary Prevention

Among women with a history of MI or clinically significant coronary artery disease, secondary prevention of CHD is an important goal. Because clinical events are more fre-

quent in women with heart disease, these trials can achieve the required power with a smaller sample size. Among the secondary prevention trials, only two had clinical cardiovascular outcomes as primary endpoints: the HERS trial of E/PT reported in 1998 (24) and the Estrogen for Prevention of ReInfarction Trial (ESPRIT) of ET reported in 2002 (50).

The HERS secondary prevention trial involved 2,763 women age 55-80 years (mean age, 66.7 years) with coronary artery disease who were postmenopausal and had an intact uterus (24). During an average follow-up of 4.1 years, treatment with oral E/PT (0.625 mg of CEE plus 2.5 mg of MPA) 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, showed that the lower rates of CHD events observed among women in the final years of HERS did not persist during the additional years of observation (51). 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 50-69 years of age (mean age, 62.6 years) with a recent first MI to placebo or ET (2 mg estradiol valerate daily) 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) (50). 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 by the study participants of medications proven effective for secondary prevention, such as aspirin, β -blockers, and statins (51). Data from ESPRIT suggests that ET administered soon after recovery from a first MI does not reduce the risk of subsequent cardiac events (50).

Colon Cancer

Colorectal cancer incidence in postmenopausal women is approximately 16 cases per year per 10,000 women (26,27). Age, family history, and diet are risk factors, and the use of oral contraception, ET, and E/PT has been associated with reduced risks (53).

One possible biological rationale for reduced risk would be a decrease in the concentrations of secondary bile acids, which are potentially tumor promoting, a hypothesis based on the lower risk observed among women who have been pregnant or taking HT. Another possibility is linked to the dominant estrogen receptor (ER) subtype in the

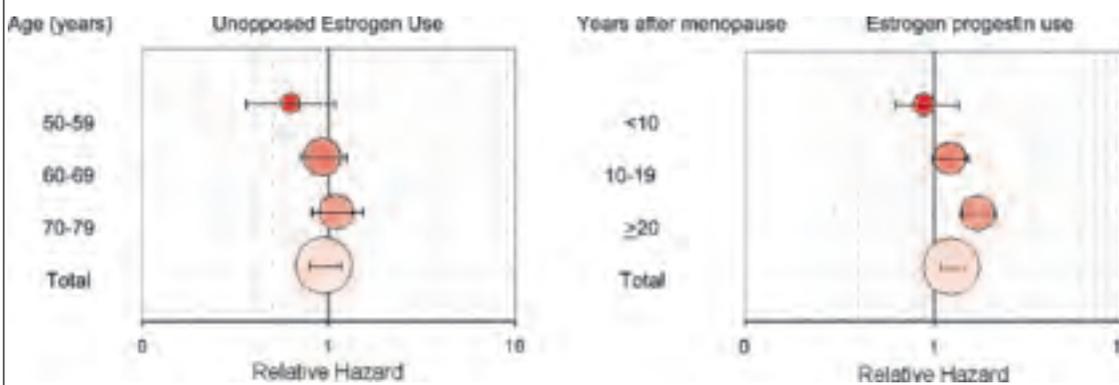
colonic mucosa, which is ER β . Evidence has emerged that this subtype is significantly decreased in colonic tumors from women.

The epidemiological evidence was summarized in a meta-analysis that included 25 studies and distinguished between risk of colon cancer and risk of rectal cancer (53). Rectal cancer incidence was not affected by HT use. However, recent use of HT was associated with a 33% reduction in the risk for colon cancer (RR 0.67; 95% CI, 0.59-0.77). In a second meta-analysis, current users of HT had a 34% lower risk of colon cancer (RR 0.66; 95% CI, 0.59-0.74) (54).

Two of three trials that include data relating to this question are consistent with a potentially reduced risk. After 6.8 years in HERS and follow-up, there were 2.5 and 3.1 colon cancer cases per 1,000 woman years in the E/PT and placebo groups, respectively (relative hazard [RH] 0.81; 95% CI, 0.46-1.45) (55). In the WHI E/PT trial, there were 9 and 16 new invasive col-

Figure 1

WHI hormone trials and CHD (nonfatal myocardial infarction and death due to CHD). Left panel: unopposed CEE use, relative hazard for CHD by age. Right panel: CEE and MPA use, relative hazard for CHD by years since menopause. Bubble point size is proportional to weight (inverse of the variance). (Data for the figure from The Women's Health Initiative Steering Committee [27] and Manson et al [47]).



ASRM Practice Committee. E/PT in postmenopausal women. Fertil Steril 2006.

Summary of CHD-Prevention Studies

Adequate level I evidence indicates that HT is not indicated for either primary or secondary prevention of CHD 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 standard therapy for secondary prevention (51). The WHI study results are relevant to long-term use of E/PT among women aged 50-79 years who are predominantly healthy and free from estrogen-deficiency symptoms. Although risks may vary with lower doses, different formulations, and non-oral routes of HT administration, a review of products used in hormone therapy studies over the last 15 years suggests that the effects would be similar to those found in the WHI studies (52).

orectal cases per 10,000 woman-years in the E/PT and placebo groups, respectively (RH 0.56; adjusted 95% CI, 0.38-0.81) (56). The reduction in risk was mainly due to a decrease in local as opposed to regional or metastatic cancers. Within the category of regional and metastatic disease, the E/PT group had a greater number of positive lymph nodes (3.6 vs. 1.6). In the WHI ET trial, there were 17 and 16 new colorectal cases per 10,000 woman-years in the ET and placebo groups, respectively (RH 1.08; adjusted 95% CI 0.63-1.86) (27). While the trial findings remain promising for E/PT, reduced colorectal cancer risk currently is not an indication to prescribe ET or E/PT.

More research is needed into the mechanisms by which estrogen and progestogen 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.

Disorders That May Be More Frequent with Hormone Treatment *Stroke*

The incidence of stroke among otherwise healthy postmenopausal women is approximately 2 per 1,000 per year, and approximately 75% of strokes are ischemic (26,27,57,58). There was no conclusive evidence for a beneficial or harmful effect of HT on stroke risk in 29 different epidemiological studies, although stroke endpoints and HT definitions were inconsistent (59). The Nurses Health Study reported a trend toward increased risk with combined continuous E/PT. Only a small nonsignificant increase in risk was observed for ET (RR 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 (57).

Stroke risk associated with E/PT now has been addressed as a secondary outcome in the HERS and WHI studies. In HERS and HERS II, combined continuous E/PT was not associated with an increased risk for transient ischemic attack (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 (58). Overall, the RH for any stroke was 1.23 (0.89-1.70), a nonsignificant increase.

About 1% of HERS patients at baseline had atrial fibrillation which increases

stroke risk, often due to cardioembolism (60). Stroke risk was increased by more than six-fold in these patients, but HERS did not have the power to assess an interaction between HT and atrial fibrillation. In a trial among patients with atrial fibrillation receiving warfarin with or without aspirin, ET was associated with a 3.2-fold (95% CI, 1.4-7.5) increased ischemic stroke risk compared with nonusers. The risk associated with E/PT was similar (61).

The WHI E/PT primary prevention trial (26) reported 29 and 21 CHD events per 10,000 woman-years in the E/PT and placebo groups, respectively, an increase in stroke risk that was not significant when adjusted for multiple comparisons (HR 1.41; 95% CI, 0.86-2.31). In all, 151 women (1.8%) in the E/PT group and 107 (1.3%) in the placebo group had strokes (62), 80% of which were ischemic. The HR was 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 been addressed, also as a secondary outcome, in three RCTs. In the ESPRIT trial among women who had a history of myocardial infarction, stroke risk with estradiol valerate treatment was 1.64 (95% CI, 0.60-4.47) compared with placebo treatment (50). In the WHI ET trial, there were 44 and 32 cases of stroke per 10,000 women per year in the ET and placebo groups, respectively, an increased risk that was verging on statistical significance after adjusting for multiple statistical testing (HR 1.39; adjusted 95% CI, 0.97-1.99) (27). Another secondary prevention trial, the Women's Estrogen for Stroke Trial (WEST), involved 664 postmenopausal women with recent stroke or transient eschemic attack. ET (1 mg micronized estradiol 17- β per day) did not reduce the risk of subsequent stroke or mortality over the 2.8 years of follow-up (RR 1.1; 95% CI, 0.8-1.6) (63).

In all five trials, the point estimate indicated increased stroke risk with HT, although no estimate was significant. The pooled RR is 1.25 (95% CI, 1.03-1.51), which is consistent with an increase in absolute risk from 20 cases to 25 cases per year among 10,000 otherwise healthy postmenopausal women. Note that the incidence rates were 21 and 32 per 10,000 women per year in the placebo groups of the WHI E/PT and ET trials, respectively.

The effect of HT on stroke risk appears to involve mainly the risk of ischemic stroke. Little is known about the characteristics of the patients who are at greatest risk of stroke while using HT.

Venous Thromboembolism

Venous thromboembolism (VTE) is an uncommon but important risk for women receiving HT. The incidence among healthy postmenopausal women is 16-22 cases per 10,000 women per year (26, 64). Data from epidemiologic studies and RCTs consistently demonstrate an increased risk of VTE events in postmenopausal women who use ET or E/PT (24, 26, 64, 65). In five epidemiological studies published between 1992 and 1997 involving 592 cases of VTE of which 130 (22.0%) 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) (66, 67, 68, 69, 70). In the HERS trial, the relative risk of VTE was similar in magnitude: 2.66 (95% CI, 1.41-5.04) (55). The excess risk was 3.9 per 1,000 woman-years, and the number needed to cause harm in 1 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 the increased risk declines from approximately four-fold in the first year to less than two-fold after the third year of use (24,66,69,70). In HERS II, during the 2.7-year unblinded follow-up period, the VTE risk declined to a nonsignificant level (RH 1.40; 95% CI, 0.6-3.0) (55).

The WHI studies confirmed the magnitude and timing of the VTE risk estimates from previous studies (26,64). In the E/PT study, 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, $P=.014$) (26). In the ET trial, there were 30 and 22 VTE events per 10,000 woman-years in the ET and placebo groups, respectively, and the risk increase was marginally significant after adjusting for multiple statistical testing (HR 1.32; adjusted 95% CI, 0.99-1.75). The VTE risk was highest in the first two years (64). The excess risks of VTE including pulmonary embolism and venous

thrombosis (approximately 1 and 2 cases, respectively, per 1,000 women per year in the ET and E/PT studies) were significantly higher with use of E/PT (64).

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 because oral estrogens are associated with greater impact on coagulation factors than transdermal or vaginal routes of administration. VTE risk was significantly lower with transdermal compared with oral administration in one study (71) but not in others, and there is a need for further research (72,73,74).

Endometrial Cancer

Endometrial cancer incidence in postmenopausal women is approximately 6 cases per 10,000 women per year (26). 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 (75). 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 RR 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 (75,76).

Combining estrogen with continuous progestogens appears to reduce the risk of

endometrial cancer associated with ET. The Million Women Study, reporting on 716,738 menopausal women who had not had a hysterectomy, found that endometrial cancer risk was increased when the last hormone use reported was unopposed estrogen (1.45; 95% CI, 1.02-2.06). Risk was lower with last use of continuous combined E/PT (0.71; 95% CI, 0.56-0.90) but not with cyclic E/PT (1.05; 95% CI, 0.91-1.22). Type of progestogen did not affect risks (76).

The WHI E/PT trial confirmed that continuous E/PT has no effect on risk for developing endometrial cancer. In the WHI trial, 5 and 6 cases of endometrial cancer were observed per 10,000 woman-years in the E/PT and placebo groups, respectively, yielding a small decrease in risk that was not significant (RH 0.83; adjusted 95% CI, 0.29-2.32) (26).

Breast Cancer

Breast cancer incidence in postmenopausal women is approximately 30 cases per 10,000 women per year (26). An association between breast cancer and hormone use would be plausible because breast cancer incidence is increased by hormonal factors such as early menarche and late menopause (77). In a 1997 reanalysis of 51 epidemiological studies on breast cancer and hormone use, breast cancer risk increased by 2.3% per year of hormone use (mostly estrogen use) compared with an increased risk of 2.8% per year of natural delay in the onset of the menopause (78). Since then, data have accumulated in RCTs involving more than 30,000 women and in epidemiological studies involving more than 1.8 million women (79) (Table 4).

With use of ET, the average risk of invasive breast cancer was 0.81 (95% CI, 0.63-1.03) in four randomized trials involving 12,643 women (19,45,63,80). With use of E/PT, the average breast cancer risk was 1.24 (95% CI, 1.03-1.50) in four random-

ized trials involving 19,756 women (42,55, 81,82). For the 19 epidemiological studies published after 1997, a review estimated the average breast cancer risks to be 1.18 (95% CI, 1.01-1.38) with current use of ET and 1.70 (95% CI, 1.36-2.17) with current use of E/PT (79). The higher average risks in the epidemiological studies may reflect the loss of contrast in the intent-to-treat analyses of the WHI studies because these studies dominate the RCT average risks. The RH for breast cancer among women adherent to E/PT (100% contrast) was 1.49 (95% CI, 1.13-1.96) (81). In the epidemiological studies, the increased breast cancer risk diminished soon after discontinuing hormones and normalized within five years (79).

Breast cancer risk was lower in minority women compared with Caucasian non-Hispanic women, among 156,570 postmenopausal women participating in the WHI observational and randomized studies. Adjustment for breast cancer risk factors accounted for the differences in Hispanic, American Indian/Alaskan Native, and Asian/Pacific Island women. Among African Americans, however, the risk was lower even after adjustment (HR 0.75; 95% CI, 0.61-0.92), corresponding to 29 cases and 44 cases per 10,000 person years for African American and white women, respectively (83). In the Black Women's Health Study, there were 615 breast cancer cases during follow-up of 32,559 women 40 years or older over 182,629 person-years. The RR for ET alone was 1.10 (95% CI, 0.85-1.41) and for E/PT 1.28 (95% CI, 0.98-2.70). The association of breast cancer with female hormone use was stronger among leaner women (body mass index <25) than among heavier women. Isolating prolonged recent use of ET or E/PT (for durations of 10 or more years), the incidence rate ratio was 3.08 (95% CI, 1.70-5.56) in the leaner women, compared with 1.43 and 0.91 in women with body mass indices of 25 to 29 and 30 or greater,

respectively, neither of which was statistically significant (84).

Breast cancer risk does not vary significantly with different types of estrogen or progestin

	Unopposed estrogen			Estrogen-progestin		
	User cases	RR	95% CI	User cases	RR	95% CI
Randomized Controlled Trials compliant women	103	0.76	(0.61-1.01)	248	1.24	(1.03-1.50)
Epidemiological studies						
Current Use	2,862	1.18	(1.01-1.38)	3,455	1.70	(1.36-2.13)
Ever Use	4,193	1.06	(0.97-1.20)	2,221	1.31	(1.12-1.53)

Adapted from Collins et al, 2005 (79).
JAMA. 2005;293:1005-1010.

preparations, with use of lower dosages or with different routes of administration (79). In six epidemiological studies, including the Million Women Study (85), the average relative risks with sequential and continuous progestin regimens were 1.85 (95% CI, 1.72-1.99) and 1.94 (95% CI, 1.78-2.11), respectively, a difference that was not significant (79). Epidemiological studies also indicate that E/PT increases the risk of lobular more than ductal breast cancer, but the number of studies remains limited. In the collaborative study, HT did not add to the risk associated with a family history of breast cancer (78). In breast cancers that arise during HT, the stage and grade do not differ significantly from those in nonusers, but breast cancers in E/PT users are significantly more likely to be ER-positive (79). Breast cancer mortality tends to be lower in observational studies among patients who were HT users (86), but in the early results from the WHI study, mortality was not better among users of E/PT (26). In an RCT involving 434 women with breast cancer who required treatment for menopausal symptoms, recurrence was 3.5-fold more likely (95% CI, 1.5-8.1) with hormone use than with alternative treatments (87).

The absolute effect of E/PT in the WHI and HERS trials adds 8 and 17 cases per 10,000 women per year, respectively, to the natural risk (26,55). The effect of hormones on breast cancer risk is similar to that of alcohol consumption, obesity, and parity (88).

In summary, breast cancer risk is increased with E/PT more than with ET, the risk returns to normal within five years after discontinuation of HT, and the epidemiological evidence is generally consistent with the trial findings. However, many uncertainties remain, such as the role of progestogen, reasons for the effects on lobular cancer, the effect of receptor status, and the impact of HT on prognosis and mortality in breast cancer.

Epithelial Ovarian Cancer

Invasive ovarian cancer incidence in postmenopausal women is approximately 3 cases per 10,000 women per year (21,89). 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 (90,91). Use of hormones during the menopause has been associated with higher ovarian cancer incidence, but there may be confounding factors because

ovarian cancer rates are higher among well-educated women and those in the highest social classes who are most able to pay for HT (92). During 5.6 years of follow-up in the WHI trial of E/PT and placebo, there were 20 and 12 new invasive ovarian cancer cases (4 and 3 per 10,000 woman-years) in the E/PT and placebo groups, respectively (RH 1.58; 95% CI, 0.77-3.24) (21). This RCT result is valid, and the sample was large, but the WHI study lacked the power needed for a precise estimate. Results of epidemiological studies mainly provide similar results. A meta-analysis of 15 case-control studies published in 2000 found heterogeneous risk estimates, and the ovarian cancer risk was not significantly higher for HT users (summary OR 1.1; 95% CI, 0.9-1.3) (93). In a pooled analysis of data from five European case control studies involving 2,501 women published in 2002, the ovarian cancer risk was 1.28-fold higher (95% CI, 1.05-1.56) for ever users of HT compared with never users (94).

Two cohort and three case control studies have appeared since these meta-analyses were published. In a 2002 Swedish case control study, epithelial ovarian cancer risk was increased with ever use of ET (adjusted OR 1.43; 95% CI, 1.02-2.00) or sequential E/PT (OR 1.54; 95% CI, 1.15-2.05) (95). Ever use of continuous E/PT, however, was not associated with increased risk (OR 1.02; 95% CI, 0.73-1.43). Another 2002 report of a cohort 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 ET users but not significantly increased in E/PT users (adjusted RR = 1.1; 95% CI, 0.64-1.7) (96). 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). In a 2002 American case control study, adjusted ORs for invasive epithelial ovarian cancer were 0.90 (95% CI, 0.61-1.33) with ever use of conjugated estrogens and 0.52 (95% CI, 0.25-1.10) with other estrogens (97). ORs for HT with ever use of progestogens combined with conjugated estrogens and other estrogens were 1.06 (95% CI, 0.74-1.52) and 1.08 (95% CI, 0.59-2.00) respectively. In a 2004 cohort study, women using ET at baseline had a higher risk of epithelial ovarian cancer during 15 years of follow-up (adjusted OR 1.72; 95% CI, 1.07-2.75) (98). In a

2004 case control study from Denmark, the adjusted OR for ovarian cancer was 1.06 higher (95% CI, 1.00-1.11) for each additional gram of cumulative estrogen but was unrelated to progestogen dosage (99). In a prospective study of 944 fatal cancers, ovarian cancer mortality was higher among users of ET (OR 1.5; 95% CI, 1.2-2.0), but the data reported for long-term ever users did not include exposure information after study initiation in 1982 (100).

Overall, the results of the WHI study, the epidemiologic studies, and the mortality study are consistent with an increased risk of ovarian cancer associated with use of ET, a risk that appears to be nullified when estrogen is combined with progestin. 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 on long-term ET and E/PT will need to address the impact of dose, duration, and prescription schedule.

Summary and Conclusions

- Hot flushes occur in over 50% of women entering the menopause and their frequency declines to 30% after three years. However, symptoms may persist 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 8 new cases per year per 10,000 women (41 and 33 invasive cases, respectively, in E/PT and placebo groups).

- The increased risk of breast cancer associated with E/PT use is observed after five years of current use and disappears several years after discontinuing therapy.

- ET treatment in women with a hysterectomy was associated with 26 new invasive breast cancer cases per year per 10,000 women compared with 33 cases in

the placebo group, a difference that was not significant.

- Epidemiological studies suggest that there is a small but significant increased risk of epithelial ovarian cancer with ET use that is not observed with E/PT. 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.

References

A complete list of references is available by contacting the ASRM Administrative office at (205) 978-5000 or via email at asrm@asrm.org.

Acknowledgments

This report was developed under the direction of the Practice Committee of the American Society for Reproductive Medicine as a service to its members and other practicing clinicians. While this document reflects appropriate management of a problem encountered in the practice of reproductive medicine, it is not intended to be the only approved standard of practice or to dictate an exclusive course of treatment. Other plans of management may be appropriate, taking into account the needs of the individual patient, available resources, and institutional or clinical practice limitations. The Practice Committee of the American Society for Reproductive Medicine and the Board of Directors of the American Society for Reproductive Medicine have approved this report.

Note from the Editor of Menopausal Medicine: The content of this issue of Menopausal Medicine has been typeset unedited.

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