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A pioneer in menopause research, Dr. Utian founded the world's first menopause clinic in Cape Town, South Africa, in 1966 and established the Cleveland Menopause Clinic in 1983.

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Managing Menopause After HERS II and WHI: Coping With the Aftermath

Barely was the long-awaited follow-up of the HERS study published,^{1,2} than the National Institutes of Health (NIH) dropped its bombshell of discontinuing the trial of estrogen plus progestin (E+P Trial) in women with an intact uterus in the Women's Health Initiative (WHI).³ Since then, there has been much water under the bridge, but let's try to consider "Where to now?"

To summarize the data, out of HERS II the conclusion on coronary heart events was that "postmenopausal HRT should not be used to reduce risk for coronary heart disease events in women with coronary heart disease."¹ In a second paper, HERS II concluded that HRT in "older women with coronary disease increased the rates of venous thromboembolism and biliary tract surgery. Trends and other disease outcomes were not favorable and should be assessed in larger trials and in broader populations."²

In short, older women with established CHD were at increased risk for further complications if treated with combined-continuous HRT. There was no statistical power to determine impact of secondary factors, such as rate of osteoporotic fractures.

Correctly, authors and reviewers suggested that the effect of HRT in a preventive mode on a younger, clinically nondiseased population, should await further studies, such as the WHI. The wait was short. The National Heart, Lung and Blood Institute (NHLBI) of the NIH announced the "earth-moving" news on July 9, 2002, that it had stopped early a major clinical trial of the risks and benefits of combined-continuous conjugated equine estrogens (CEE) and medroxyprogesterone acetate (MPA) in healthy postmenopausal women because of an increased risk of invasive breast cancer. The large multicenter trial, a component of the WHI, also found "increases in coronary heart disease, stroke, and pulmonary embolism in study participants on estrogen plus progestin compared to women taking placebo pills. There were noteworthy benefits of estrogen plus progestin, including fewer cases of hip fractures and colon cancer, but on balance the harm was greater than the benefit."⁴

While the merits and demerits of the data and the wisdom of the decision to terminate this arm of the WHI study will be debated for years, the manner in which the study was terminated was poorly planned, abrupt and inhumane. Predictably, the media response was enormous, ranging from thoughtful to sensational. Panic was caused, numerous women discontinued therapy, and women and their health providers alike have been thrown into a state of confusion, distrust and quandary of what to do next.

The NHLBI conclusion that harm was greater than benefit was clearly magnified by its concentration on percentiles of relative risk, rather than the pertinent issue to women of absolute risk. Indeed, review of the *JAMA* article demonstrates absolute risk to be low, invariably a fraction of 1%.³ Thus, the 26% relative increase in invasive breast cancer translates into 38 cases among HRT users vs 30 cases among placebo users per 10,000

women-years; the 29% increase in CHD translates into 37 cases on HRT vs 30 cases on placebo/10,000; stroke increased 41%, with 29 vs 21/10,000; and venous thromboembolism doubled, with 34 vs 16/10,000. On the benefit side, the 33% reduction in hip fracture was 10 on HRT vs 15 on placebo/10,000, and the 37% reduction in colorectal cancer was 10 vs 16/10,000. There was no difference in total mortality.

This arm of the WHI does provide us with a wealth of information and opens multiple new questions. Table 4 of the article³ should be a placemat on every practitioner's desk. The challenge we all face is to translate the meaning of all this to the individual woman sitting on the opposite side of the desk, confused and wanting a balanced recommendation.

So what can we initially conclude from all the information presented thus far?

1. Continuous-combined CEE+MPA is of no value in reversing established coronary heart disease or preventing CHD in apparently healthy women.

2. Continuous-combined CEE+MPA increases the risk of myocardial infarction, deep venous thrombosis and thromboembolism, particularly in the first 12 to 18 months of therapy.

3. The slight increase in invasive breast cancer occurs earlier than anticipated from observational studies (i.e., within 5 years). The increase was marked at year 4, with a trend to a later decline in number of events. This would appear to confirm that HRT provides a growth-promoting rather than a causative role in breast cancer. But, with the premature termination of the study, this question was not answered.

4. All of the above problems are more likely related to the attenuating effect of continuous MPA on CEE, as the groups using CEE alone in the WHI have not demonstrated these. Whether there is any role at all for the long-term regimen of any combined-continuous HRT in current standard doses is highly doubtful. At present, where long-term therapy is being used, a continuous-cyclic regimen (i.e., adding progestogen cyclically every 1 or 2 months) may be more favorable, but this needs to be proven. This regimen would reduce exposure to progestogen.

5. Continuous-combined CEE+MPA shows early benefit in reduction of hip fracture and colorectal cancer.

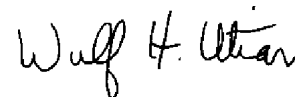
6. Estrogen alone may well still be proven to have a favorable benefit-to-risk ratio. At the very least, the NHLBI owes us all an immediate preliminary report on the 6-year data as an interim analysis.

The importance of individualizing patient care has long been emphasized. Never has it been more important than now. Before prescribing HRT, there must be a clear and strong indication for therapy, and risk vs benefit carefully considered. Short-term therapy for symptoms still necessitates careful monitoring. Longer-term therapy, now probably defined as beyond 2 years, mandates even more rigorous monitoring and an annual risk-to-benefit evaluation.

Menopause medicine is growing more complex, and pharmacotherapeutic options are broad—and not always necessary. To assist practitioners in dealing with these issues, NAMS will update all its educational materials, including the *Menopause Core Curriculum Study Guide* and its consumer education materials, and there will be a series of practical articles in *Menopause Management*. NAMS will also keep its Web site (www.menopause.org) current with all the news as it breaks.

One fact is of no doubt. The Society's annual scientific meeting this October in Chicago is an *absolute must-attend event*. NAMS has convened a special study group to prepare a report on long-term HRT that will be presented at the meeting. Register early on the Web site, as attendance is limited.

I wish you all strength in meeting the challenges of the next few months.



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