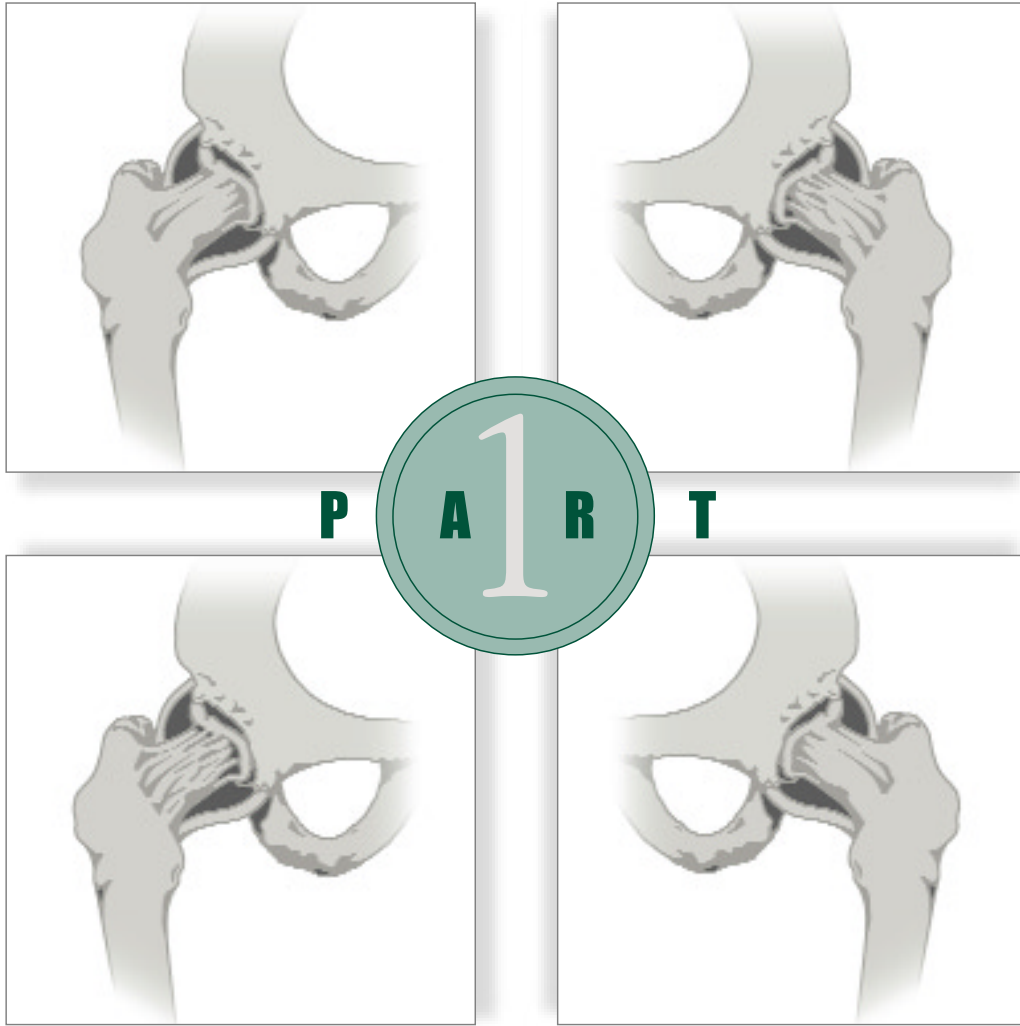

OSTEOPOROSIS: THE ERA OF THE BISPHTHONATES

S U P P L E M E N T



*Two leading clinicians
respond to the results of the
Women's Health Initiative
(WHI) study*

INTERVIEWS WITH:

Felicia Cosman, M.D.

Endocrinologist, Helen Hayes Hospital

Osteoporosis Specialist

*Associate Professor of Clinical Medicine
at Columbia University*

Clinical Director of

The National Osteoporosis Foundation

New York, NY

Sol Epstein, M.D.

Professor of Medicine and Geriatrics

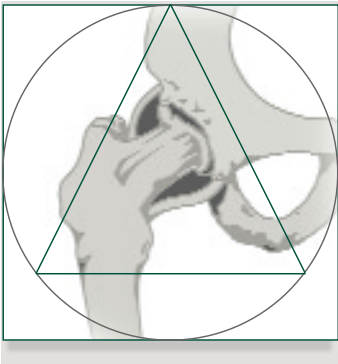
Director of Osteoporosis Research

at Mt. Sinai University Hospital and Medical School

New York, NY

INTRODUCTION

Publication of the results of the Women's Health Initiative (WHI) study¹ overturned much of the conventional wisdom regarding hormone replacement therapy and engendered much discussion and debate in both the lay and professional media. This supplement to Part 1 of the continuing education program, *Osteoporosis: Era of the Bisphosphonates* features the personal responses of the editors of this program, Felicia Cosman, M.D., and Sol Epstein, M.D., to the WHI results.



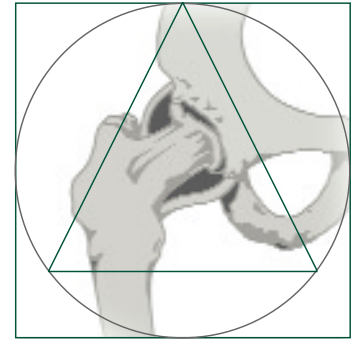
1. Lacey JV Jr, Mink PJ, Lubin JH. Menopausal hormone replacement therapy and risk of ovarian cancer. *JAMA*. 2002;288:334-341.

“... a very busy month of patient phone calls.”

Question: Hormone replacement therapy (HRT) has come to be viewed by many as the solution to a wide variety of health problems in postmenopausal women. How did these beliefs develop?

*An interview with
Felicia Cosman, M.D.*

Dr. Cosman: The use of estrogen for the prevention or treatment of a number of concerns relating to the health of postmenopausal women has been around for about 50 years. Perhaps the biggest “selling point” for estrogen was the belief that it reduced the risk for cardiovascular disease. Many health agencies and women’s health groups endorsed HRT for this use, because cardiovascular disease is the number one cause of mortality in women. The data supporting the use of estrogen to prevent heart disease come from observational studies that have been ongoing since the 1970s. Most of these studies are quite consistent in showing a reduction in the risk of heart disease. However, we have known for a long time that some of these studies are compromised by a cohort bias. These are not randomized clinical trials; the women who chose to take estrogen differ from those who do not in socioeconomic status, educational level, and general nutrition. In fact, a recent meta-analysis of the observational studies showed that if you control for socioeconomic status, the positive association between estrogen use and cardiovascular disease risk reduction is eliminated.



The other big “selling point” for estrogen in terms of chronic disease prevention is, of course, the prevention of osteoporosis. Until quite recently, the data supporting this usage also came primarily from observational studies. One of the gratifying results of the recently published Women’s Health Initiative (WHI) study was that it confirmed that HRT does in fact reduce the risk of osteoporotic fractures. Over the past 10 to 15 years, many began to believe that estrogens could delay or prevent cognitive decline. Estrogens have long been known to reduce menopausal symptoms, such as hot flashes and vaginal atrophy.

Q. Would you briefly summarize the results of this study?

Dr. Cosman: The WHI was stopped early, when a predetermined limit was achieved in global index of risk. Perhaps the most surprising result was the approximately 30% increase in the risk of coronary heart disease events associated with HRT. There was also a 40% increase in the risk of stroke. This an important finding, although the overall risk remains low. It was thought by some that even if HRT increased the risk for hemorrhagic stroke, maybe it would reduce the risk of thrombotic stroke related to atherosclerotic plaque accumulation. That is clearly not the case. The risk for venothromboembolic disease, both deep-vein thrombosis and pulmonary embolism, was approximately doubled. The risk of invasive breast cancer was increased by about 25%. The latter findings are consistent with prior clinical trials and observational studies. By contrast, the benefits of HRT included a 37% decrease in the risk of colorectal cancer, a 34% decrease in hip and clinical vertebral fractures, and a reduction in the risk of all osteoporosis-related fractures of approximately 24%.

Some questions remain, however. We still don’t know if HRT is protective against Alzheimer’s disease, because there aren’t enough good data. We also don’t know if the effects of Prempro™ (the brand of HRT used in the WHI trial) extend to other brands of HRT. I would think yes for breast cancer risk, but I’m less certain if that holds true for cardiovascular disease and stroke.

Q. Some of these results caught many people by surprise, particularly in regard to cardiovascular disease. Could you summarize your views before the publication of the study?

Dr. Cosman: The Heart and Estrogen/progestin Replacement Study (HERS), which was published about a year before the WHI, showed that the same HRT regimen used in WHI did

not reduce the risk of cardiovascular disease-related events compared with placebo. In fact, there was an increase in the risk of cardiovascular disease during the first year of the study. This was a dramatic outcome because, if anything, we expected to see a benefit from HRT in subjects who already had established heart disease. It was thought that the treatment effect would be most evident in these subjects and that we would see a reduction consistent with that seen in observational studies. This result alone “shook up” the field of women’s health. HERS was conducted in women with established heart disease, so the question remained: would HRT work as a primary preventive therapy? The results of the WHI clearly showed that the answer is no.

The epidemiologic data regarding an increased risk of venothromboembolic events were also confirmed in HERS, and it was the first study to demonstrate an increase in the risk of gall bladder disease. HERS included 2,760 women, which may not have been a large enough population to show significant effects on overall breast cancer risk. The study also did not show reductions in the risk of hip or other fractures.

Q. This raises the question, if estrogen is not protective against cardiovascular disease, then what accounts for the lower incidence of the disease among premenopausal women compared with men?

Dr. Cosman: It may be that endogenous estrogens are different from exogenous estrogens. If you look at age-matched groups of premenopausal and postmenopausal women, there is a higher incidence of cardiovascular disease in the postmenopausal women. There is accumulating evidence that the body may respond differently to estrogen once it has been in an estrogen-deficient state for a while. Apparently, the use of exogenous estrogen in women who are estrogen-deficient cannot return them to a premenopausal state.

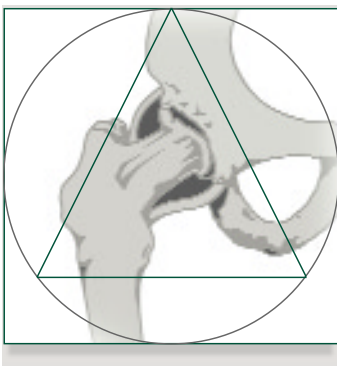
Q. You raise an interesting point. I understand that many of the women who entered the WHI trial were over age 60, so they had been estrogen deficient for several years.

Dr. Cosman: That’s correct; the age range was 50-79. The cardiovascular findings seemed similar across the three decades of ages in this study. However, there weren’t that many women in their early 50s at entry. The mean age was 63, so I don’t think the study fully answers the question about using HRT in the very early postmenopausal group (within one or two years of last menses). In fact, early postmenopausal women with troublesome menopausal symptoms have been the primary candidates for HRT in the past five years. I’m not sure if we can extrapolate the vascular disease findings from the WHI population to women in the very early postmenopausal years.

Q. The study has been in print for about six weeks. Do you sense any movement toward a consensus among your colleagues?

Dr. Cosman: We’re continuing to evolve our opinions on this issue. The American College of OB/GYN has come out strongly, saying it is reasonable to use HRT for menopausal symptoms, but it should be used for the shortest duration possible. For the treatment of osteoporosis, other drugs should be considered. It’s a strong statement, but I think that’s where the consensus of opinion is going. We’re going to continue to use HRT in women who experience severe menopausal symptoms, but this is a minority — perhaps 25% to 30% — of postmenopausal women. We’ll use the lowest possible dose and try to taper and discontinue it as soon as possible. Although HRT clearly works to prevent fractures, there are too many safety concerns to justify continuing it long-term for this purpose.

Q. The WHI was rather noncommittal about the safety of the estrogen/progesterone combination relative to estrogen alone. Do you have an opinion on this issue?



Dr. Cosman: I think the fact that the other randomized clinical trial using estrogen alone is ongoing is very important, and suggests that the risk of unopposed estrogen is not as great as the risk of combined, continuous HRT. I think we probably will see some increase in the risk of breast cancer with estrogen alone, but that it will be a smaller risk than that seen with combined, continuous HRT. I also think we'll see a smaller increase in the risk for cardiovascular disease and perhaps for stroke. I think that unopposed estrogen is a safer way to go, but it certainly cannot be considered in women who have a uterus and I think that we'll see some of the same problems, just of a lower magnitude. There may also be a question of increase in ovarian cancer risk in women on long-term unopposed estrogen who had hysterectomies with ovarian conservation.

Q. Can you discuss some of the reactions of your patients when they learned of the results of the WHI? You must have been swamped with phone calls.

Dr. Cosman: Yes, it's been a very busy month of patient phone calls. There were some women who panicked and wanted to come off therapy the day the news broke. I also have another group of women who are quite comfortable staying on therapy until their next scheduled office visit. Women who are on HRT because they are at high risk for osteoporosis sometimes experience a dramatic bone loss if their therapy is withdrawn. In these women, we need to find an alternative treatment. I think that a lot of women should come off HRT as a result of the WHI data, but it's not an emergency. I believe that tapering is the most sensible way to withdraw therapy, and in my experience it usually prevents the onset of menopausal symptoms. In many cases, I initiate bisphosphonate therapy during the taper to prevent bone loss as HRT is withdrawn.

Q. Have you had many patients who resisted the withdrawal of HRT because they felt they were benefiting from its effects?

Dr. Cosman: With the exception of a few women who had very severe menopausal symptoms, I have not. Over the past five years, I have been slowly reducing the proportion of my patients who are on HRT. I have initiated discussions with all of my patients after five to seven years of therapy, indicating that I would like them to come off HRT at some point in the next few years. I was particularly concerned about the risk to the breast, especially after long-term use.

Q. It sounds like you were not blindsided by the results of the WHI.

Dr. Cosman: I was not; the results were exactly what I expected, except for the results on heart disease. That was the big surprise.

Q. How are you treating the few women in your practice with severe menopausal symptoms?

Dr. Cosman: I go with the lowest possible estrogen dose, 0.45 mg or even 0.3 mg of conjugated equine estrogens, or 0.5 mg of estradiol, which are often effective in preventing hot flashes. These doses may be adequate to protect bone as well, although I'm still not comfortable with long-term, low-dose HRT. However, I think it's a reasonable approach, based on limited data, to go with the lowest possible dose. In some women, I consider alternative treatments, such as antidepressants. I've found that venlafaxine, in particular, is effective in reducing hot flashes. Like HRT, I would use the antidepressants for as brief a period as possible to control menopausal symptoms. ■ ■ ■



Although HRT clearly works to prevent fractures, there are too many safety concerns to justify continuing it long-term for this purpose.

“... physicians need to discuss the risks and benefits of HRT with each patient.”

*An interview with
Sol Epstein, M.D.*

Question: For many years, hormone replacement therapy has come to be seen as a solution to a wide variety of health problems in postmenopausal women and even as a kind of elixir of youth. How did this situation come to develop?

Dr. Epstein: Estrogens have been around for nearly 60 years. It seemed logical that, if the ovaries ceased to function you could replace the hormones produced by the ovaries and prevent the changes that accompany estrogen deficiency. Epidemiological studies and case record reviews conducted in the 1970s showed that morbidity and mortality from cardiovascular disease were much lower in women who had taken hormone replacement therapy compared with those who had not. However, it has since been realized that a number of problems compromised the accuracy of these observations. First, there were few properly designed, randomized controlled trials. Second, there was a selection bias. Women who gravitated toward hormone replacement therapy tended to be healthier and better informed, and therefore not representative of the general population. Thus, the history of hormone replacement therapy has been plagued by observational, case-controlled, or cohort studies that had not been well conducted.

Q. What was the general belief about the effect of HRT on other diseases?

Dr. Epstein: It was generally accepted that HRT was beneficial for relief of menopausal symptoms, such as hot flashes, vaginal dryness, and perhaps urinary incontinence. HRT did become somewhat controversial when studies showed a small but significant increase in the risk of breast cancer. Other studies looked at its effects on bone mineral density and fractures. No one was convinced that there were good data showing a beneficial effect on fractures. There were a lot of observational studies noting improvements in mental health, and decreases in colon cancer and Alzheimer's disease. In effect, until the Women's Health Initiative was initiated, perception had become reality concerning the benefits of HRT. This occurred despite the fact that the data were neither robust nor compelling, with the exception of the data concerning the relief of menopausal symptoms.

Q. Would you briefly summarize the results of the Women's Health Initiative Study?

Dr. Epstein: The WHI served an excellent purpose. It was a very large, randomized clinical trial and used what is considered to be the popular dosage form of hormone replacement therapy: conjugated equine estrogens, 0.625 mg/day plus medroxyprogesterone acetate 2.5 mg in one tablet. This is the most commonly prescribed dosage form because it is convenient to take and women don't have the inconvenience of monthly menstrual periods.

There were 8,506 women in the treatment group and 8,102 in the placebo group; this was a sufficient number to define the endpoints. On May 31, 2002, after a mean of 5.2 years of follow-up, the Data and Safety Monitoring Board recommended stopping the trial of estrogen plus progesterone versus placebo. This came about because the statistics for invasive breast cancer exceeded the stopping boundary for this adverse effect. To put it simply, the risk-benefit ratio for HRT favored the risk. The increased risk for breast cancer, around 26%, became apparent after four years, when the two groups started to diverge significantly. The WHI study also showed an increased risk of cardiovascular disease, which occurred early, of about 26%. Stroke increased at a slightly higher rate for the treatment group and pulmonary embolism increased substantially. However, there were some



benefits, with significant reductions for the HRT group in fractures. Spine, hip, all osteoporotic fractures, and total fractures were reduced. In addition, there was a 37% reduction of colorectal cancer among the treatment group.

It's important to note that, although the risk-benefit ratio appeared to favor the risk, HRT did not increase all-cause mortality. In addition, it should be noted that about two-thirds of patients were over age 60 at study entry — rather high for a study of risk reduction in postmenopausal women. Furthermore, about 70% of these women had an increased body mass index and one-third were treated for hypertension. By and large, though, this was a generally healthy population and representative of the world of women who are being given hormone replacement therapy. In terms of osteoporosis, the study confirmed what many in the medical community had already believed, which was that HRT with estrogen in a variety of forms can reduce fractures. What was more important, is that the study showed it reduces fractures in women who have not been screened for osteoporosis.

Q. Were you surprised by the results of the study?

Dr. Epstein: I was not surprised by the increased risk of thromboembolic disease, because this is clearly stated in the package inserts for HRTs, and everyone is well informed about the risk of deep-vein thrombosis and pulmonary embolism. As for the increased risk for breast cancer, this must be understood in context. HRT results in about 8 additional cases per 10,000 per year. With huge epidemiological studies, this can turn out to be significant. In terms of increased risk for an individual patient, it is quite small.

Q. So what is the bottom line for a practicing physician?

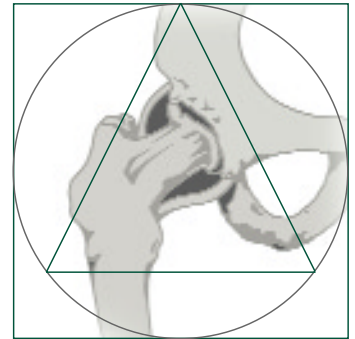
Dr. Epstein: First of all, the trial provided extremely useful information. There is no doubt that, if a woman has menopausal symptoms, the most effective drug is estrogen. However, if a woman is at risk for coronary heart disease, thromboembolic events, or stroke, she should not receive hormone replacement therapy. As for the risk of breast cancer, the trial showed that the longer a woman takes HRT, the greater the risk. So the bottom line is, you use HRT to treat menopausal symptoms for the shortest possible time with the lowest possible dose. If a woman has menopausal symptoms and osteoporosis, the same principle applies. After stopping the HRT, I would add another antiresorptive drug, such as a bisphosphonate. If a woman has no menopausal symptoms and has osteopenia/osteoporosis, my drug of choice would be a bisphosphonate.

Q. Will this become the standard of care?

Dr. Epstein: I think there are a number of issues that will determine what will become the standard of care. First of all, the trial used combination therapy and we don't really know the effects of progesterone. Secondly, it used what may be considered a relatively large dose of conjugated equine estrogen, 0.625 mg. There are data that show that a dose of 0.45 mg increases bone mineral density while relieving menopausal symptoms as effectively as the higher dose.

Q. The WHI study was rather noncommittal about the safety of the estrogen/progesterone combination. What is your view on this question?

Dr. Epstein: There are some data indicating that, in terms of heart disease, progesterone may worsen the risk. There is a trial underway of estrogen alone; it may clarify this issue. We also don't know if the WHI results are unique to conjugated equine estrogens, or if some other delivery route, such as transdermal, may provide the same benefits without the risks. All of this needs to be explored.



If a woman has no menopausal symptoms and has osteopenia/osteoporosis, my drug of choice would be a bisphosphonate.

Q. How did your patients react to news of this study?

Dr. Epstein: Many patients became frightened and confused. And not only patients — many OB/GYNs became confused about how to interpret the results. My view is that physicians need to discuss the risks and benefits of HRT with each patient, the decision being tempered by the implications of the study results.

Q. Has this study changed the way you use HRT?

Dr. Epstein: It has, in the following ways. As I noted, I try to use the lowest effective dose. Second, I treat for shorter periods. Third, I am more selective in terms of which patients I put on HRT. There are many medical and legal ramifications. Careful screening of patients for cardiovascular disease may become a routine part of HRT therapy. Ultimately, though, I hope it will remain a decision between the physician and patient. I've heard that there is an effort underway by one of the OB/GYN societies to come out with general guidelines, but I don't know the details.

Q. Do you have some patients who are resisting the cessation of HRT?

Dr. Epstein: Yes, I have patients who are prepared to accept the risk because they feel so good. Whether it's perception or reality, they feel that their mood and sense of femininity are enhanced by HRT. Unfortunately, the data supporting these effects are neither robust nor compelling.

Q. I understand that the *Archives of Internal Medicine* has accepted a study for publication which shows that, after withdrawing from estrogen therapy, women experience an immediate and significant bone loss. Since many women will now be ceasing HRT, it sounds almost as if we're facing a nationwide medical crisis.

Dr. Epstein: Absolutely; if HRT is being given for low bone density, then stopping the drug will result in accelerated bone loss. These women must be given effective antiresorptive therapy and my choice would be a bisphosphonate, because these drugs have the strongest evidence supporting their efficacy in fracture prevention. ■ ■ ■

