'Time to Move Forward' on Hormone Therapy

The Women's Health Initiative study had its limitations, according to Dr. Leon Speroff.

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LA JOLLA, CALIF. — It's time to rekindle enthusiasm for postmenopausal hormone therapy, Dr. Leon Speroff said at the annual meeting of the Association of Reproductive Health Professionals. "In my view, postmenopausal hormone therapy is in a stalled position and it's time to move forward," said Dr. Speroff, professor of obstetrics and gynecology and reproductive endocrinology at Oregon Health and Science University, Portland.

"The initial negative impact of the Women's Health Initiative is over, we know the study's limitations, we know that some of the conclusions promoted in the media were not correct, and we know that the risks that have been promoted by the Women's Health Initiative are incredibly small and perhaps not real," Dr. Speroff said in an interview.

Dr. Speroff pointed out several problems surrounding the WHI, including diagnostic and selection biases, high drop-in and drop-out rates, poorly presented media reports, sound-bite interpretations by "experts," epidemiologists giving clinical advice, and the writing of position papers by various medical organizations that, in Dr. Speroff's opinion, "were profoundly influenced by medical-legal fears."

While data from the WHI suggested that estrogen with progestin increased the risk of breast cancer, Dr. Speroff said that he believes the therapy may actually be beneficial when used early in menopause. He said that his suspicion was fueled by paradoxical findings from worldwide observational studies showing that while hormone users had an increased risk of breast cancer, they had reduced risk of mortality.

One explanation was that hormone users had more mammograms and their cancers were detected earlier. Subsequent studies corrected for this, looking only at women who were having mammography, and reports emerged documenting that estrogen-receptor positive hormone users who developed breast cancer had lower-stage, lower-grade disease, said Dr. Speroff, a consultant with Warner Chilcott, which markets Femtrace, and a recipient of research grants from Wyeth, Organon USA Inc., and Barr Laboratories Inc. "That struck me as the answer to the apparent paradox … that what we are seeing is earlier detection of less-aggressive disease, and thus the tumors of hormone users have better outcomes."

However, surgeons at the University of Utah, Salt Lake City, have given Dr. Speroff a different explanation: "They argued that mammography doesn't detect the tumor itself … that imaging detects the stromal reaction around the tumor and … that hormone exposure causes differentiation of the tumor and slower growth, allowing more time for the stromal reaction and thus earlier detection."

In any case, he added, both explanations add up to earlier detection. "All the studies find the increased risk fast, and it takes about 10 years for a malignant breast cell to become clinically detectable. Every single study has found the increased risk only in current users. After discontinuation, the risk returns to baseline and, to this day, not a single study has found an increase in hormone users in noninvasive, in situ disease," Dr. Speroff said at the meeting.

Dr. Speroff added that the latest report on breast cancer from the WHI was issued this summer, and for the first time, all of the risk factors that influenced breast cancer had been taken into account and adjustments had been made. "The increased overall risk of breast cancer in the canceled estrogen-progestin arm after adjustments is no longer statistically significant," said Dr. Speroff, adding that in the updated results, patients who adhered to treatment throughout the study had a significant reduction in the risk of breast cancer.

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Exposure to estrogen and progestin may result in earlier detection for breast cancer patients, said Dr. Leon Speroff.

Physicians are warned, however, not to automatically conclude that the difference in results in the two arms reflects the effect of progestational agents, because the participants in the two arms were not identical.

"In terms of both cardiovascular disease and breast cancer, there are major differences comparing the two arms, and therefore it's not appropriate to conclude that the difference represents a progestational effect," he said. "So where we are today with breast cancer is we're not sure whether there truly is an increased risk or whether we're seeing an impact on preexisting tumors, and the possibility remains that exposure to estrogen and progestin may actually be beneficial, causing greater differentiation and earlier detection and better outcomes."

Dr. Speroff continued, "I tell clinicians that until we have definitive randomized trial data—which we may never have—whatever the patient wants to do is the correct decision. It takes about 10 minutes talking to a patient to know what she wants. However, it's important to point out to her that in case series involving over a thousand patients, whether your tumor receptor was positive or negative, it didn't make any difference."

Out of the controversy over the link between hormone therapy and coronary heart disease (CHD) there has emerged a theme, or hypothesis, that it takes healthy cardiovascular endothelium to have a maximal beneficial response to estrogen exposure, continued Dr. Speroff.

For example, in the Nurse's Health Study, which looked at conjugated equine estrogens plus medroxyprogesterone acetate vs. placebo in more than 1,660 women, the only statistically significant reduction in CHD occurred in women who began estrogen early in their postmenopausal years, with no difference between the two treatment arms, he said.

At adjudication of WHI data, Dr. Speroff added, 10% of the coronary diagnoses were changed and CHD was no longer statistically significant—facts he said received no publicity whatsoever. "The only significant increase in coronary events in the WHI estrogen-progestin arm occurred in the women who were 20 or more years away from menopause; these were the oldest women in the study [N. Engl. J. Med. 2003;349:523]. When you subtract that group of women, there was no increase in coronary events … and after adjudication there was no increase in coronary disease in the estrogen-only arm [Arch. Intern. Med. 2006;166:357]. The WHI reported this as no beneficial effect, but if you read the report carefully, I believe you can find supporting evidence for a primary prevention effect" from hormone replacement.

Dr. Speroff concluded, "If there's one thing that's not going to change in coming years, it's the media, and it's time we become active in objecting to this policy where the major journals provide the publications to the media before they become available to you and me and the public. It's time that, as organizations and individuals, we begin to protest this particular policy."

Dr. Steven Goldstein, who described himself as being "in the middle" on the issue of hormone therapy, agreed with Dr. Speroff.

"Some major journals [reporting WHI data] were in a frenzy to get air time," Dr. Goldstein, professor of obstetrics and gynecology at New York University, said in an interview. Broadly speaking, reporting on the initiative represented a failure to educate the public on the difference between relative and absolute risk, he said.

"In this era of evidence-based medicine, people glom onto the randomized, controlled trial as being the gold standard of clinical evidence, and it should be. However, if you do that, you'd better be sure that the patient sitting opposite you in the consult room is exactly like the women in the study; otherwise, the results are not necessarily relevant," he said.

"However, what Dr. Speroff has done I think is try to reslice the deck and reanalyze the statistics, which is no more valid than what he's accusing the WHI of doing," said Dr. Goldstein, adding that he would rather get patients and physicians to recognize that "the 51-year-old woman who has 15 hot flashes a day and can't sleep can be helped with preparations that are not the same as those tested in the WHI, and that extrapolation from the WHI is unfair and inappropriate."

Dr. Goldstein added that the information coming out of adjudication is not very valuable if suddenly "there's one less case so it's not statistically significant, or one more case and it is. That's tenuous information when you have thousands of people involved and people are fallible; so you're obviously dealing with a situation that is not clear cut."

He said that the "pretty significant difference between the two arms of the WHI study" supports an epidemiologic study of over 46,000 postmenopausal women, in which those taking estrogen plus progestin were at greater risk for breast cancer compared with women taking estrogen alone (JAMA 2000;283:485-91).

"And the Million-Women study in England, whose flaws were somewhat overcome by the sheer number of women involved, showed three times as much breast cancer with estrogen plus progestin as with estrogen alone. And that wasn't just Prempro; that was any formulation," Dr. Goldstein explained (Lancet 2003;362:419-27), adding that women are being overtreated with progestogen in an attempt to prevent uterine cancer. "If you look at the literature, unopposed Premarin for 6 months results in simple hyperplasia in 7% of women. We're treating 100% of women with a uterus to protect seven."

Dr. Speroff's proposition that hormone therapy may actually protect women by causing greater differentiation and earlier detection "is an incredibly interesting hypothesis, but I can't in good conscience tell my patients that they should therefore take hormone therapy because if they're destined to get breast cancer this is going to make early detection more likely and improve their survival. I hope that's true, but it's not going to be my motivation for hormone therapy," Dr. Goldstein said.

When asked to comment on Dr. Speroff's presentation, Dr. Wulf H. Utian, president of the North American Menopause Society, said, "In many ways I agree with what Dr. Speroff says. As huge as the WHI was, it was not a gold standard study. The bottom line is that we really need to be more reasonable and less emotional about hormone therapy." ■