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By Lynne Peterson

SUMMARY

More and more experts are weighing in on the side of a very limited role for hormone therapy – as short-term therapy for severe symptoms of menopause (hot flashes), not as a preventive for anything. In this environment, hormone therapy use in general – and Prempro use in particular -- is likely to continue to decline. Many clinicians have been slow to accept this message, but the voices are getting more common and louder, and additional data and analyses are expected that should reinforce the message. Although the WHI findings were only with Premarin and Prempro, experts and regulators generally agreed that the findings must be considered to apply to other hormone products until and unless they are shown to be safer.

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NATIONAL INSTITUTES OF HEALTH: SCIENTIFIC WORKSHOP ON MENOPAUSAL HORMONE THERAPY

Bethesda, Maryland
October 23 and 24, 2002

The National Institutes of Health (NIH) sponsored a two-day forum on the results of the Women's Health Initiative, a study of hormone replacement therapy (HRT) in more than 16,000 women that was cut short due to safety issues. The study panicked many women, and doctors phones began ringing off the hook. By early November 2002, some experts estimated that about 28% of women had stopped taking Wyeth's Prempro -- a fixed-dose combination of Premarin (conjugated equine estrogen) and Cycrin (medroxyprogesterone acetate). While the study was well-regarded, there was still confusion among doctors and patients, and NIH and WHI officials said the findings needed to be openly discussed, but there was only one message at this meeting: limit the use of hormone therapy.

BACKGROUND

The WHI trial was designed to run for 8.5 years, but the data safety monitoring board recommended on May 31, 2002, that the arm with Prempro be stopped, after a mean of 5.2 years (range 3.5-8.5 years). The DSMB cited unacceptably high adverse events. The Premarin arm and placebo arms are continuing. In an article in the July 17, 2002, issue of the Journal of the American Medical Association, the WHI researchers concluded: "All-cause mortality was not affected during the trial…(but) this regimen should not be initiated or continued for primary prevention of CHD…(The) increased risks for cardiovascular disease and invasive breast cancer were present across racial/ethnic and age strata and were not influenced by the antecedent risk status or prior disease. Hence, the results are likely to be generally applicable to healthy women in this age range."
(See Chart on page 2)

HRT FORUM

The meeting was calm, professional, and science-based. There was debate and disagreement, but more on details than the general findings of the WHI. A speaker said, "We need to calm everyone down. Hormone therapy is not that big a risk, but it is not the benefit we thought it was."

However, for two days, organizers pounded home one message:

> **Hormone therapy should be limited to short-term use in women with severe symptoms of menopause and who have been advised of the risk as well as the benefits, so they are making an informed decision. There is no role for HT in disease prevention.**

WHI Results (*based on data through April 30, 2002*)

Event	Prempro events per 10,000 patient-years	Placebo events per 10,000 patient-years	Prempro events v. placebo	Relative risk of Prempro v. placebo
Coronary heart disease -- non-fatal MI and CHD death (primary endpoint)	37	30	7 more	29% increased risk
Stroke	29	21	8 more	41% increased risk
VTE	34	16	22 more	112% increased risk
Breast cancer (primary adverse outcome)	38	30	8 more	26% increased risk
Colorectal cancer	10	16	6 fewer	37% risk reduction
Endometrial cancer	54	50	4 more	nss
Hip fracture	10	15	5 fewer	33% risk reduction
Global Index (balance of risks and benefits)	170	151	19 more	12% increased risk
Total deaths	231	218	15 more	nss

Source: Journal of the American Medical Association

There was resistance to this message from some of the doctors in the audience, and it was reminiscent of the reluctance of gastroenterologists to accept H. pylori as the cause of most ulcers, and more than one speaker made this analogy. It seemed that many doctors who treat women with hormone therapy may be just as reluctant to give up their long-held beliefs about the value of hormone therapy. A WHI investigator said, "What we have is a whole series of denials of data that have been coming out. We have had four years to get our arms around the idea that hormones may not be helpful for heart disease…We just have to accept that we were wrong on some of these issues."

The HRT products that currently have FDA approval are:

- 5 combo products – 4 oral, 1 transdermal patch
- 15 estrogen-alone products – oral, topical gel, injections, patch, vaginal ring
- 6 progestins: oral, injection, and gel

These products are approved to treat menopause conditions, including: vasomotor symptoms, vulvar vaginal atrophy, and prevention of osteoporosis. They are not approved for prevention of cardiovascular disease or 'hormone replacement." In fact, the FDA does not like the term HRT (hormone replacement therapy), preferring instead to call it hormone therapy (HT) or "menopausal hormone therapy." Many, but not all, experts have now adopted the HT designation, so both terms are still being used.

WHI investigators laid out the data supporting their findings. They reviewed other trials that preceded WHI, and they explained, in great detail, how they conducted the WHI trial, why the decision to halt the trial was made, and the trial findings – and they insisted the WHI study is "not just another confusing report." One speaker said, "What we must face now is that rather than asking why shouldn't you take hormones, we now need to ask why should you take hormones. And in the non-GYN mind, that is: How serious are the symptoms that can only be treated with hormones?" An oncologist said, "It seemed people gave hormones for any severity of symptoms, and now I think there will be more focus on severity of symptoms. Women with severe symptoms will want therapy." An OB-GYN said, "If women get the message, they will be able to determine if their symptoms are serious enough to take the risk of taking hormones. I personally have hot flashes, but they are not severe enough to take HRT. That is my personal choice. If I couldn't tolerate the hot flashes, maybe I would be willing to take HRT."

The absolute risks of HT are small, but a biostatistician warned, "The longer we go on with therapy, the higher the risk gets. That tells us to periodically try to stop hormone therapy and minimize duration of use…(But) I don't think any women are likely to benefit from hormones...The net effect in a 50-year-old woman with symptoms is 1:1,000 per year for a bad event, and I can't decide if the symptoms justify the risk, but what about a woman with a family history of breast cancer who herself is at a two-fold risk of breast cancer, or a smoker with a two-fold increased risk for coronary event or stroke, or a cardiac patient who has a five-fold risk of a coronary event?"

Average Increase in Risk
(per 1,000 Patients Per Year)

	1 year	5 years
Based on Risk Factors		
Average risk patient	1.2	6.0
Family history of breast cancer	1.5	7.5
Smoker	2.0	10.0
Coronary heart disease	3.8	19.0
Number Needed to Harm		
Average risk patient	800	165
Family history of breast cancer	650	130
Smoker	500	100
Coronary heart disease	250	50

Experts from various organization and medical societies weighed in – and they, too, generally agreed there will be an extremely limited role for HT in the future.

U. S. Preventive Services Task Force. An official policy position was presented that recommends against the use of combined estrogen and progestin therapy for preventing cardiovascular disease and other chronic conditions in postmenopausal women." The Task Force, sponsored by the Agency for Healthcare Research and Quality, "found evidence for both benefits and harms of combined estrogen and progestin therapy…(but) concluded that harmful effects of the combined therapy are likely to exceed the chronic disease prevention benefits for most women…(and) the evidence is insufficient to recommend for or against the use of estrogen alone...The Task Force concluded that combined hormone therapy could increase bone mineral density and reduce the risk of fractures and may reduce the risk of colorectal cancer. They found equally strong evidence, however, that combined hormone therapy increases the risk for breast cancer, blood clots, stroke and gallbladder disease…(and) actually increase the risk of heart attacks."

North American Menopause Society. An official said, "Use should be the shortest duration possible taking into account issues of quality of life…HT maintains quality of life for non-symptomatic women…WHI data cannot be directly extrapolated to women with premature, early or symptomatic perimenopause."

American Society for Reproductive Medicine. An official said, "Some doctors have said HRT is so dangerous it should not be provided. Estrogen is still the most effective treatment for symptoms, and for some only estrogen provides relief…Vasomotor symptoms should be the primary reason for providing therapy…To withhold estrogen could impact severely on some women…These findings should not lead to abandonment of estrogen in all women…We urge continued research…WHI should not be viewed as the final or last word."

British Women's International Study of Long Duration Oestrogen after Menopause (WISDOM). Although no scientists from the Medical Research Council spoke at the meeting, the British government announced the decision to halt its own 5,700-patient hormone therapy trial on the first day of the NIH meeting. In July 2002, Britain decided to continue with its study but stopped enrolling additional women and appointed an Independent International Committee (IIC) of advisors to review the WHI results and other hormone therapy research. The IIC recommended the trial be halted because it was "unlikely to provide medical evidence that would influence clinical practice."

American College of Obstetricians and Gynecologists (ACOG). Since many of the prescriptions women get for HT come from OB/GYNs, particular attention was paid to the findings of an ACOG task force. An ACOG official said, "WHI is a well-designed, appropriately-powered, well-conducted, strong study…ACOG concludes:

- Combined HT is no longer recommended for the prevention of cardiovascular disease and, if prescribed for that purpose, should be discontinued.
- The increase in breast cancer was not evident until year four of the study, but you can't assume that shorter use is safe.
- For osteoporosis, ACOG recommends therapies such as bisphosphenates or SERMS be considered. However, for women at risk or who can't take alternative medications, HT can be of benefit.
- In colorectal cancer, the apparent benefit reduction is not sufficiently robust to recommend its use solely for prevention of colorectal cancer.
- HT for vasomotor symptoms should be as short-term as possible with the lowest effective dose. Long-term use should be discontinued in asymptomatic patients.
- For genitourinary symptoms, alternative methods -- creams, tablets and rings should be considered. They do not increase systemic levels appreciably, though there is little long-term safety data on these.
- For women quitting HT, there is no definitive data on a tapering strategy. Some women may have symptoms and need to restart therapy."

Not all OB/GYNs agreed with this limited role for hormone therapy. In fact, a few dug in their heels, disputed the WHI findings and praised the benefits of HT. A prominent New York OB/GYN said, "Until something else is available, we will need to use HRT for some women who need help. And we need to offer them more than layered clothing. I think it is wrong to take this scientific information and make unscientific conclusions. You can't extrapolate for this asymptomatic, older population to a younger population with symptoms." A Virginia OB/GYN said, "Many of us feel WHI is not applicable to younger women. We think there is a preventive benefit for them. I think the WHI rhetoric has slammed the door on younger women who might show a prevention benefit."

There also were a lot of complaints from attendees about the WHI data, particularly:

How it was released. There were numerous complaints about the public way NIH released the data, but officials insisted there was no way to notify this many people without some complaints about the process. One speaker said, "We were not pleased about how fast the information had to be

disseminated. We would have preferred other processes to educate physicians…and we hope to do things differently in the future."

Lack of information on non-oral estrogen and other oral hormone products.

Which breast cancer patients were at highest risk. A Wyeth official pointed out that 75% of the women who got breast cancer had not previously used HT. The relative risk for the rest of the women was similar to placebo.

A decline in cardiac events during year 5 in the placebo arm of the trial.

NEW DATA

Additional WHI data analyses and other studies are in progress that should shed additional light on the value of HT, including:

- A WHI analysis of the ovarian cancer risk is underway and should be reported soon.
- Analyses of the role of Prempro in improving quality of life are not yet complete.
- The estrogen-only arm of WHI is continuing, and investigators insisted that women have not been dropping out of that trial because of the termination of the combination therapy arm.
- Alzheimer's Disease and mild cognitive disease studies are ongoing with estrogen and may determine whether hormone therapy has a positive or negative effect on cognitive function and dementia. *(See below)*
- A dietary modification trial is underway.
- A calcium/Vitamin D intervention study is underway.
- A look at lobular vs. ductal breast cancer in WHI will be discussed in the December 2002 issue of ***Cancer.***

QUESTIONS THAT WERE RAISED – AND SOMETIMES ANSWERED – ABOUT THE WHI DATA INCLUDE:

1. Is there a role for hormone therapy as preventive therapy in:

a. *Coronary heart disease?* No.

A WHI investigator said, "(Prempro) is not to be used for CHD (primary or secondary)." An Ohio OB/GYN said, "I was in the group that thought HRT was beneficial – because of cardiovascular disease – and (the separation) of aging from menopause hadn't been made until WHI. In my mind, it is important to understand you can't reverse aging…You can't take a pill for the rest of our life to make us young again. WHI showed us that HRT – at least with this preparation – is not physiologic and is not a replacement." Another speaker said, "It is clear there is no cardiovascular benefit."

b. *Colorectal cancer?* No.

An oncologist said, "My personal opinion is that HRT should not be used for prevention (even of cancers)."

c. *Osteoporosis?* No.

Experts agreed that women on HT have a lower rate of hip and clinical vertebral fractures fractures, but most (including several prominent osteoporosis experts) recommended against using EP as an osteoporosis prevention therapy. Rather, they suggested the use of bisphosphenates or SERMS. A prominent osteoporosis expert who was in the audience said she no longer sees a role for hormone therapy in even the most severely osteoporotic patients. A speaker said, "HT should be used only in those women at significant risk for osteoporosis and in whom alternative therapies have been carefully considered." The president of the American Society of Bone and Mineral Research (ASMBR) said, "In non-osteoporotic women, you need to treat 1,790 women to prevent one fracture, but in women with osteoporosis, the number needed is 24."

Osteoporosis Therapies:
Pooled Estimate of Risk:Benefit

Therapy	Risk Reduction
HRT	.78
Alendronate (Fosamax)	.51
Risedronate (Actonel)	.68
Vitamin D	.77
Raloxifene (Evista)*	.91

*Significant effect on spine BMD but no effect on non-spine fractures

d. *Alzheimer's Disease?* Maybe.

This is still under investigation. The Deputy Director of the National Institute on Aging (NIA) said, "Basic biological studies suggest a neuroprotective effect, and some epidemiology studies suggest a role for estrogen in prevention of Alzheimer's…The longer the duration of the study, the more likely a positive effect, it appears…To date, we have not been able to discern any effect of making these findings public on the recruitment of new subjects, so these trials are continuing and continuing to recruit." Among the ongoing studies are:

- A 160-patient study (13 now enrolled) comparing an Estrada patch (50-100 mcg/day) to a patch+ medroxyprogesterone that should be completed by 2005.
- A one-year, 900-patient trial (408 now enrolled) comparing Premarin and Prempro to placebo, looking at elements of dementia and memory decline.

- An NIA study of the WHI (WHISCA), with 2,302 patients.
- The WHI study of cognitive aging, which has 2,298 patients now enrolled, looking at Premarin and Prempro. Patients continuing in this trial were asked to sign new consent forms, and researchers said the patients are doing that and staying in the trial. One commented, "For many of the subjects, particularly those with a first degree relative with Alzheimer's, the risks of Alzheimer's outweighed other risks."
- Wyeth's WHIMS study of 7,480 patients age 65 and older looking at estrogen and estrogen+progestin vs. placebo on all-cause probable dementia, mild cognitive impairment and progression of dementia. The combination arm ended in June 2002, and that data should be published by early 2003. The estrogen only arm continues as designed.
- An NIA study of tamoxifen vs. raloxifene (CO-STAR), which just started and plans to recruit 1,600 women age 65 and older, looking at the rate of change in memory and other cognitive abilities

2. Do the findings apply to all age groups, including younger menopausal women (<50 years old)? Yes.

Relative Risk of CHD

Age	Prempro	Placebo
50-59	.21%	.13%
60-69	.35%	.28%
70-79	.71%	.60%

A Virginia OB/GYN said, "Many of us feel WHI is not applicable to younger women. We think there is a preventive benefit for them. I think the WHI rhetoric has slammed the door on younger women that might shown a prevention benefit." A WHI oncologist defended the findings, saying, "The data on cancer was waited heavier to events in later years because we thought the first years were less likely to promote cancer, so the analysis was heavily weighted to downstream years, with a p value of 0.007." A biostatistician said, "I would be worried that HRT would have a worse effect on younger, healthier women."

3. How can the WHI findings be translated into treatment decisions?

- **Women should not be taking hormones for long periods, even for hot flashes.** A WHI investigator said, "WHI says it is not appropriate to initiate HRT in older women as we were doing in the U.S…It removes (Prempro) from coronary heart disease prevention strategy." An Ohio OB/GYN said, "This is not just another study, and don't tell anyone it is."

***4. Did statin use affect the data?* No.**

Questions were raised as to whether statin therapy could have affected disease outcomes. A WHI investigator said, "Statin use was low in both groups, so it was not statin use that affected year 5 data."

5.How can the WHI findings be translated into treatment decisions?

- **Women should not be taking hormones for long periods, even for hot flashes.** A WHI investigator said, "WHI says it is not appropriate to initiate HRT in older women as we were doing in the U.S…It removes (Prempro) from coronary heart disease prevention strategy." An Ohio OB/GYN said, "Get informed consent if you prescribe hormone therapy…Stopping cold turkey is not well accepted and is like surgical menopause for many women. Consider tapering the dose with patches…Patches are a way to taper the dose, by cutting them into smaller and smaller pieces."
- **Doctors need to be certain to explain the risks to women and get signed consent forms if they do prescribe hormone therapy.** A WHI investigator said, "On balance, there was a tremendous emphasis on HRT as women went through menopause, and we need to provide informed consent to patients which wasn't done before."
- **Alternative medications can be dangerous.**
- **The use of estrogen to treat mood changes associated with menopause is not advised.** A National Institute of Mental Health (NIMH) official said, "In perimenopausal women who meet the criteria for clinical depression, estrogen has a beneficial effect on mood that may be separate from its effect on hot flushes…(and) a longitudinal study suggests that there may be increased risk of developing depression in some women at menopause…(but) efficacy (in treating depression) in post-menopausal women is unlikely, the duration of effect is unknown, the mechanism of effect is unknown, and the role of (estrogen) withdrawal in depression is unknown."

***6. Does the WHI data apply to other hormone therapy products?* Not directly, but other products have not been proven to be any safer.**

Only Prempro was tested in the WHI, and the CEE is a complex mixture of estrogens and steroids, and the medroxyprogesterone acetate is not a component of any other combination product. However, experts generally agreed that the findings have to be assumed to apply to all other hormone therapies unless and until those agents are proven not to have similar effects. A Wyeth official said, "We feel that from a clinical standpoint one cannot ignore the generalizability to other HT products." Another speaker said, "Based on the evidence available, the potential risk of breast cancer and

cardiovascular disease should be considered when prescribing postmenopausal hormone therapy products, regardless of the estrogen or progestin used, the route of administration or the regimen." An ACOG official said, "The WHI findings apply only to Prempro. (But) ACOG feels other regimens cannot be assumed to be safer or more effective."

The FDA appeared to agree that the WHI study raises questions about all HT products. An FDA official said, "The other products have Premarin wording in their labels, and they will not be able to drop the Premarin warnings until they prove a difference. We will assume similarity unless proven otherwise, but we do not plan to take HT off the market." This official also said there is no concern within the agency over the safety of oral contraceptives in light of the WHI findings. Another FDA official said, "The WHI toxicity findings are generally congruent with potential "class" effects of estrogen and progestin, (but) it is not possible to extrapolate the dose/toxicity findings directly to other related products...Quantitative extrapolation to similar products is not possible, though we can think of class effects."

A two day meeting of the FDA's Reproductive Health advisory committee was scheduled for November 11 and 12, 2002, but that has been cancelled. An FDA official said there will be no more meetings of that advisory panel for the remainder of this year. Apparently, the decision to cancel the scheduled panel came out of the acting commissioner's office, and a source described it as "a political decision."

7. *Is there still a role for hormone therapy to treat women with severe hot flashes during menopause?* Yes.

This is the one area where almost everyone agreed that there may still be a role for hormone therapy. Many experts said that HT is beneficial and should be considered for women with severe symptoms. An Oregon researcher reported on a review of the literature comparing the effect of different estrogens on hot flashes, saying, "The women with the most symptoms have the most relief…oral and transdermal estrogens are all effective in reducing hot flashes."

However, other experts urged women and their doctors to consider other options before trying hormone therapy. A biostatistician said, "We know estrogen reduces hot flushes. There are alternatives, but some symptomatic women may opt to try hormones first, instead of putting up with symptoms…Hot flashes are common and very variable, from a nuisance to debilitating. Usually they are transient; 30%-50% of women improve in a few months, and most resolve in two to five years…Hormone therapy is not appropriate for women with tolerable symptoms, but only a woman herself can judge how serious the symptoms are – and it depends on a woman's individual risks."

Before trying HT, some experts recommended women:

- Achieve and maintain ideal body weight.
- Regular physical activity.
- Stop smoking.
- Lower blood pressure, LDL and triglycerides; raise HDL.
- Keep a diary to assess triggers.
- Avoid spicy foods, caffeine and alcohol.
- Wear layered clothing.
- Keep ambient temperature low.

However, while many participants acknowledged these things help, they scoffed at them as unrealistic alternatives to hormone therapy. Thus, experts also discussed other pharmaceutical alternatives, and offered these assessments of possible therapies.

➢ **Don't work.** Numerous agents are being used for menopausal symptoms that **don't work very well** if at all, including: vitamin E, evening primrose oil, soy isoflavones, dong quai, red clover, naloxone, the beta blocker propranalol, ginseng, yam cream and Chinese medicinal herbs. An one expert said, "None have been shown to decrease vasomotor symptoms significantly better than placebo."

➢ **Don't work well.** Other agents **work but not as well as estrogen** in treating hot flashes including: progestins, androgens, tibolone, alpha-adrenergic agonists (clonidine, lofexidine, methyldopa – these all reduce hot flashes but can cause dizziness and other side effects), anti-dopaminergic agents (these are not FDA-approved), bellergal-S (ergotamine tartrate, belladonna alkaloids and phenobarbital – which reduce hot flashes but have a potential for addiction). An expert said, "Veralipride 100 mg per day reduces hot flashes."

➢ **May work.** Other things that may work but which have not been tested in clinical trials include: SERMS, mirtazapine (Organon's Remeron), gabapentin (Pfizer's Neurontin), black cohosh (which is approved and reimbursed in Germany), and Vitex (chasteberry).

➢ **Most effective.** SSRIs have been shown to substantially reduce hot flashes. Doctors in the audience did not appear to like this suggestion, noting that SSRIs have their own issues and side effects. A National Institute of Mental Health (NIMH) official said, "We've seen efficacy with venlaxafine (Wyeth's Effexor), paroxetine (GlaxoSmithKline's Paxil), fluoxetine (Eli Lilly's Prozac), sertraline (Pfizer's Zoloft)…but up to 23% of patients may experience sexual dysfunction."

FDA ISSUES

The key questions for the FDA right now with respect to HT are:

The implications for Prempro. However, an FDA official said there are no plans to order Prempro withdrawn from the market.

The implications for all combination estrogen/progestin products. An official said, "Wyeth has new data on the generalizability of the WHI findings that we will be reviewing. We think there are some class effects, and we've suspected that for a long time."

Future drug development. The FDA is struggling with future HT trial designs, and it did not get any direct guidance from speakers at this Forum. An FDA official asked for guidance, but no one was willing to offer advice. Another FDA official said, "A new estrogen would have to have two trials, with replication of the results. An estrogen that is not new but is using a different route of administration would need one trial…An indication for the prevention of osteoporosis would require a two-year, placebo-controlled trial, typically with 150-300 patients." While the FDA studies the WHI data, sources said it is unlikely to approve any new trial protocols of other products in the category.

The FDA is considering holding a public advisory meeting, but timing has not been decided. Among the areas that are likely to be affected by WHI are:

- Current product labels. The Prempro and Premarin labels already have been changed to incorporate a warning. An FDA official said, "What about others? What should their label look like? Are there more label changes that need to be made? None of that is decided yet."
- Trial lengths. The FDA is considering a change in the length of trials to better assess safety.
- Trial size. A change in the number of required patients in trials is being considered.
- Generalizability of the WHI results. The FDA is considering whether and how to apply the lessons form WHI to other products, particularly as relates to composition and dose.

The FDA also has questions about:

- Prevention indications. An official said, "We need to be assured of a positive benefit/risk analysis in people without symptoms."
- Relationship of dose or duration to toxicity.
- Relationship of route of administration to toxicity. An official said, "Orals go through elaborate metabolism and have a very different PK profile than transdermal, and we don't know at this point how that impacts the risk. That is a burning question."
- Maximizing benefits by selecting patients who are at a higher chance of benefiting (e.g., women with more severe menopausal symptoms or women at a higher risk of osteoporosis.

Other experts also generally agreed that the findings raise questions about all HT products. A WHI investigator said, "These data do not apply to other doses, formulations, or routes of administration (e.g., patch)…(but) it cannot be assumed that other formulations will have different outcomes." An Oregon researcher reported on a review of the literature comparing the effect of different estrogens on hot flashes and said, "We found progestins did not influence the effect…higher doses have increased effect but may have more side effects…both oral and transdermal delivery systems have similar effects but were not compared head-to-head…the effectiveness is comparable between agents, and the addition of progestin does not influence effectiveness."

For some women, a SERM -- i.e., Eli Lilly Evista (raloxifene) -- is an alternative to HT for treating or preventing osteoporosis, but the WHI findings have frightened some women away from SERMS as well as HT. A speaker said, "We need to ask patients if they are stopping medications. We find they are stopping their SERM too because they think it is an estrogen. So we have a big education job ahead."