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Menopause and the hormone controversy: Clarification or confusion?

Abstract: Hormone therapy in perimenopause and menopause remains a controversial and often confusing management strategy for healthcare providers. To assist in providing women quality healthcare, recently published new guidelines help provide direction for NPs.

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There is a lack of consensus on the part of women's healthcare providers and general confusion experienced by their patients about the role of prescription hormone therapy in women's healthcare. For more than 60 years, estrogen therapy has been available to women who transition into menopause for relief of symptoms. During the 1980s, due to increased rates of endometrial cancer in women taking unopposed estrogen, medroxyprogesterone acetate (MPA) was added to conjugated equine estrogen (CEE). Unfortunately, this widely prescribed drug combination led to consequences that were not recognized until the early 2000s.[1]

Cardiovascular disease is the leading cause of death in women 65 and older, and the second-leading cause of death in women 45 to 64. It is more common in menopausal than premenopausal women; however, the relationship between cardiovascular disease and diminishing estrogen levels remains unclear. In 2002, the Women's Health Initiative (WHI) study, which compared estrogen-progestin to estrogen alone in menopausal women, was instituted for the purpose of improving overall health, preventing cardiac disease, and treating menopausal symptoms, was halted due to increased rates of invasive breast cancer.

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Key words: complications of hormone replacement therapy, hormone therapy, menopause, menopause and evidence-based guidelines

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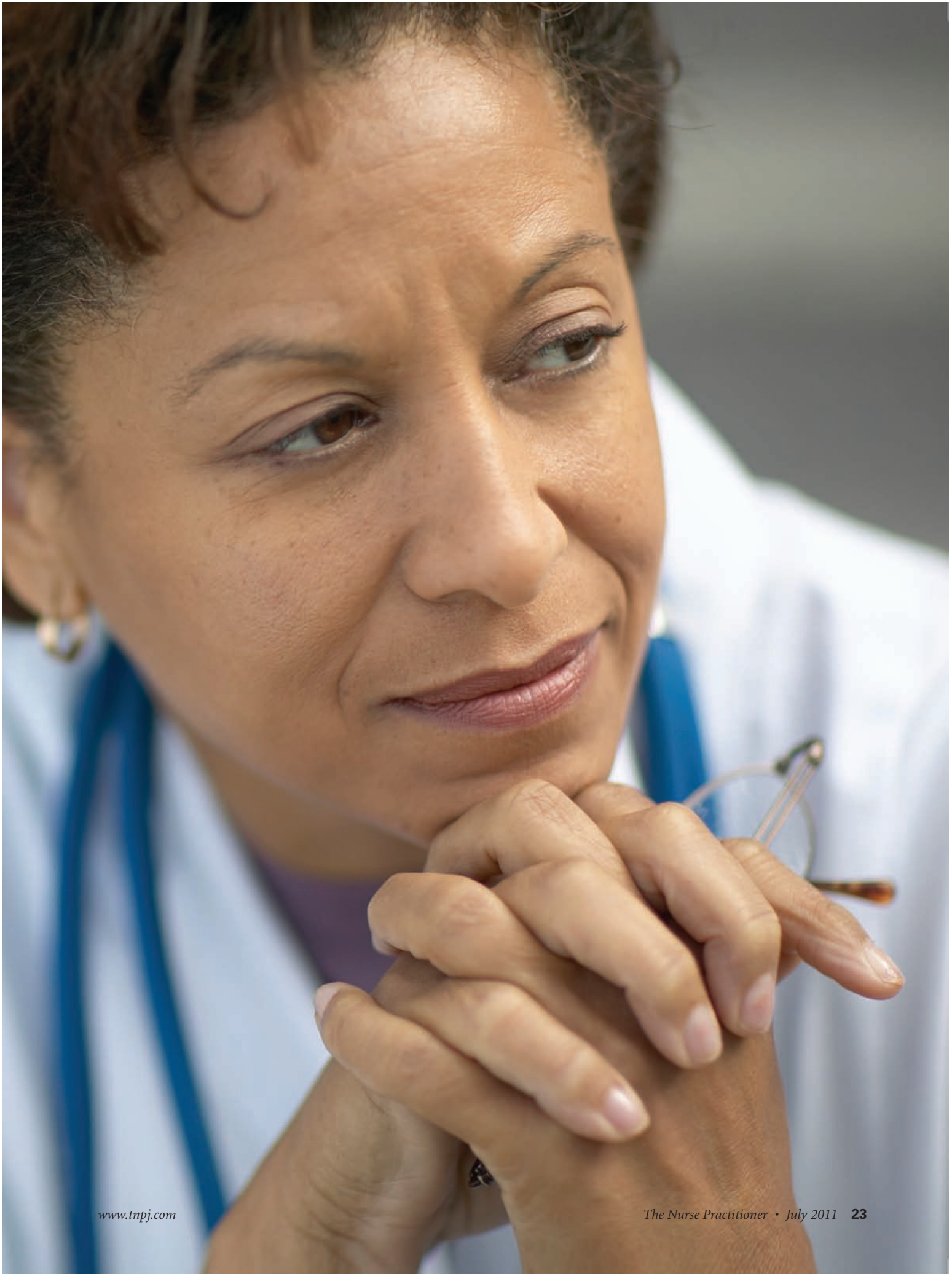

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This decision to stop the combination therapy arm of a major study prompted healthcare providers to reevaluate the practice of prescribing hormone therapy. The early results of the WHI study brought into question the safety of menopausal hormone therapy, and thousands of women stopped taking hormone therapy.[2]

Historic studies

Prior to 1998, there were many observational studies that demonstrated that postmenopausal women taking estrogen had lower rates of coronary heart disease (CHD) than women who were not taking estrogen.[3]

The Heart and Estrogen/progestin Replacement Study (HERS) was the first randomized controlled trial of placebo compared to the daily use of CEEs plus MPA. HERS studied 2,763 postmenopausal women (uterus intact) with known coronary disease at risk for nonfatal myocardial infarction to determine the rate of nonfatal myocardial infarction and deaths due to CHD. The women were younger than 80 years (average age 66.7 years), and average follow-up was 4.1 years.[3]

In 1999, The Postmenopausal Estrogen/Progestin Interventions (PEPI) trial was designed to determine the effect different preparations of progestin had on cardiac risk factors that included levels of C-reactive protein, soluble E-selectin, von Willebrand factor (vWF), and factor VIIIc.[4] PEPI was a 3-year, multicenter, randomized controlled trial. Five groups were studied: placebo versus CEE alone or CEE in combination with MPA (two groups) or micronized progesterone (see *Five groups studied and frequency of administration in PEPI trial*). A secondary outcome was to evaluate any changes to six common symptom groups associated with the menopause transition (cognitive/affective, weight/appetite, musculoskeletal, breast discomfort, anxiety, and vasomotor).[5]

The sample consisted of a subset of 383 women of the total 875 enrollees. Exclusion criteria included women who experienced menopause before age 44, menopause for less than 1 or more than 10 years prior to enrollment, hysterectomy within 2 months, body-mass index 40 kg/m^2 or greater, or any contraindication to hormone use. Average age of subjects was 56.3 years, and the predominant race was White.

Five groups studied and frequency of administration in PEPI trial

Group	Frequency
1. Placebo	Daily
2. CEE 0.625 mg	Daily
3. CEE 0.625 mg + MPA 10 mg	Daily CEE/MPA days 1-12 of each month
4. CEE 0.625 mg + MPA 2.5 mg	Daily
5. CEE 0.625 mg + micronized progesterone (MP) 200 mg	Daily CEE/MP days 1-12 of each month

When the WHI study was published in 2002, it supported many of the findings found in the HERS and PEPI trials. The WHI was a randomized, double-blind, primary prevention trial of 16,608 postmenopausal women between 50 and 79 years (average age 63.3) with an intact uterus who enrolled between 1993 and 1998. Exclusion criteria consisted of any prior cancer (except nonmelanoma skin cancer), any medical condition limiting survival to less than 3 years, adherence and retention concerns (such as, alcohol abuse, dementia), or vasomotor symptoms.[6,7] The primary outcome was CHD and secondary outcome was hip fracture; invasive breast cancer was the primary adverse outcome. Although the planned duration of the trial was 8.5 years, at 5.2 years of follow-up, the estrogen-progestin arm was stopped due to the excessive rate of invasive breast cancer.[6] A second arm of the study, composed of 10,739 women (average age 63.6 years) with prior hysterectomy who received either CEE or placebo, continued for more than 6.8 years with initial results reported in 2004.[7] (See *Major studies on hormone replacement therapy between 1998 and 2002.*)

Unofficial study outcomes: The significance of menopausal symptoms

These studies provided data that allowed for the exam of how hormone therapy affected vasomotor symptoms, cardiovascular issues, osteoporosis, and breast cancer.

Vasomotor symptoms

Hot flashes, or flushing, is the most identifiable effect of the menopause transition. As many as 75% of women experience these symptoms, which begin with a sudden sensation of heat centered on the face and chest, which rapidly becomes generalized.[8] These flashes last between 2 and 4 minutes, and are frequently associated with perspiration. The most probable cause is the instability in the thermoregulatory center of the hypothalamus, related to the decreased levels of circulating estrogen and progesterone. This lability leads to sudden and transient vasodilation of the skin's blood vessels, which causes the flushing sensation and rise in the temperature of the skin.[8] The perspiration that follows a flush is a direct result of the body attempting to cool itself. While the exact physiologic cause of vasomotor instability is not completely understood, the effects of hot flashes on women range from imperceptible to debilitating.

Although PEPI examined symptom relief in six symptom groups, vasomotor symptoms was the only group that showed consistent improvement over placebo in all arms of the study at both year 1 and year 3. At year 1, risk reduction for all treatment arms was significant ($P < 0.001$); the reduction of

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Major studies on hormone replacement therapy between 1998 and 2002

Study	Date	Enrollees	Age (mean, years)	Duration of Study (mean, years)	Inclusion criteria	Therapy	Outcomes **P = primary** **S = secondary**
HERS	1998	2,763	66.7	4.1	Known CHD, less than 80 years, post-menopausal, intact uterus	Placebo versus CEE + MPA	**P** = nonfatal myocardial infarction or CHD death **S** = HF, angina, stroke, PVD, coronary revascularization, cardiac arrest, TIA
PEPI	1999	383	56.3	3	Postmeno-pausal, intact uterus, BMI of 40 or less	Placebo versus CEE or CEE + varying doses of MPA or micronized progesterone	**P** = CHD **S** = Bone density, endometrial hyperplasia
WHI	2002	16,608	63.3	5.2	Uterus	Placebo versus CEE + MPA	**P** = CHD **P** adverse = invasive breast cancer **S** = hip fractures, colorectal cancer, other CHD
		10,739	63.6	6.8	Without uterus	Placebo versus CEE only	**P** = CHD **P** adverse = invasive breast cancer **S** = hip fractures, colorectal cancer, other CHD

BMI = body mass index; CEE = conjugated equine estrogens; CHD = coronary heart disease; HERS = Heart and Estrogen/progestin Replacement Study; HF = heart failure; MPA = medroxyprogesterone acetate; PEPI= Postmenopausal Estrogen/Progestin Interventions; PVD = peripheral vascular disease; TIA = transient ischemic attack; WHI=Women's Health Initiative.

vasomotor symptoms was greatest (Odds ratio [OR], 0.17) in the CEE + MPA (group 4). CEE alone, while the least protective against placebo (OR, 0.28), still provided a significant reduction in hot flashes and other vasomotor symptoms. Odds ratio for the CEE and micronized progestin (MP) arm and the CEE and cyclic MPA were 0.21 and 0.23, respectively.[5] By year 3 of follow-up, the reduction of vasomotor symptoms in the treatment arms was less dramatic ($P < 0.03$). Women taking CEE and micronized progesterone were least likely to exhibit symptoms (OR, 0.26); women taking CEE were most likely (OR, 0.53). CEE and continuous MPA was more protective (OR, 0.39) than CEE and cyclic MPA (OR, 0.43).

The WHI and HERS trials did not evaluate the effects of estrogen and progestin combinations on vasomotor symptoms. However, a Cochrane systematic review substantiated the findings of the PEPI trial in its review of published studies analyzing the effects of hormone therapy. In its evaluation of randomized controlled trials, the meta-analysis revealed that any dosage of hormone therapy reduced vasomotor symptom frequency by 75%.[8] The comparison also showed a positive effect of hormone therapy on the severity of hot flashes, night sweats, and insomnia (OR, 0.13) when compared to placebo. The analysis of estrogen versus estrogen-progestin showed a greater reduction in severity of symptoms in the combined hormone therapy groups (OR, 0.10) versus estrogen only (OR, 0.35).[8]

Cardiovascular disease

Cardiovascular disease is the leading cause of death in women.[9] Prior to the publication of the WHI and HERS, hormone therapy was purported to be universally cardioprotective. This protective effect was demonstrated in basic science research and studies with animal models, whereby the biologic evidence that estrogen can exert protective effects on the heart and blood vessels was seen. As women were prescribed hormone therapy with increasing regularity, observational studies supported this theory. When these data were evaluated in aggregate, a reduction in CHD events in women on hormone therapy (estrogen-progestin or estrogen alone) was seen.[10]

Coronary heart disease

When the HERS trial data were published, it was the first study that showed no risk reduction in myocardial infarction or death in women with known cardiac disease receiving CEE and MPA (relative risk [RR], 0.99). Risk was not reduced in spite of the intervention group having lower LDL and higher HDL. The data showed more events in the first year of the study than at years 4 or 5. These results were substantiated in the much larger WHI trial. The WHI showed an increased risk of CHD events in healthy women receiving CEE and MPA (hazard ratio [HR], 1.29). Interestingly, like HERS, risk was increased in year 1 (HR, 1.78), yet

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in the WHI study, year 5 carried the highest risk of CHD events (HR, 2.38). Based on the results of these two studies, it was concluded that hormone therapy should not be continued or initiated for the primary prevention of CHD.[11]

In 2004, almost 2 years after the release of the initial WHI trial, data were published from the CEE-only treatment arm of the study (this group of women was eligible to receive unopposed estrogen because they did not have a uterus). The CHD risk in this population was lower than in the group on CEE and MPA and almost equal to the risk of placebo (HR, 0.91). Risk in the CEE group was statistically significant in year 1 and trended down over time. Only those women 50 to 59 years of age demonstrated the cardioprotective effect seen in earlier observational studies (HR, 0.56).[7]

Venous thromboembolism

Venous thromboembolism (VTE) is a relatively common disease that affects women and includes pulmonary embolism or deep vein thrombosis (DVT). Hormone use at any point in the life span can increase the risk of VTE.[6,12] When the HERS data were published, the risk for VTE in the group receiving hormone therapy was elevated and remained elevated over the course of follow-up (RR, 2.89). WHI data from the CEE and MPA arm demonstrated even higher risks for VTE in year 1 (HR, 3.60). The trend showed an initial lowering of risk and then an elevation at year 5 (HR, 2.26, 1.67, 1.84, and 2.49 for years 2 through 5, respectively). A subgroup of women with previous VTE was followed, and those taking hormone therapy appeared to have the highest risk of future VTE events (HR, 4.90). The CEE-only group also reported increased VTE risk in those taking hormone therapy, although not as great as the combined therapy trials (HR, 1.33). The risk for DVT and pulmonary embolism was higher (HR, 1.47) in the estrogen-only group versus combined hormone therapy group (HR, 2.07) at any dose.[7]

Stroke

Stroke is the third-leading cause of death for women, and although the number of deaths from stroke has declined substantially, the incidence of stroke may be increasing. Nonetheless, stroke remains the leading cause of functional impairment among both men and women.[13] Stroke risk in women appears to be affected by estrogen exposure. Estrogens affect vascular endothelium and smooth muscle, inflammatory pathways, lipids, and other blood elements. In animal models, initiation of estrogen replacement at or after surgical removal of the ovaries showed less atherosclerosis or cerebral artery occlusion.[14]

The HERS data (women with coronary disease) indicated the increased stroke risk (HR, 1.13) in the hormone therapy group was not statistically significant and showed no clinical benefit with hormone therapy intervention for reduction of stroke.[3] The WHI trial of otherwise healthy women on hormone therapy showed a greater risk for stroke (HR, 1.41) than the HERS trial of women with CHD. The absolute excess risk per 10,000 person-years was 8 strokes more in the women on CEE and MPA. Interestingly, the risk for stroke increased in years 2 through 5 (HR, 1.72, 1.79, 1.84, and 1.87, years 2 through 5, respectively) from relatively no risk in year 1 (HR, 0.95).[6] The data from the CEE-only arm of the trial further supported increased stroke risk (HR, 1.39) with estrogen, resulting in 12 more strokes per year in absolute excess risk, per 10,000 person-years. Only those in the 50- to 59-year-old group demonstrated a risk similar to that of the placebo group (HR, 1.08), while the older age groups had a higher risk of stroke.[7] A meta-analysis of 28 trials (including HERS and WHI) showed an overall increased risk of stroke of approximately 30% (RR, 1.29; CI [confidence interval], 1.13 to 1.47) due to hormone therapy (estrogen-progestin or estrogen alone).[15]

Osteoporosis

Most cases of osteoporosis occur in menopausal women, and the first indication of osteoporosis may be a fracture. Osteoporotic fractures are associated with significant morbidity and mortality, particularly in older women. For example, of those women who suffer a hip fracture, 25% will die within 1 year of complications related to the fracture, and 25% will require long-term care (50% of those women will have long-term loss of mobility).[16] Within the first years of menopause, women who do not take hormone therapy have rapid bone loss associated with lower levels of circulating estrogen.[17]

The HERS study did not find a decrease in fracture risk with combined hormone therapy.[18] In the PEPI trial, those in the placebo group lost an average of 1.8% of spine bone mineral density (BMD) and 1.7% of hip BMD by 36 months. Those taking hormone therapy gained BMD at hip (1.7%) and spine (3.5% to 5.0%). Furthermore, women taking CEE plus continuous MPA had greater increases in spine BMD (5%) than those on the other three regimens (average of 3.8%). In addition, older women, women with low BMD initially, and those who had no previous hormone therapy had greater gains in BMD overall.[19]

The WHI trial found that women taking combined hormonal therapy gained 3.7% in total hip BMD in 3 years compared to 0.14% in the placebo group.[11] In women taking estrogen alone there was a 30% to 39% reduction in hip fractures compared to placebo (rates were 11 versus 17 per 10,000 person-years, respectively [$P \leq 0.01$]). Vertebral BMD was not evaluated as an outcome in the WHI; however, the incidence of reported vertebral fractures was lower (11 versus 17 per 10,000 person-years, $P \leq 0.02$), indicating a significant reduction in treatment versus placebo groups.

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Researchers were concerned about lowering the dose of estrogen to reduce the risk of endometrial hyperplasia and breast cancer while preserving or increasing bone density. Because of the risk of endometrial hyperplasia and breast cancer, lowering the dose of estrogen has been proposed to attain the beneficial effects on bone density. For example, low doses (0.3 and 0.45 mg/day CEE) have been suggested as having a protective and dose-dependent effect related to BMD, with 0.625 mg/day of CEE having the greatest impact on BMD.[20] Forms of estrogen other than CEE have been evaluated, including ultra-low doses of transdermal (0.014 mg/day) and oral micronized 17beta-estradiol (0.25 mg/day).[21] Findings have shown that low doses confer protection to both hip and spine.[22] Additionally, vaginal rings delivering systemic doses of 17beta-estradiol (0.05 and 0.1 mg/day) increased BMD to the spine (2.7% and 3.3%, respectively [$P < 0.001$]) from baseline and total hip BMD (1.7% and 1.8%, respectively [$P < 0.001$]). This dose effect was not supported by the results found when the low-dose vaginal ring currently available (0.0075 mg/day) was used. This low-dose vaginal ring had no effect on lumbar spine BMD and decreased hip BMD by 1.2%.[23]

Studies indicate that hormone therapy significantly reduces the risk of fracture in older women; however, if treatment is discontinued, in 5 years the risk of fracture returns to the level of someone who has never taken hormone therapy.[24]

Breast cancer

Cancer is the second-leading cause of death for women in the United States.[16] The WHI trial of CEE + MPA was halted when the risk of invasive breast cancer was found to be increased compared to placebo. Follow-up analysis found that the total number of breast cancers and invasive breast cancers were increased 53% in those taking CEE + MPA.[25] Tumors were also larger, and at a more advanced stage at diagnosis when compared to placebo. The number of abnormal mammograms was also significantly greater in the treatment group versus placebo, suggesting possible stimulation of the growths or changes in breast tissue that may obscure the diagnosis of early breast cancers.[25] An increased risk of invasive ductal carcinoma was found in women using combined hormone therapy for longer durations. Between 5 and 14.9 years, there was a 1.5-fold increase (95% CI, 1.0 to 2.3); ≥15 years, there was a 1.6-fold increase (95% CI, 1.0 to 2.6). There was also a 3.7-fold increase in risk of invasive lobular carcinoma between 5 and 14.9 years (95% CI, 2.0 to 6.6), and a 2.6-fold risk (95% CI, 1.3 to 5.3) for those taking estrogen-progestin for more than 15 years.[5] Following the release of the 2002 WHI report, use of hormone therapy decreased substantially in the United States and Europe, resulting in a 43% reduction in the incidence of breast cancer from 2002 through 2005, further demonstrating a relationship between the incidence of breast cancer and combined hormone therapy.[25,26]

Women taking unopposed estrogen, even for 25 years or longer, had no increased risk of breast cancer.[5] Other studies had the similar finding that unopposed CEE did not increase the risk of breast cancer, and could decrease the risk of early-stage disease and ductal carcinomas.[27] Although there was no increase in risk for breast cancer, one study found that women taking unopposed estrogen had more than a 2-fold increase in the risk of benign proliferative breast disease.[28] There is some suggestion that proliferative breast disease may be a precursor to breast cancer, although more studies are needed.[29]

The addition of progestin to estrogen has an adverse impact on breast cancer and is more detrimental overall than estrogen alone.[5,30] Eleven years of follow-up in the WHI further substantiates that CEE + MPA is associated with the greater incidence of breast cancer and the more common finding of node-positive breast cancer. Mortality from breast cancer appears to be increased with combined hormone therapy.[25]

Summary of 2010 position statements and implications for practice

The Endocrine Society, a nationwide advocacy and educational organization founded in 1917, concludes there is high-quality evidence to demonstrate a significant reduction in the frequency and severity of hot flashes with hormone therapy, as well as relief with lower doses of estrogen.[14] The North American Menopause Society (NAMS), a nonprofit organization founded in 1989, also holds the position that estrogen therapy with or without a progestogen is the most effective treatment for menopause-related symptoms and their consequences.[31]

The Endocrine Society concluded that although observational studies suggested that hormone therapy may prevent CHD and atherosclerosis, this was not evident in the WHI study with older women initiating hormone therapy more than 10 years after menopause. The risk for CHD increased in this population indicating a lack of benefit for prevention of heart disease. The Society suggests further research in the 50 to 59 year age group is needed to better understand the harms and benefits, given that this is the demographic for hormone therapy.[14] NAMS concludes that hormone therapy cannot be recommended as the sole or primary indication for cardiovascular risk reduction in any women, regardless of age. Women ages 50 to 59 or within 10 years of menopause onset using hormone therapy do not appear at greater risk for CHD events.

According to the Endocrine Society, there is high-quality evidence to support the 2-fold increased risk of VTE with hormone therapy use. Current evidence suggests that women with a prior history of VTE and those with factor V Leiden may be at greatest risk for future VTE with hormone therapy use.[14] NAMS concludes that current observational studies

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showing no increased risk with transdermal delivery of estrogens warrant further study in randomized controlled trials.[31]

According to the Endocrine Society, a one-third increase in risk of stroke in healthy postmenopausal women is supported with moderate-quality evidence. There is moderate-quality evidence to suggest no reduction in the incidence in older women with vascular disease present. There is only low-quality evidence to demonstrate that lower-dose estrogen therapy will not increase stroke risk.[14] NAMS concludes that evidence does not support hormone therapy as effective for risk reduction of recurrent stroke in those with established cardiovascular disease or for prevention of first stroke. NAMS states that hormone therapy cannot be recommended for primary or secondary prevention of stroke.[31]

There is high-quality evidence, according to the Endocrine Society, that estrogen or estrogen-progestin is as effective as bisphosphonates in preventing early postmenopausal bone loss and augmenting bone mass in late postmenopause. There is sufficient evidence from randomized controlled trials that hormone therapy reduces postmenopausal osteoporotic fractures, hip and vertebral fractures even in women who do not have osteoporosis.[14] Hormone therapy is not recognized as a treatment for osteoporosis, but many systemic products are FDA approved and available for the prevention of osteoporosis. NAMS recommends extended use of hormone therapy as an option for women who have reduction of bone mass, regardless of menopausal symptoms.[31] Additionally, it recommends hormone therapy under the following conditions: for prevention of further bone loss and/or reduction of osteoporotic fracture, when alternate therapies are not appropriate or cause significant adverse effects, or when the benefits of extended use outweigh the risks.[31]

The Endocrine Society's conclusions regarding breast cancer vary. High-quality evidence indicates that mammographic density of breast tissue increases with use of estrogen only and estrogen-progestin. Moderate-quality evidence suggests that estrogen alone for less than 5 years may reduce the risk of breast cancer in patients starting therapy many years after the onset of menopause. Estrogens increase the risk of breast cancer after more than 5 years of use, while estrogen-progestin increases the risk of invasive breast cancer within 3 to 5 years of initiation and continues to rise with duration of therapy. If estrogen alone or estrogen-progestin is stopped, the risk of breast cancer returns to approximately that of nonusers by 3 to 5 years.[14]

Conclusions by NAMS differs, stating that estrogen-progestin increases the risk of a diagnosis of breast cancer 3 to 5 years beyond initiation, but data are unclear on the effects of continuous or sequential use of progestogens. Likewise, the form of progestogens may have an influence on risk for breast cancer. Early studies indicate that micronized progesterone with estrogen may not be associated with an increased risk if used up to 5 years, but more research is required. Proliferation of breast tissue and mammographic density are related more to estrogen-progestin, impeding diagnostic interpretation more so than estrogen alone. The estrogen-alone arm of WHI showed no increased risk of breast cancer after an average of 7.1 years of use.[31]

Summary

Further studies are warranted to identify the lowest effective dose, the optimal form of estrogen, and the ideal method of drug delivery in reducing symptoms.[8] Work is underway to evaluate transdermal forms of drug delivery, with preliminary reports of favorable results on the outcomes of stroke and VTEs, while alleviating hot flashes and symptoms.[12,32]

A thorough risk assessment is necessary to identify the significant risks and benefits of hormone therapy for each patient. Presenting these risks and benefits to patients allows the NP to assist them in making a knowledgeable decision. NPs need to continue to use clinical judgment based on the available science, to evaluate whether hormone therapy is appropriate for each patient, whether short or long term.

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