Trends-in-Medicine

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SUMMARY

The government's decision to terminate the Prempro arm of a major clinical trial has women worried, and they are being inundating their doctors with telephone calls. Many want to stop HRT, and doctors seem to agree – especially for women who have been on it for a long time. Doctors will still recommend HRT for some new patients whose symptoms are severe, but mostly for short periods of time. The outlook is for HRT use to drop drastically, perhaps as much as 50% over the next year. This is generally viewed as a class problem, and Wyeth's Premarin and Prempro are likely to decline in proportion to the overall market. While this is not a short-term problem, most sources do not believe it will become the litigation nightmare like the Dalkon Shield and silicone breast implants.

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Hormone Replacement Therapy

Seventeen doctors (10 obstetricians/gynecologists and 7 family practice doctors) as well as 9 menopausal women were interviewed to determine how doctors and patients will react to the news that a major clinical trial was halted by the National Heart, Lung, and Blood Institute (NHLBI). The trial, a component of the Women's Health Initiative, was a primary prevention study of hormone replacement therapy (HRT). Subsequent to these interviews, a National Cancer Institute study reported an increased risk of ovarian cancer in women with at least one ovary who have had a hysterectomy from taking estrogen.

THE TRIAL

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

- Wyeth's **Premarin** (0.625 mg/day estrogen) – women without a uterus
- Wyeth's **Prempro** (a single daily tablet with 0.625 mg/day estrogen plus 2.5 mg/day medroxyprogesterone 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 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."

WHI Results as of April 30, 2002

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

Source: Journal of the American Medical Association

Doctors believe this is a valid trial, and most are not disputing the results. A Washington DC OB/GYN said, "Relative risk talk is scary, but absolute risk is what's important, and it's low. But I respect NIH and we were all looking forward to the results of the WHI study in a couple of years. When the powers that be are concerned enough to stop the study, I stand up and listen." A California OB/GYN said, "In many ways this is not new information, but this is the first prospective, well-designed study that is scientifically valid." A Colorado family practice doctor said, "The report is important and will affect how we practice. The study just adds additional data to what we already knew."

However, several doctors criticized the media for highlighting the increase in relative risk without explaining that the absolute risk is still extremely low. A Colorado family practice doctor said, "In all of the media frenzy, it seems lost that there was no difference in overall mortality." A Wisconsin family practice doctor said, "The media has been focusing on the negative effects and not talking much about the reduction in fractures or colon cancer. It was a good study, but the investigators stopped it early because of the risk/benefit balance, but women might come to a different judgment. I don't quarrel with the values, but the take-home message is that an early and ongoing relationship with your family doctor is important."

A few doctors also are skeptical of the findings. A Florida OB/GYN said, "The data is still conflicting. In 10-14 days, you will see reputable professors raising issues about this study, and part of that will be that patient selection was done in a way that introduced bias." Another Florida OB/GYN said, "The average age in the trial was 63, and my average patients is 45-50 years old." An Illinois family practice doctor said, "It's odd that we've been promoting the cardiovascular benefits of HRT with documented studies for many, many years, and one study negates it all. A large number of studies put the breast cancer risk (with HRT) at less than 4% in the past. Now, this study claims that the risk is greater than 20%. Only time and further studies will tell what will happen."

Patient Reaction

Women are very concerned. Seven of the nine menopausal women on HRT said they plan to stop taking their hormones; two are continuing. Another woman who was about to start HRT said she now will *not* do that.

- A 75-year-old woman in Maine who has been on HRT for more than 30 years said she is stopping it as soon as she gets back from vacation, "I was already worried about the tissue changes that showed up on my mammogram. My doctor said they were due to the Prempro but nothing to worry about. It's time for me to stop the hormones."
- A 55-year-old woman said, "I've been taking HRT more than 10 years, and Prempro most of that. I sailed right through menopause without any symptoms at all. I think it's time for me to regain control of my body. I'm calling my doctor now."
- A 50-year-old Florida woman said, "I decided to stop my HRT after the first news broadcast. I'll talk to the doctor about taking Fosamax (Merck, alendronate) for my bones, I guess."
- Another woman said, "I've been taking (Pfizer's) FemHRT (ethinyl estradiol, norethindrone acetate) since June 2000. My doctor wanted to put me on it in January 2000, but I resisted. I finally let her talk me into it, but mainly because I could not find any other method to get rid of my hot flashes, which were driving me crazy. I plan on quitting in the next year or so because of the risks."
- A fifth said, "I've been using the Vivelle (Novogyne) estrogen patch since 1988, and I don't plan to stop. I love the way I feel now, and it helped increase my HDL (cholesterol). If my doctor gives me any grief (about continuing), I'll shop for a new doctor."

The concern over HRT is not limited to women with an intact uterus who are taking combination estrogen/progesterone. A hysterectomized woman on estrogen alone said, "I've been taking Premarin since 1992. I tried going without it, and my hot flashes and night sweats were terrible. I have 21 tablets left, and I will finish them slowly over the next two months and not go back on. I would much rather live with hot flashes and night sweats than have an increased risk of cancer or heart problems." Another commented, "I'm trying to get off my estrogen pill. I had already cut my dose in half two weeks ago. Now, I'll stop."

In fact, doctors' phones have been ringing off the hook. Most doctors reported they have been swamped with telephone calls from anxious patients. In fact, some have set up special telephone lines, arranged a dedicated voice mailbox with a canned message, prepared scripted responses for their staff, and sent fax or mail messages to patients. A Louisiana doctor said, "The media reports are creating a lot of fear and confusion. Women have a strong fear of breast cancer." An Illinois doctor said, "The study and the publicity are scaring the devil out of women and creating distrust with their physicians who have been extolling the benefits of HRT for years." A Maryland doctor said, "I've had a lot of calls. Even my mother called. Women in America are terrified of breast cancer." A Florida doctor said, "I've been inundated with calls. Women are hysterical."

Most doctors are telling their callers to make an appointment to come in and talk about it. A Florida doctor said, "There is no blanket answer. The pros and cons dramatically fluctuate by patient. I'm telling them we have to sit down with their chart, look at how long they've been on HRT, look at their risk factors, etc." A California doctor said, "I tell them to come in to discuss it. It's too much to do over the phone."

Advice for Existing Patients

The WHI trial and resultant publicity will make doctors more cautious about prescribing HRT and cause them to counsel patients more carefully. A Florida OB/GYN said, "Ninety percent of women are on hormones for symptom relief, and

those patients are willing to accept some risk. But I will do more intensive discussions with patients about it." A Maryland OB/GYN said, "I told my mother to stay on it. Overall, mortality is not worse with HRT. But I will change the way I counsel women a little to make it clearer that there is an increased risk of breast cancer and heart disease, that we are treating the symptoms and how they feel." A California OB/GYN said, "Other than hot flashes, HRT may not be useful at all."

OB/GYNs generally are recommending that women who have been on HRT for a long time go off of it. A Maryland doctor said, "If a woman has been on HRT for over five years, we need to think why she is taking it." A Massachusetts doctor said, "I'll stop women who have been on HRT for a long time." A California doctor said, "For women on HRT for many years, the evidence to continue is just not there." A New Hampshire doctor said, "There is no blanket answer. I won't recommend stopping; it will be a joint discussion, and how long they've been on will be a factor." A Washington DC doctor said, "If 100% of my patients want to stop, they have my blessing because it doesn't do them or me any good if they won't take it. It's worth testing to see if they can go off without unacceptable symptoms."

Many family practice doctors are taking an equally, if not more, conservative approach. An Oklahoma doctor said, "I'm advising my patients to stop HRT if they have been on it a long time…The study has reinforced my position that I really don't think long-term HRT use is ideal management." An Illinois doctor said, "I'm telling my existing patients to stop HRT and will only continue therapy if the patient refuses to stop…My HRT prescribing will decrease drastically. There would be too great a liability not to do so." A Louisiana doctor said, "I will no longer recommend combination (estrogen/progestin) products for long-term use in post-menopausal women." A Pennsylvania doctor said, "I'm not trying to convince women to stay on HRT if they want to get off. Before, HRT was offered to women unless there was a reason not to offer it, and now I am shying away from that approach. Women have always been somewhat leery of HRT generally. I used to have to be something of a salesman to get them to start it, and you have to really believe in something to sell it, and I'm having trouble believing in HRT now for long-term use."

Advice for New Patients

Most doctors expect to continue to prescribe HRT to new patients for symptomatic relief of menopausal symptoms – hot flashes, sleep disturbances, moodiness, vaginal dryness, etc. However, most plan to use shorter courses of therapy.

OB/GYN comments:

- "If someone comes in who is just menopausal and the hot flashes are severe, I am not averse to suggesting HRT for months or up to a year maybe to help with symptoms, but I won't advise them to continue for a long time."
- "There won't be any change in my advice, but women will be nervous about starting HRT."
- "I certainly still will put women on HRT – more for symptom relief in the short term, with frequent reassessments at set intervals. Nothing else helps menopause symptoms as well. Other things can be done for osteoporosis prevention and vaginal dryness but not much else helps other menopausal symptoms."
- "If a patient has bad hot flashes, and in past she would say thank you for the HRT. Now, she may refuse. It won't necessarily be me but the patient who makes the change."
- "New patient starts will be harder to do. Patients will be reluctant to take HRT. They will come to the office very symptomatic with hot flashes and perhaps agree to treatment, but there is a big gulf between leaving with a prescription and going to the pharmacy and filling it."

Family practice doctor comments:

- "I haven't added any new patients since the announcement. If patients ask for HRT, I will discuss short-term use with them."
- "For many women, HRT has been extremely beneficial, so taking it away solely on the basis of this study would be wrong."
- "I probably will do a start and stop approach. There is no science behind that idea, but I think that is the approach I will take. One belief that women have clung to that has not served their health well is the consuming fear of breast cancer. If I ask a woman what she is most afraid of it, it is always breast cancer…If mortality is the risk you worry about, there are a lot of things to be more worried about than breast cancer."
- "Patient preferences might change, but my recommendation won't."

The Outlook for HRT Use

Doctors predicted the number of women on HRT will decline drastically over the next year. Even doctors who have been fairly conservative in their HRT use predicted huge drops in HRT prescriptions going forward. A Washington DC OB/GYN said, "Initially, HRT use will be down about 30%, but over time it will recover about half of that."

Outlook for HRT Use

Specialty	% of menopausal women on HRT Now	in 12 months	% change
OB/GYN	63%	35%	Down 44%
Family Practice	50%	21%	Down 58%
Total	57%	28%	Down 51%

A Schering AG official estimated that 40% of HRT prescriptions are written by OB/GYNs and 60% by family practice doctors. Though a sharp decline in HRT use will

occur among both OB/GYNs and family practice doctors, the drop may be greatest among family practice doctors.

- An OB/GYN said, "Primary care physicians (PCPs) need to see a lot of patients in a short time, so they only have a few minutes with each patient. The discussion of estrogen has crept into that 15 minutes, and you can only discuss so much in 15 minutes. Estrogen was part of that 15 minutes, and every PCP felt obligated to discuss it, and now they will feel less obligated to discuss it. PCPs will be the first casualty in hormones. Many doctors also will be worried that if they prescribe hormones, they might get sued, so they will be less proactive unless some national medical bodies come in and provide 'cover' by putting in black and white when HRT could or should be used….Because of the malpractice environment, doctors now will have to take a lot more time, write a note in the chart, discuss the risks. In the past, doctors may have felt obligated to give estrogen to prevent cardiovascular disease. Now, they would be prescribing a pill to make her feel a little better but she runs the risk of developing five to seven serious diseases that she will blame you for getting. So, doctors will be gun-shy and say, 'Why should I prescribe something that can come back to haunt me?'"
- A family practice doctor countered, "Family practice doctors have a better opportunity to take time with patients than OB/GYNs do. We see the women more often, not just once a year for a Pap smear, but in the office and in the community. And because we share decision making more than some OB/GYNs, we are less likely to be sued than specialists. Unless a slick lawyer is able to get an inherently dangerous product claim on a national level, these cases will turn on informed consent, and I think family doctors do as good a job as any on that."

An international position paper on HRT is expected soon, but it will not have the data from the WHI study, so it is unlikely to provide doctors with the guidance they would like on HRT use. The American College of Obstetricians and Gynecologists (ACOG) set up a task force to study this issue and make new HRT clinical practice recommendations, but it will be at least several months before that is ready.

The drop in Premarin and Prempro use is expected to decline in proportion to the overall reduction in HRT use. Some doctors are blaming the combination of estrogen and medroxyprogesterone, but most suggested the culprit is the medroxyprogesterone, which they identified by the brand names Prempro (Wyeth) or Provera (Pharmacia), another medroxyprogesterone. A few also are blaming Premarin by name. A Florida doctor said, "The problem is Premarin and Prempro, not the estrogen. What this study does is implicate progesterone as not beneficial." A New Hampshire doctor said, "Provera appears to be the problem." A Georgia doctor said, "This is only a Prempro issue." A New England doctor said, "Some people feel the progestin is the major culprit, but I think the estrogen is involved as well." A California doctor said, "The study shows that Prempro is a uniquely bad agent, and there is a lot of data that Provera is not a good agent." A Midwest doctor added, "I won't drop Prempro, but I will talk to women about the issue of progestin. The advantage of Prempro is that it is easy and on formularies."

Generally, doctors consider the issue to be a class effect, applying to all progestin/progesterone products, so few doctors plan to switch to alternative hormone products. A Pennsylvania family doctor insisted, "I will not switch medications." A Georgia OB/GYN said, "I will drop Provera for Prometrium (Schering AG, natural micronized progesterone)." A Florida OB/GYN said, "I'll use more of FemHRT." A Massachusetts OB/GYN said, "I may use an estrogen patch for a couple of months and then add a progestin other than Provera." Another doctor said, "You can speculate that the Prempro arm got in trouble because of the Provera, but if you give Premarin without Provera, you run the risk of uterine cancer. You might use a different progestin, such as Prometrium, but there are no studies that show this is better; it's just speculation. In this climate, I don't think many doctors are going to recommend that the risk will be lower by taking Premarin and Prometrium as two different pills. The scenario that only Prempro caused the problems won't fly. Companies may try to distance themselves from Prempro, but it will be their responsibility to prove their risk/benefit profile is different. I don't think they can say this is only a Prempro effect. They'll try to say it, but I'm not sure patients will buy that."

This decline in HRT use is not likely to be just a tempest in a teapot or a short-term issue. Sources predicted that this study will have a long-term impact on HRT use. A Midwest doctor said, "This is a long-term issue. Who would enter into a study now that could potentially increase their risk for heart disease and cancer? Use of HRT will drop off dramatically." A Louisiana doctor said, "This is a complete reversal of thought and recommendations, with long term implications." Another doctor said, "There will be a flurry of articles in all the popular magazines. This is not going to go away in 24 hours. This will be discussed over and over again in women's magazines and national publications for some time to come. So, our patients will be so bombarded with risks and complications that many will stop on their own and few will start – or they may start in the dead of night without telling their friends."

There have been some suggestions that HRT may become a major source of litigation, and attorneys already are planning advertising to locate women who may have had adverse events while on HRT. An OB/GYN said, "There will be a huge reaction for a few months and probably a slight decrease long-term in the HRT market. This could be like the Dalkon Shield." Another OB/GYN said, "Why should a doctor go out of the way to take the risk of a patient developing something just to get rid of hot flashes. They will say tough it out, take soy, call in three months, etc." A family doctor said, "This will be a long-term issue. It won't be like the Dalkon Shield, but there will be significant decrease in use." Another family doctor said, "There will be a cloud over HRT use, but it isn't likely to become a silicon breast implant-type issue because the women won't be 'worth enough' to the lawyers."

Some other products may benefit from the decline in HRT use, particularly osteoporosis treatments like Eli Lilly's Evista

(raloxifene, a SERM) and Fosamax. A Louisiana doctor said, "Many women will choose to switch to a SERM for (osteoporosis)." A Maryland doctor said, "For bone, I'll tell patients to take alendronate or something like that. For their heart, I'll tell them to amend their lifestyle." An Oklahoma doctor said, "I may use more Evista."

Newer, lower-dose formulations of existing products that are in development are not viewed as a solution to the problems raised by the WHI study, but some OB/GYNs indicated they are likely to use them. A Maryland OB/GYN said, "They should do well. People will try the lower dose first. Patients won't request it, but doctors will suggest it." A California doctor said, "Any time you reduce the dose, you reduce the risk – but you can reduce the dose now. And I don't expect patients to request this." An Oklahoma doctor commented, "We always use the lowest dose available, but my guess is that low-dose formulations will have a hard sell with doctors and patients."

Family practice doctors were even less enthusiastic about the outlook for lower dose progesterone products. A Pennsylvania doctor said, "That might be appealing. It is rational and predictable – but it may not prove true. It will appeal to some doctors and some patients, but we don't know for sure if it makes a difference." A Maryland doctor said, "I suspect a lower does Prempro will not be looked on very favorably. It will not be viewed as a better alternative, and patients won't request it." An Illinois doctor said, "It won't be seen as a better alternative. The study didn't address whether the side effects were dose-related or if they were related to the mediations themselves. The public will surely view it as related to the medications themselves. Patients won't ask for this once they hear about the WHI study."

Schering AG hopes to differentiate its new HRT, Angeliq -- which is on the market in Europe but not yet approved by the FDA – from Prempro. The company claims that Angeliq is a different estrogen molecule, and the progestin in it interacts differently with the receptor site. However, doctors were dubious. One said, "Any hormone replacement will face a harder time and have a very difficult time convincing the public and the medical community of any potential benefits." Another commented, "Angeliq will face a harder time now." A third said, "Angeliq would do great if it had a tremendous study, but it won't have that, so it will be hard to market it." Another said, "Angeliq should do okay once people understand this is a Prempro study and doesn't translate to other progestins." ♦

Estrogens	Estrogen Patches	Progesterones and progestins	Combination Estrogen/Progestin
Wyeth's Premarin	Novartis' Estraderm	Pharmacia's Provera	Wyeth's Prempro and Premphase
Mead Johnson's Estrace	Berlex's Climara	Wyeth's Cycrin and Avgestin	Novartis' CombiPatch
Duramed's Cenestin	Novogyne Pharmaceuticals' Vivelle and Vivelle Dot	Pfizer's Norlutate	Pfizer/Duramed's FemHRT
Fielding's Gnodiol	Pfizer's Fempatch	Johnson & Johnson's Micronor	Johnson & Johnson's Ortho-Prefest
Abbott's Ogen	Women First HealthCare's Esclim	Schering AG's Prometrium	Pharmacia's Activella
Solvay's Estratab	Theratech's Alora	Generic MPA and generic progesterone	
Monarch's Menest			
Compounded Tri-Est and Estriol			