

THE CONTROVERSIES SURROUNDING PERIMENOPAUSAL AND MENOPAUSAL HORMONE THERAPY: A REVIEW

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The purpose of this paper is to critically review the controversies surrounding hormone therapy without the bias and/or passion, which it has provoked during the last several years, especially after the publication of the Women's Health Initiative (WHI) study. Hopefully this will allow the practitioner to objectively inform the patient so that she, in turn, may be able to make an informed decision rather than one motivated by fear, media sensationalism, and lack of understanding.

History

The WHI was a large multi-center placebo-controlled study funded by the National Institutes of Health (NIH) primarily planned as a cardiovascular disease prevention trial studying the effects of hormone therapy on coronary heart disease (CHD). Secondary outcomes included hip fracture, invasive breast cancer, endometrial, colorectal and other cancers, stroke, pulmonary embolism or death due to other causes. There were two arms of the study. The first involved women with an intact uterus who were given either conjugated equine estrogen 0.625 mg (Premarin®) and medroxyprogesterone acetate 2.5 mg (MPA) (Prempro®) or a placebo. The second arm of the study comprised women who had undergone a hysterectomy and were given conjugated equine estrogen 0.625 mg (Premarin®) or a placebo. Asymptomatic postmenopausal women age 50 to 79 were enrolled. The original study design called for 16,000 women to be enrolled in each arm. The planned duration of the trial was 8.5 years.

On July 9, 2002, the writer's group for the WHI held a press conference. They reported that they were stopping an ongoing study of hormone therapy because they had found a significant increase in the risk of breast cancer in the study population of women taking estrogen and progesterone. They recommended that patients on hormone therapy call their caregivers to determine whether they should continue taking hormones in view of this increased risk of breast cancer that was found. Our office received 150 calls that day from distraught patients extremely anxious about taking hormones. Our experience was not

unique. Two years later there is still fall-out from that report with patients expressing anxiety and uncertainty about taking hormones.

On July 17, 2002, the Journal of the American Medical Association (JAMA) published the study *Risks and Benefits of Estrogen & Progestin in Healthy Postmenopausal Women: Principal Results from the Women's Health Initiative Randomized Controlled Trial*.¹ That article reported that the estrogen plus progestin arm of the study was stopped after 5.2 years because "the statistic for breast cancer crossed the designated boundary established by the Data Safety Monitoring Board (DSMB)." The DSMB concluded that "the evidence for breast cancer harm along with the evidence for some increase in cardiovascular disease, stroke and pulmonary embolus outweighed the evidence for benefit for fractures and the possible benefit for colon cancer." The article reported that there was an increase in the risk of breast cancer of 8 women per 10,000 women per year when compared with the placebo group. They also noted that there was an increase in the number of cardiovascular events of 7 women per 10,000 per year; an increase of 8 women per 10,000 with strokes, increase of 18 women per 10,000 with blood clots, 6 fewer women per 10,000 with colon cancer and 5 fewer women per 10,000 with hip fractures.

Two years later, on April 14, 2004, the WHI investigators published the second arm of the study titled *The Effects of Conjugated Equine Estrogen in Postmenopausal Women with Hysterectomy: The Women's Health Initiative Randomized Control Trial*.² The study was stopped after 6.8 years. In that arm of the study, instead of enrolling 16,000 women as planned, only 10,739 were enrolled. In addition, 53.8% of those women discontinued the Premarin® prior to the end of the study. An equal number stopped taking the placebo. The writer's group reported there was a slight decrease in the risk of cardiovascular disease that was not statistically significant (relative risk 0.91–95% confidence interval 0.75 to 1.12). The incidence of breast cancer was decreased, (relative risk 0.77–95% confidence interval 0.59 to 1.01) barely lacking statistical significance.

Each of the issues raised by the previously mentioned clinical outcomes will be evaluated independently.

Hormone Therapy and Breast Cancer

The WHI study group reported that they found an unacceptably high increase in the risk of breast cancer of 8 women per 10,000 women on estrogen and progestin. They concluded that the hormones caused this increased incidence of breast cancer. However, there are some questions about the data. As reported in the first WHI article, the relative risk of breast cancer was 1.24 with a 95% confidence interval of

1.02 to 1.54. Note that this is barely statistically significant. When standard adjustments of the data were calculated for studies of this nature (the Bonferroni Correction) the risk of breast cancer loses statistical significance, with a 95% confidence interval 0.97–1.59.³ Demographic characteristics of the Prempro/placebo group included a mean age of 63.3 years with 45% age 60–69 and 22% age 70–79. Seventy-four percent of the enrollees had never used hormone therapy, 20% had used hormone replacement therapy (HRT) at some time in the past and 6% were current users who passed the 3-month "wash out" period. The average length of time off hormones was 18 years. The average length of follow-up for the clinical trial was 5.2 years with a maximum follow-up of 8.6 years. However, 42% stopped the Prempro® prior to the end of the study, as did 38% taking the placebo. The authors stated that the dropout rate did not affect their conclusions.

It was assumed by the authors that the increase in the incidence of breast cancer was caused by the hormones. However, when the doubling times for breast cancer cells are calculated, it takes an average of 10 years to go from the first cancer cell to a clinically apparent lesion 1 centimeter in diameter.⁴ The subjects in the Women's Health Initiative study group were exposed to hormones for an average of 5.2 years. Thus, hormone therapy could have accelerated an already existing cancer, but there was no evidence that the hormones caused the cancer. This premise is supported by the following:

1. The WHI reported that there was no statistically significant increase in carcinoma-in-situ (CIS) rate. If the hormone therapy had caused the observed increase in breast cancer, one would expect the CIS rate to be increased. Since there was no significant increase in the CIS rate, it is more likely that one or both of the hormones stimulated an already existing, but undiagnosed, cancer.
2. In the Breast Cancer Detection Demonstration Project, breast cancer mortality 10 years post-diagnosis for women who were receiving hormones at the time of the diagnosis was half the mortality of non-users (relative risk = 0.5; 95% confidence interval 0.3 to 0.8). Thirteen studies since 1990 have reported improved mortality and survival rates for women taking hormones at the time of diagnosis, consistent with the Breast Cancer Detection Demonstration Project results.⁵
3. The increase in survival of hormone therapy users may be due to surveillance bias because of increased frequency of examinations and more consistent mammography. However, tumor biology likely plays a role, since numerous studies over many years have demonstrated hormone users have smaller tumors that are

less anaplastic and more localized than non-hormone therapy users.⁵

4. In a cohort study of over 41,000 women with a family history of breast cancer, those on hormone therapy had no increased risk of breast cancer.⁶
5. In a large study of current or former oral contraceptive (OC) users age 35 to 64 years, contraceptive use was not associated with an increased risk of breast cancer.⁷ If hormones cause breast cancer, one would expect to find an increased incidence in this population of women who have been on a higher dose of hormones when compared to women on postmenopausal hormone therapy.
6. Over 50 observational studies in the last 25 years reporting on the long-term use of either estrogen alone or estrogen and progestin, have yielded mixed and inconclusive results in regard to breast cancer.^{5,9} Many of those studies reported a consistently lower risk of death due to breast cancer in the hormone users compared to non-users.⁹
7. The estrogen-only arm of the study reported a decrease in the risk of breast cancer that barely lacked statistical significance.²

The conclusion of the Women's Health Initiative writer's group that estrogen and/or progesterone causes an increase in the risk of breast cancer is statistically weak and supporting data from other studies is lacking. The assumption that conjugated equine estrogen is biologically similar to all other estrogens (e.g., synthetic or plant derived), and that MPA is similar to all other progestins (progesterone or 19-nor-testosterones) is by the WHI writer's group own admission, tenuous at best. There is no data to support the premise that the WHI study results can be extrapolated to other delivery systems (transdermal or vaginal absorption). The biology of the breast cancer cell makes it unlikely that the hormones administered for an average of 5.2 years caused the increased incidence of breast cancer, but rather stimulated already existing, albeit undiagnosed, cancer in the WHI study population.

Hormone Therapy and Heart Disease

The Women's Health Initiative reported an increase in the risk of cardiovascular events of 7 women per 10,000 per year. During the course of the 5.2-year study, when each year was analyzed, the risk ratios were as follows:

Year	Risk Ratio	Year	Risk Ratio
1	1.78	4	0.99
2	1.15	5	2.38
3	1.06	6	0.78

It is interesting to note three things in that data: (1) the relative risk of 1.78 in year one (2) the relative risk of 2.38 in year five and (3) the gradual decrease in relative risk in the remainder of the study.

The increased risk of cardiovascular events in the first year of taking hormones has been well known for many years from the Heart and Estrogen Replacement Study (HERS)¹¹ among others. Animal model studies demonstrate that there is destabilization and subsequent rupture of atheromatous plaques when those plaques are exposed to estrogen, primarily during the first year. After that first year, the animal model studies demonstrate a significant decrease in the rate of cardiovascular events and atheromatous plaque formation.⁸ Thus, the increased incidence of cardiovascular events in year one in this elderly population who had not been exposed to hormones for many years is no surprise.

The most striking piece of data was the large increase in relative risk in year five. In that year, the relative risk markedly increased to 2.38. However, when the data was analyzed by others, it was found that the increase was not due to an increase in the cardiovascular events in the Prempro® group but rather to an unexplained paucity of events in the placebo group. The reason for that significant drop in events in the placebo group was never explained.¹⁰ Postulates include increased use of aspirin or statin drugs that year or the small numbers of events involved in the study. That question remains to be elucidated.

The WHI study demonstrated a progressive decline in the cardiovascular events as is consistent with animal model studies. Retrospective human studies have consistently shown cardiovascular benefit in postmenopausal women who use hormone therapy for the longer term.^{12,13} No significant increase or decrease in cardiovascular events was seen in short-term studies such as the WHI and HERS.¹¹ HERS evaluated postmenopausal women who had documented coronary heart disease (CHD) to determine whether hormones used after a myocardial infarction (MI) would improve outcome. The HERS study did find an increased risk of CHD in the first year followed by a decreased risk of MI in years 3–5, with a plateau after that, up to 6.8 years. On that basis, hormones are not recommended after an MI.

There are a number of effects of hormones on lipids and cardiovascular disease. Estrogen is well known to decrease cholesterol and increase HDL with a resultant decrease in cardiovascular events.¹³ Progestins, on the other hand, vary significantly in their effects on lipids. MPA increases cholesterol and decreases HDL. Prometrium "the natural progesterone" is neutral in regard to lipids. Norethindrone (a 19-nor-testosterone), is a common progestin in birth control pills and is in some hormone therapy formulations. It slightly decreases cholesterol and increases HDL, thus is more lipid friendly.¹³ The Clarkson studies in monkeys have

shown a decrease of 70% in atheromatous plaque formation when oophorectomized monkeys are given estrogen as compared to placebo controls.⁸ When oophorectomized monkeys on an atherogenic diet were not given estrogen for 2 years (equivalent to six human years) and then started on estrogen, there was no positive effect on cardiovascular disease. Only when started immediately after oophorectomy was the decrease in atherogenesis noted.⁸

The WHI study was observing an elderly population that had not been on hormone therapy for many years. That group was started on a full dose of estrogen in the form of Premarin® and a “lipid unfriendly” progestin. Those hormones destabilized pre-existing atheromatous plaques that resulted in the increase of cardiovascular events in the first year. The fifth year “increase” in relative risk was actually due to a decrease of events in the placebo group and was unexplained by the WHI writers. It would have been very interesting to see the next two data points which would have indicated whether there was a continued decline in the risk of cardiovascular events or whether there would have been an increase in the following years. Unfortunately, since the study was stopped, additional data will not be forthcoming.

Fredrick Naftolin²⁰ et al analyzed the WHI data in regard to the perimenopausal subset of the study. They found there were only 574 women age 50–54 in both the Prempro® and the placebo groups together. By their analysis, the study was 10-fold underpowered. They stated that to make any conclusion about women in early menopause regarding CHD, defining clinical management or mandating discontinuation of hormone therapy for this group is not appropriate.²⁰

Hormone Therapy and the Risk of Venous Thrombosis

On October 6, 2004, the Women’s Health Initiative writer’s group published an article in JAMA titled *Estrogen plus Progestin and Risk of Venous Thrombosis*.¹⁴ Venous Thrombosis (VT) included deep vein thrombosis (DVT) and pulmonary embolus. Of the approximate 8,000 women who were on Prempro®, 167 had VT compared to 76 in the placebo group. The WHI report noted that the increased risk of VT was highest in the first year of therapy, but continued throughout the 5 years of treatment. That increased risk of VT related to estrogen use has been known for many years and the WHI data is consistent with numerous other studies of orally administered hormones. The assumption was made that all hormone therapy had the same effect in regard to venous thrombosis. However, two recent studies of women using transdermal estrogen demonstrated no increased risk of venous thrombosis.^{11, 15}

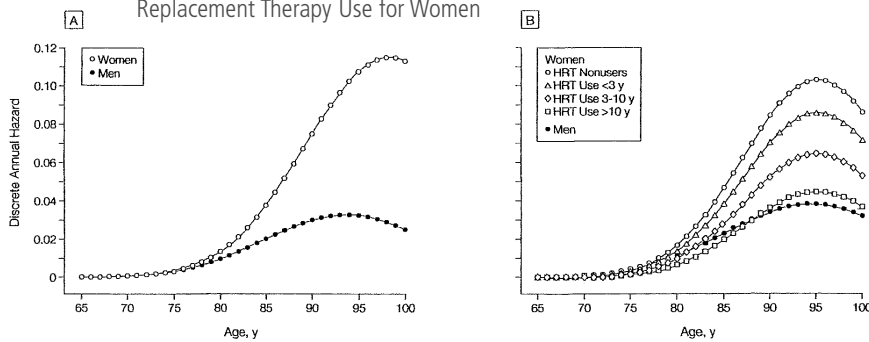
It is important to note that transdermally administered estrogen has significantly different effects on a variety of important clinical issues when compared with orally administered estrogen whether conjugated equine estrogen (Premarin®) or estradiol (Estrace®). It has been well known for some time that a transdermally administered estrogen reduces triglycerides when compared with orally administered estrogens. In addition, transdermal estrogen decreases c-reactive protein (CRP) and activated protein C, both implicated in cardiovascular disease.¹⁶

Hormone Therapy and Alzheimer Disease and Dementia

In May 2003, the WHI study group published *The Women’s Health Initiative Memory Study (WHIMS)*.¹⁷ This study was an analysis of a sub-group of the original WHI Prempro/placebo trial involving 4,894 postmenopausal women age 65 years or older and free of probable dementia at baseline. In the WHIMS study, 47% were 65 to 69 years old, 35% were 70 to 74 years old, and 18% were 75 or above. Of the 2,229 women in the group assigned to hormone therapy (Prempro® 2.5), 40 were diagnosed with dementia during the 5.2 year study period. Of the 2,303 women in the placebo group, 21 were diagnosed with dementia. The hazard ratio (HR) was 2.05 with 95% confidence interval of 1.21 to 2.38. The WHIMS writer’s group concluded that estrogen plus progestin therapy increased the risk of dementia in postmenopausal women age 65 or older.

There is an interesting study of residents in Cache County, Utah, that examined the relationship between the use of hormone therapy and the risk of Alzheimer disease (AD) among elderly women.¹⁸ The curves are shown in Figure 1. In that study, women had a significantly higher incidence of AD compared to men. However, women who were on hormone therapy for more than 10 years prior to the onset of AD were much less likely to have dementia and paralleled the decreased frequency of dementia noted in males. The conclusion of the study was that women have a significantly increased risk of AD compared to men, and that prior use of hormone therapy is associated with a reduced risk of AD. However, there is no apparent benefit with hormone therapy use, unless such use has exceeded 10 years. Thus, it appears that the neuro-protective effect of hormone therapy occurs only if it is used before the damage to neurons occurs. Short-term use of hormone therapy is of little or no benefit and once damage occurs, hormone therapy cannot reverse the damage. It is possible that hormone therapy could increase the rate of deterioration once dementia is established. Thus, the use of hormone therapy in an elderly population that had not previously been on hormones could have an adverse effect in regard to dementia and AD.

Figure 1. Estimated Discrete Annual Hazard of Alzheimer Disease for Men and Women by Age, and by Duration of Hormone Replacement Therapy Use for Women



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Both figures indicate risks estimated from an individual with the mean value of 13 years of education and no $\epsilon 4$ alleles at APOE. A, The curves depict the annual hazards predicted by fitting the base model including an age-by-sex interaction term. The annual hazard for Alzheimer disease (AD) appears similar for men and women before 80 years of age but diverges rapidly afterward with an excess risk found in women. B, The curves depict the annual hazards predicted by fitting model 7 of Table 3 to the women with available hormone replacement therapy (HRT) exposure information and, in filled circles, the corresponding annual hazards for men after omitting the terms for HRT. There were 35 instances of incident AD among 1357 men. Ordinate values for women differ slightly from those in panel A due to omission of women lacking HRT exposure information, several of whom experienced incident dementia.

Hormone Therapy and Stroke

In the WHI study, the incidence of stroke was slightly increased in the Prempro® group over the placebo group (relative risk 1.41–95% confidence interval 1.07–1.85). The HERS trial also assessed stroke and there was no increased incidence in that high-risk population.¹¹ The multiple medical problems and the requisite medications elderly patients require makes any meaningful study of that population in regard to hormone use and stroke extremely difficult.

Hormone Therapy and Osteoporosis

Studies of bone density and osteoporosis consistently find that bone density is improved on hormone therapy with a decrease in the risk of fracture in subsequent years. However, if a woman is unwilling or unable to use hormone therapy and bone loss is evident, then several other non-hormonal therapies can be utilized. First and foremost, whether on hormones or not, calcium and vitamin D along with weight bearing exercise is essential. Medical therapies include bisphosphonates, raloxifene and calcitonin nasal spray. Parathormone injections are available for patients with osteoporotic fractures in the worst-case scenario. Estrogen, bisphosphonates, raloxifene and calcitonin slow osteoclast resorption of bone while parathormone stimulates osteoblast activity and thus can reverse bone loss.

Benefits of Hormone Therapy

The transition to menopause has three phases: Perimenopause, Transition to Menopause and Menopause. During perimenopause (age 40 to 55), major symptomatology include hot flashes, night sweats, insomnia, menstrual irregularity, abnormal uterine bleeding, psychological symptoms, sleep disturbance, decreased libido, and more. In the transition to menopause (age 55 to 65), vaginal atrophy, dyspareunia, urge and stress incontinence, skin atrophy, arthritic symptoms and decreased libido are all issues that may need to be addressed. Last but

not least, at menopause (age 60+), the issues are osteoporosis, arthrosclerosis, and Alzheimer disease. It is important to note that once arthrosclerosis or Alzheimer disease has developed, hormone therapy will not reverse the process.

For women in the perimenopausal phase, hormone therapy clearly has benefits in regard to the quality of life. The WHI studies are not relevant for this group. The small size of the perimenopausal population in the first WHI study was inadequate to define either clinical management or to mandate discontinuation of hormone therapy.²⁰ Withholding hormone therapy from this population is unnecessary as risks for any adverse events are low. Oral contraceptives (or patches or vaginal rings) work very well for women in their 40s, controlling the inevitable abnormal uterine bleeding and the troublesome hypothalamic symptoms of the perimenopause.

As women move into the transitional phase, the most intrusive symptoms abate, but other issues may emerge that often can be helped by hormone therapy, such as vaginal dryness, decreased libido and joint pain (there are estrogen receptors in joints).

In the menopause, which is marked by long-term stability, issues such as brain function and osteoporosis are paramount. Hormones clearly improve both when they are used long term. If a patient prefers not to use hormones, other therapies are available that address those problems. Cognitive function is improved if the individual engages in challenging mental exercises on a regular basis. Osteoporosis was discussed previously. Atrophic vaginitis, commonly an issue in the late menopause, can be treated effectively by using vaginal estrogen with little or no systemic effect.

The WHI writer's group and the U.S. Food and Drug Administration recommended that hormone therapy be used only for menopausal symptoms at the lowest effective dose for the shortest possible time.² A "black box" warning to that effect is required on all hormone therapy medications. However, the North American Menopause Society (NAMS) on October 6, 2004, published their position regarding hormone therapy use in peri- and postmenopausal women. The NAMS

Panel headed by Wulf Utian, MD, PhD, reviewed the relevant issues regarding hormone therapy. They recommended that hormone therapy be used for a time consistent with treatment goals, provided the patient is monitored regularly. The Panel stated that the decision to continue hormone therapy or not should be individualized and they made no stipulation as to when to reduce or stop therapy.¹⁹

Conclusion

The WHI was a large, multi-center, randomized controlled trial of an elderly population of asymptomatic postmenopausal women. The authors concluded that there was an increased risk of breast cancer. However, in the Prempro® arm of the study, their uncorrected data was barely statistically significant and when adjusted, no longer achieved statistical significance. The authors assumed that the hormone therapy caused the increased incidence of breast cancer, but an alternative explanation of their data would be that the estrogen/progestin combination stimulated an already existing, albeit undiagnosed tumor. This postulate is primarily based on the lack of a significant increase in the CIS rate in the study and the average of 10 years it takes for breast cancer to become clinically apparent, based on the doubling times of the breast cancer cell. The Premarin® arm of the study showed a decrease in the risk of breast cancer that did not reach statistical significance.

The slight increase in the risk of cardiovascular disease in the study would be explained by the unmasking of preexisting disease in this elderly population, who were given hormones for a short period of time. In reporting their findings, the authors assumed that all estrogens, progestins and delivery systems have the same effect on the cardiovascular and coagulation system. There is substantial data to indicate otherwise.

The WHI authors make the statement that, based on their study, hormones should be used for the shortest duration at the lowest possible dose. The FDA agreed, and now requires a “black box” warning to that effect on all hormonal preparations. However, the WHI study is only relevant to an elderly population who has not had systemic hormones (either endogenous or exogenous) for many years. A population of postmenopausal women who have been on hormone therapy since the onset of menopause appears to be very different biologically, at least in regard to cardiovascular disease. That population also appears not to be at a significantly increased risk of breast cancer in the long term, based on 40 years of observational studies. Thus, the NAMS statement that hormone therapy can be used for a time consistent with treatment goals (unspecified), with no stipulation as to when to reduce or stop therapy, is the more reasonable approach at our present level of

knowledge. Future studies, particularly evaluating the long-term effects of hormone therapy started in the perimenopause will be most helpful in answering the many questions surrounding this very critical personal and public health issue.

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