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Quick Pulse

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ESTROGEN REPLACEMENT THERAPY FOR MENOPAUSE: HOW DOCTORS AND PATIENTS ARE REACTING

Eleven obstetricians/gynecologists and family practice doctors were interviewed to determine the initial reaction of doctors and patients to the news that the National Heart, Lung, and Blood Institute (NHLBI) has stopped the estrogen-only (ERT) arm of the Women's Health Initiative (WHI). Neither patients nor doctors appear very concerned, and little impact on estrogen use is expected.

On May 31, 2002, NHLBI stopped the combination estrogen/progestin (Wyeth's Prempro) arm of this same trial, citing an unacceptably high incidence of cardiovascular disease and invasive breast cancer. The estrogen-only arm (Wyeth's Premarin) was stopped in March 2004, due to an increased risk of stroke.

The WHI trial was a three-arm, randomized, controlled primary prevention study of women between the ages of 50 and 79, with a mean age of 63:

- Wyeth's Premarin (0.625 mg/day estrogen) – hysterectomied women (without a uterus)
- Wyeth's Prempro (a single daily tablet containing 0.625 mg/day estrogen plus 2.5 mg/day medroxy-progesterone acetate) – 8,506 women with an intact uterus
- Placebo – 8,102 women with an intact uterus

The trial was designed to run for 8.5 years, but on May 31, 2002, the arm with Prempro – a fixed-dose combination of Premarin and Cycrin (medroxy-progesterone acetate) – was stopped, after a mean of 5.2 years (range 3.5-8.5 years). The data safety monitoring board (DSMB) cited unacceptably high adverse events. The Premarin and placebo arms of the WHI trial were allowed to continue.

The National Institutes of Health (NIH) is now advising the 11,000 health post-menopausal remaining women in the trial to stop taking their study drug. Researchers reported that after an average of nearly seven years of follow-up, estrogen alone:

- Does not increase or decrease heart disease, which was a key question of the study.
- Increases the risk of stroke. The increased risk is similar to what was found in the Prempro arm, in which there were eight more strokes per year for every 10,000 women on Prempro compared to than those taking the placebo. On its website, the NIH notes, "The NIH believes that an increased risk of stroke is not acceptable in healthy women in a research study. This is especially true if estrogen alone does not affect (either increase or decrease) heart disease, as appears to be the case in the current study."
- Decreases the risk of hip fracture.

When the Prempro arm of the WHI trial was stopped, doctors were swamped with calls from concerned patients, many of whom demanded to be taken off hormone replacement therapy (HRT). Some doctors even had to set up special telephone lines and dedicated voice mailboxes to handle the deluge.

In contrast, the news about estrogen is not generating many calls to doctors' offices. A Massachusetts doctor said, "So far, I haven't had patients calling to talk about or stop their estrogen therapy." A Georgia doctor said, "The furor has pretty much died down." A California doctor said, "They don't really call a lot. They go off it on their own and then let you know. The recent reports may make a few women reconsider, but not a lot of calls are expected. Breast cancer risk is more important than the stroke risk. Younger women don't worry about it, but patients on therapy 10+ years do." Another West Coast doctor said, "I've only gotten one phone call this time as compared to two or three weeks of calls (with HRT). It's been a very common conversation in the office regarding whether patients should go off estrogen. Calls may pick up a little, but I think this halt of the study has had much less press. It also didn't have much in terms of findings. In fact, most believe the good news – no increase in breast cancer or heart disease – by far outweighs the bad." An Arkansas doctor said, "I've had some calls, but it is not as bad as when the HRT data was released."

Most doctors do not expect the new WHI announcement to have a significant impact on their use of estrogen.

- A Georgia doctor said, "It probably won't affect my use; it's already pretty low these days."
- A California doctor said, "It won't have much impact in my practice…(but) it will add more fear to the general population because of media reporting."
- Another California doctor said, "It will have much less impact than the stopping of the combination arm of the trial."
- A Missouri doctor said, "The important thing is…how women will react to the news…The issues are confusing – future risks vs. current symptoms."
- An Iowa doctor said, "I don't intend to change my approach (or lack of it) to estrogen."
- An Indiana doctor said, "I don't expect it to have any impact."
- A Michigan doctor said, "The impact won't be huge. Remember that this regimen is used only by women without a uterus, which is not a large portion of the population concerned."

In fact, some doctors considered the findings to be "good" news. A Texas doctor said, "This is wonderful news! No increased risk of breast cancer or heart disease on estrogen alone. That's terrific." An Arkansas OB/GYN said, "It will have very little impact. We knew ERT was not cardio-protective, and we suspected it reduced fractures. While the fact that it increases strokes is bad, the fact that it didn't increase breast cancer was good. I think these cancel each other out. The FDA already recommends limiting the length of ERT treatment to be five years or less with a switch to other osteoporosis prophylaxis after hot flashes are reduced, so this doesn't suggest a big change in current recommendations."

Despite the new WHI findings, doctors do not expect to see much decline in their use of estrogen in the near future. On average, 36% of these doctors' menopausal patients are currently on either ERT or HRT. In one year they estimated that an average of 32% of their patients would still be on either ERT or HRT. A doctor said, "A lot of my patients who stopped HRT because of the previous study re-started it because their quality of life was worse secondary to hot flashes…I try to decrease dosages now and stop HRT/ERT when their hot flashes are gone. Also, patients with risk factors for heart disease are only started after discussion and informed consent. Any medications we take have risks involved, and only with individualizing the treatment to the patient will we keep the risks to a minimum. Remember that estrogen is the best medication for the reduction or cessation of hot flashes, which bother a segment of post-menopausal women." A New England primary care doctor said, "I'll still prescribe estrogen for menopausal symptoms. It is still very much indicated for that." A Texas gynecologist said, "Women can now continue to take estrogen and just be monitored for endometrial hyperplasia – taking progesterone only every six months!" A California doctor said, "I will still prescribe estrogen – just at a lower dose." An Arkansas doctor said, "The findings won't have any impact because the safety with breast cancer evens out the stroke risk. I will counsel patients about the stroke risk, but the patients may be more concerned."

The findings also aren't having much impact on which estrogen products doctors prescribe, though it is reinforcing the use of lower dose estrogens. A Georgia OB/GYN said, "My prescribing patterns have changed over the last two years and probably won't change much more." A California OB/GYN said, "I use a lot of patches already. It is a good option. Every few months, I'm finding myself targeting lower and lower doses of estrogen." A New England doctor said, "Before I make up my mind what to do, I need to see the study data. What laypeople and the media forget or do not understand is that the rates presented are population rates, and the increase is the number over what normally occurs in the population…For every 10,000 women taking HRT, there were eight more strokes per year than for women on placebo. This is reported as a relative risk of 24% – namely 38 cases per 10,000 women rather than 30 cases per 10,000 women. The individual risk for a blood clot or stroke from HRT is each about $1/10^{th}$ of 1%." An Arkansas doctor said, "I possibly will use more lower dose ERT."

Some doctors see the results as a statement on Wyeth's Premarin only – not all estrogens. A California doctor said, "That's already happened. We use human identical

replacement, bio-identical forms, and the lowest dosage." A primary care doctor said, "I prefer topical and bio-identical hormones. I've never been a fan of Premarin, which is what this was a study of. This was **not** a study of estrogen replacement; it was a study of Premarin – conjugated estrogens."

However, doctors do see a long-term impact on hormone replacement therapy – estrogen or combination estrogen/ progesterone.

- A Massachusetts doctor said, "There's already been a long-term effect."
- A Georgia doctor said, "I expect a long-term effect, or at least an impact until a new study comes out or the hot flashes really get to too many women!"
- A California doctor said, "It remains to be seen. It depends on what other research comes up. The statistics aren't that impressive and don't come close to showing a causal relationship."
- A West Coast physician said, "I think that the collection of the many articles that have been published recently regarding estrogen therapy will have a long-lasting effect. This one problem has had the least effect, but it will be great news for, especially, hysterectomied patients who don't need a progestin."
- An Arkansas doctor said, "This isn't very big news. There will be little change, and only a temporary reaction. The big news we are all waiting for is the studies that will be out soon that will determine if Evista (Lilly, raloxifene), an osteoporosis prevention drug, really does decrease breast cancer and heart disease. If the preliminary data is confirmed by the ongoing large studies, then there will be a major change in the way we practice medicine."
- A family practice doctor said, "Hopefully, there will be a drive to look at other formulations to see their effects."
- Another family practice doctor said, "There will be long-term changes in views, as before. Remember, this is an issue for long-term post-menopausal use. It doesn't really affect decision-making for short-term perimenopausal use."

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