

Hormone Replacement Therapy Update - 2007

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Over the past few years, the information on hormone replacement has been confusing and at times contradictory to both patient and physician. The North American Menopause Society has an initiative to align the practice of menopausal health care with the current science and not the media's reporting of the science. As a Certified Menopause Clinician, I hope I can update, clarify, and simplify the current data and state of affairs. Since I am married to an internist and review his journals, I realize there is a big gap in the information and practices between specialties. I cannot keep up with other specialties, but I hope I can update you on the status of postmenopausal hormone therapy (PMHT) and allay the rampant fear and misunderstandings about this therapy.

The presence or absence of estrogen affects several organ systems in clinically important ways. These include the heart, breast, bone, brain, colon, and female reproductive organs. The clinical issues that can be affected are coronary artery disease, cancer of the breast, colon and reproductive organs, brain function, osteoporosis and stroke. Other lesser known effects will also be discussed. Thoughts on patient education and evaluation will be briefly addressed. I will cite a few references, but a detailed reference list is available on my website.

CARDIAC

There are more than 60 retrospective studies on postmenopausal hormone therapy (PMHT) and its relationship to heart disease. They overwhelmingly show a 30 to 50 percent reduction in coronary artery disease with hormone use when it is initiated in early menopause, as it is normally done in clinical practice.

- ◆ ◆ Over a hundred studies have demonstrated estrogen's beneficial effects on the vasculature to include a reduction in LDL, an increase in HDL, a decrease in the

migration of smooth muscle cells into the arterial lumen, the limiting of the secretion of endothelin-1, a potent arterial vasoconstrictor, the promotion of coronary artery vasodilation via nitric oxide and prostacyclin, the lowering of homocysteine levels, and the decrease of arterial thrombosis by reducing levels of clotting factor VII, fibrinogen and anti-thrombin III. Studies have shown a significant decrease in the development of plaque in the carotid arteries in healthy women with as little as two years of estrogen therapy when initiated early in menopause.

- ◆ ◆ Three large observational studies have also shown considerable reduction in heart disease. In the Nurses' Health Study of over 70,000 women, followed since 1975, the age-adjusted risk of CHD was reduced by approximately 40% in current users. (Ann Intern Med 2000; 133: 933 - 941.) In the Lipid Research Clinics studies, a prospective 8.5-year study of 227 women, in current users there was a 63% reduction in coronary disease. (Circulation 1987; 75: 1102 - 1109.) In the Leisure World study of 8800 women, current users had a 53% reduction in myocardial infarction and an impressive 40% reduction in all cause mortality after 15 years of use. (Arch Intern Med 1991; 151: 75 - 78.) This 40% reduction in all cause mortality is seen in European studies as well.

- ◆ ◆ So what about the WHI (Women's Health Initiative) and heart disease? It is important to remember the WHI was a secondary, not primary prevention study. The 16,000 plus women were on average 18 years past menopause and only 574 were between ages 50 and 54. Women with menopausal symptoms were excluded from the study! Overall, in the 1st 1/2 of the study, there was an increase of 6 CHD events per 10,000 women per year in the combined estrogen and progestin (Prempro) group, with no increase in mortality. In fact, rate of deaths were lower in Prempro group. This increase in CHD was seen only in the first year of use. Thereafter there was no increased risk, and a tendency towards a decreased risk. This first year increase in CHD was seen in the group of women more than 20 years from menopause at initiation of hormone use. If this group was excluded, there was no increased risk in the other groups. This is very similar to the results seen in the

HERS and PEPI trials of secondary cardiac prevention, that is, combined hormone therapy slightly increases the risk of clotting events in the first one or two years of use and progressively decreases the risk in subsequent years. There is also the suggestion that statin use eliminates this initial increase risk. Note also that statin use was not assessed in either the placebo or hormone group during the WHI study and could have confounded the results.

- ◆ ◆ Recent analysis of the 2nd half of the WHI, where hysterectomized women were randomized to take Premarin vs. placebo, showed a relative risk of .56 in the estrogen only users in the 50-59 year old group at the initiation of therapy (i.e. a 44% reduction in risk) and relative risk of .72 in the estrogen-progesterone (Premarin-Provera) users if PMHT was initiated within 4 years of menopause. In other words, when estrogen replacement therapy was initiated before age 60, as it is usually done clinically, heart disease was reduced 44% in estrogen only arm and 28% in estrogen and progesterone arm.
- ◆ ◆ It is important to note the difference between primary and secondary prevention trials and the timing of the initiation of hormone therapy. Evidence suggests that in women with healthy vessels the continuous presence of estrogen protects those vessels, but if significant plaque is already present, estrogen can destabilize the plaque and lead to microemboli. This would explain why estrogen protects women's vessels when started in early menopause but is not beneficial, and can even be harmful, if started 15-25 years after the onset of menopause. Fortunately, the practice of waiting 15-25 years to initiate the replacement of estrogen is not commonly done.

BREAST CANCER

Many women fear breast cancer and are concerned and confused about its relationship to PMHT.

- ◆ ◆ Few women realize they are approximately 12 times more likely to die from heart disease than from breast cancer. Fortunately, there have been many studies on the effects of exogenous hormones on breast cancer. Although none is ideal, overall the effects are minimal at best, with some studies showing a slight increase while others a slight decrease in risk.

- ◆ ◆ The lower overall mortality from breast cancer in hormone users has been reported in almost all studies. In Trudy Bush's 1997 reanalysis of 51 studies, a 14% increased risk in current ever-users and a 35% increased risk of detection in long-term current users was shown. These tumors were more localized and better differentiated. This probably reflects a growth effect on an existing early tumor, allowing earlier detection or detection bias. No increased risk was found in past hormone users or users with a family history of breast cancer. This increased risk of breast cancer detection resolves immediately upon stopping PMHT. This would not occur if estrogen were a true carcinogen. Furthermore, studies on PMHT have never shown an increase in breast carcinoma in-situ. This decreases the likelihood of PMHT directly causing breast cancer, but does suggest accelerated growth of a preexisting cancer site.

- ◆ ◆ The Women's Health Initiative (WHI), a study of women on average 18 years into menopause, showed an increased risk of 8 invasive breast cancers per 10,000 women per year after 5.2 years of use. Breast cancer mortality, just 8 women in the 16,000 women trial, was low and the same in both the combined therapy and the placebo group. Again as in other large studies, there was no additional increased cancer risk with combined estrogen progesterone therapy in those patients with a family history of breast cancer. In the estrogen only group at 6.8 years the relative risk of breast cancer was reduced by 23%. Unfortunately, the study was ended for other reasons, just as this reduction in breast cancer risk was approaching statistical significance. After the recent adjudication of the data, a statistical reduction of

invasive intraductal breast cancer was found. (JAMA April 12, 2006.) No publicity was given to this finding.

- ◆ ◆ So where does this leave our patients? We can reassure them there have been many studies looking at the issue of breast cancer and PMHT. The effect, of hormones, whether slightly increasing or decreasing their risk, is small. I tell my patients their lifetime risk of acquiring breast cancer is approximately 1 in 9, if they survive to age 90. The risk of dying from breast cancer is very low (4/100) and hormone therapy does not contribute to that risk. In fact almost all studies show slight decrease in mortality from breast cancer in hormone users. Women are approximately 12 times more likely to die from heart disease than breast cancer. Both alcohol use and obesity contribute more to breast cancer risk than any use of hormones. Also, a family history of breast cancer is not a contraindication to PMHT.

- ◆ ◆ For breast cancer survivors, the issue of HRT is very complex. As more women survive breast cancer this issue arises in severely estrogen deficient and symptomatic women or young women with sexual side effects. Studies have shown that premature castration of females by chemotherapy or surgery results in premature cardiac death. In women castrated before age 35 years, there is an adjusted risk ratio of approximately 800% for nonfatal myocardial infarction. (Am J Obstetric- Gynecology 1981; 139 (1): 47 - 51.) Most studies on hormone therapy are small case controlled studies. These have not shown an increased risk of reoccurrence in either estrogen receptor positive or negative patients. M.D. Anderson currently has a study underway in estrogen receptor negative or unknown status, and at five years, estrogen use has not yielded an adverse effect on disease-free survival. In survivors with severe urogenital atrophy, certain forms of vaginal supplementation will improve local symptoms. As an aside, I often see these women put on SSRIs. These often further increase sexual dysfunction and raise endogenous estrogen levels.

COLON CANCER

Both the Nurses Health Study and The Women's Health Initiative demonstrated an approximately 35% decreased risk in occurrence of colon cancer and death from colon cancer in the women on hormone therapy, with longer use and current use conferring the most benefit. Since this is the third most common cancer and the third most common cause of cancer death in women, this information needs to be conveyed to women.

ENDOMETRIAL CANCER

The risk of endometrial cancer is increased on unopposed or estrogen only therapy. The addition of a progestin is necessary to reduce this risk. The risk of endometrial cancer with combined therapy is small, and actually lower than the risk in women not on any hormone therapy.

OVARIAN CANCER

Data measuring the effect of hormone therapy on the risk of ovarian cancer is inconclusive. Adequate trials are difficult due to the rare nature of ovarian cancer with a lifetime incidence of 1 case per 400 women. Some data suggest a slightly positive association while equal amounts of data show a negative association. If any effect is present, it is likely very small.

STROKE

The effect of hormone therapy on stroke risk and fatality is important, as stroke is the second most common cause of death in women. The effects appear to be related to the age and the presence of independent thrombophilic tendencies in the patient and the method of delivery of the hormone. In cohort studies, such as the National Health and Nutrition, early initiation of PMHT and prolonged therapy reduced both stroke incidence and mortality. In the WHI, where the average age of women was 63, stroke was increased by 12 strokes per 10,000 women-years in the estrogen only arm (Hazard Ratio=1.39), though stroke was not increased at all when estrogen was initiated before

age 60. In the combined arm there were 8 more strokes per 10,000 women-years (HR=1.41). There was no increased risk of fatal stroke in either arm of the study. Oral hormones appear to increase the likelihood of stroke a very small amount, but decrease the severity in older women. Of note, stroke risk does not appear to be increased when estrogen is non-oral. Transdermal estrogen does not increase the production of clotting factors by the liver.

VENOUS THROMBOSIS

A two-fold increase in the risk of venous thrombosis (VTE) has been demonstrated in the WHI, HERS trial and Nurse's Health Studies. With PMHT, this risk is primarily in the first two years of use and falls dramatically afterwards. This translates to an increased risk of 18 cases per 10,000 women per year. Fortunately the mortality from a VTE is less than 1%. Transdermal delivery does not appear to cause this increased risk.

COGNITIVE EFFECTS

The fear of dementia and Alzheimer's disease is paramount in our patients. Many are caring for elderly relatives with impaired cognition and are very concerned about their own memory issues and risk of dementia. Today's 50-year-old women are likely to live to almost 90, and over half will suffer from dementia. This is a huge public health concern.

- ◆ ◆ At menopause, women often have memory issues, particularly problems with verbal retrieval and short-term memory. Insomnia exacerbates both memory issues as well as multitasking problems. The number one reason my patients choose and continue on PMHT is cognition – they say they can just think better. The corpus callosum (multitasking connections), the verbal cortex, and the hippocampus (Alzheimer's location) have many estrogen receptors. Blood flow to many areas of the brain is markedly decreased due to the focal cerebral vasospasm associated with hot flashes and estrogen brain receptors are decreased with the decrease in estrogen. Over fifteen long-term retrospective studies have looked at the effect of hormone therapy on Alzheimer's disease and the trend has been towards a 30-70%

reduction in dementia with hormone use, with the greater reduction in those patients who initiated hormones at menopause and took the hormones the longest. In the WHIMS (Women's Health Initiative Memory Study), the patients were average age of 71 at the initiation of hormone therapy and observed for four years. These older women showed are increased risk of vascular dementia and mild cognitive impairment. None received estrogen in early menopause when estrogen therapy could have avoided repeated cerebral vasospasms and episodes of focal brain anoxia. In this much older group the hazard ratio in the treatment group was 1.76 for vascular dementia and 1.41 for mild cognitive impairment or probable dementia, compared to the placebo group.

- ◆ ◆ In the Leisure World, Cache County (Utah), and Nurses Health studies (totaling approximately 160,000), women were started on hormones at menopause and were followed longitudinally, using PMHT for prolonged periods of time (5 to 20 years). Women on PMHT performed markedly and statistically significantly better on batteries of cognitive testing. Performance improved with increasing duration of use. More and more, early and prolonged hormone use seems to be helpful in slowing cognitive decline and decreasing the incidence of Alzheimer's. For estrogen to prevent Alzheimer's disease it must be started early to reduce hot flashes, and minimize anoxic episodes in the brain.
- ◆ ◆ Sleep disturbances increase around menopause and are a major patient complaint, globally affecting the quality of a woman's life when life's demands are complex. Sleep studies demonstrate the multiple therapeutic effects of PMHT on many aspects of sleep, to include a decreased latency phase and an improved restorative phase. There is no sleep medication that has as many demonstrated benefits.

ESTROGEN'S EFFECT ON BONE

80% of patients affected by osteoporosis are women. Estrogen, with its many effects on bone metabolism, can prevent and treat this common and crippling disease.

Estrogen decreases osteoclast bone reabsorption, prolongs the survival of osteoblasts, decreases renal loss of calcium, and increases the absorption of calcium from the gut and promotes the production of the active form of vitamin D. Estrogen helps maintain the microarchitecture of bones which provides more strength at a given bone density.

- ◆ ◆ Many studies have shown a 50-60% reduction in arm and hip fractures and up to an 80% reduction in the more common vertebral fractures in estrogen users. The WHI also showed an approximately 35% reduction in hip and spinal fractures with 5-7 years of use. This protective risk was both time and dose related and was further enhanced in women who had adequate calcium intake. Although this fracture reduction is attenuated at lower doses, even lower doses of estrogen are still protective. This reduction in fracture is dose related. It is attenuated but still protective at lower doses. Estrogen is the only drug ever shown to decrease hip fractures in women who are not osteopenic or osteoporotic.
- ◆ ◆ Estrogen's protective effects on bone disappear rapidly if estrogen is stopped. Thus, bone loss resumes and eventually patients are likely to end up on more expensive and potentially worrisome drugs like Fosamax, and gastrointestinal side effects are not uncommon. Estrogen, of course, causes neither of these problems.
- ◆ ◆ Long-term use continues estrogen's effectiveness in reducing fractures. Since lower doses still provide some fracture reduction, this may be offered to older women. The low dose transdermal patches do not increase stroke risk, but does help maintain bone density.

ESTROGEN'S EFFECT ON SEXUALITY

Sexuality is an important aspect of menopause that is often not addressed. As women and their partner live longer and erectile dysfunction medications prolong male sexual function, the issues associated with sexuality become more pronounced. With estrogen deprivation, all women will eventually experience anatomical and physiological changes. All women, without the addition of estrogen, will experience urogenital atrophy

marked by thinning of the vaginal epithelium, loss of compliance, vulvar and clitoral atrophy, and decreased erogenous area sensitivity. Most women also note a decreased interest in sex and ability to become aroused. Based on Bassoons recent large study on female arousal and sexuality, most of the female sexual response is located in the cognitive centers of the brain, which have many estrogen receptors. This, coupled with the pain associated with urogenital atrophy and intercourse, contributes to a decline in sexual activity in estrogen deficient women. The addition of testosterone without the presence of estrogen does little to restore sexual functioning. My patients often tell me doctors tell them to stop taking their hormones but never inquire about their sexual activity. With a willing and able partner, many of my patients are sexually active into their 80s, but only if estrogen is present.

ESTROGEN EFFECTS ON HOT FLASHES AND NIGHT SWEATS

Most menopausal women experience vasomotor symptoms, i.e. hot flashes and night sweats. For some women these are severe and disabling, disturbing sleep and decreasing ones quality of life. It is important to assess frequency, severity, and to what extent a woman's life is affected. Unfortunately I do not have time to review the studies on herbal and other remedies for the treatment of vasomotor symptoms but most do not perform better than placebo, and for some there are substantial side effects. Estrogen is the therapy of choice for vasomotor symptoms, and the dose can be adjusted for effect. Realize increasing conjugated oral estrogens, (i.e. Premarin) increases sex hormone binding globulins, which may actually increase hot flashes and alter thyroid levels. Transdermal regimens may provide better relief in these patients.

OTHER POTENTIAL BENEFITS

Estrogen works at approximately 400 receptor sites. The potential effects are many. Estrogen decreases insulin resistance in postmenopausal women and improves their lipid profile. In the WHI, combined PMHT users had less diabetes, probably due to their improved insulin sensitivity. Several studies show estrogen reduces both the incidence and the severity of osteoarthritis and this benefit is increased with more prolonged use. Tooth loss is less in estrogen users due to its bone preserving effect on the jaw, as well

maintaining oral lubrication and healthy gums. Estrogen works in the eye to maintain moisture, thus decreasing post-menopausal dry eyes and allowing some patients to continue wearing contact lenses. Intraocular pressure is also lower in estrogen users. There are several studies that suggest a significant reduction in the incidence of macular degeneration with PMHT. Recent studies have also shown estrogen regulates regions of the brain involved with mood. Estrogen decline in the perimenopause and early menopause is associated with an increased incidence of depression. This depression is often responsive to estrogen therapy. Women with chronic depression may have more symptoms and difficulty regulating their antidepressants. The supplementation with estrogen facilitates antidepressant therapy.

POSTMENOPAUSAL HORMONE THERAPY

The choice to use and continue hormone therapy is both important and complex due to the many potential benefits and few risks. The climate of fear generated by the media and the misinformed have denied many women a clear choice and evaluation of the science. This needs to end so women can make good choices for their current and future health.

There are many types of hormones and hormone delivery systems, each with its own characteristics. These need to be tailored to the individual, much the way hypertension management is individualized. One size does not fit all women. I spend a lot of time with my patients reviewing their history, their expectations and fears, and tailor a regimen unique to each of them. Sexual issues need to be addressed. Therapies need to be modified over time. Patients are reassured this is not a lifetime decision and therapy will be addressed, updated and modified based on their needs and the current science.

With an aging population and women living over a third of their life in menopause, this time of transition needs to be appropriately evaluated and treated. There is no substitute for a healthy lifestyle. For many women the proper PMHT augments and prolongs wellness.

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