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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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Women's Health Initiative, Round 2 — Is This the Opportunity to Clear the Air on Postmenopausal Hormone Use?

The dogmatic pronouncements of the demise of postmenopausal hormone therapies (the “last nail in the coffin”) since the termination of the estrogen and progestogen therapy (EPT) arm of the Women's Health Initiative (WHI) in July 2002 appear to have been premature. The latest data reported with the termination of the estrogen-only arm of the WHI have given postmenopausal estrogen therapy (ET) serious revitalization.

One fact that has been lost sight of in the flurry of rhetoric during the past 2 years is that the WHI was never a study about menopause treatment. Rather, the WHI was, from the beginning, a study designed to confirm whether observational data demonstrating a protective effect against coronary heart disease with use of EPT or ET could be confirmed for women starting such therapies several years after menopause. What has been completely overlooked is the simple fact that despite some abuse for unproven preventive indications in older women, the overwhelming number of prescriptions for postmenopausal hormones are written for women ages 45 to 60 to relieve menopause symptoms. Moreover, more than 75% of these users actually discontinue use within 24 months.

It is therefore appropriate, now that we have such a huge body of new data, that we completely reconsider the current status for hormonal therapies in two populations: 1) symptomatic menopausal women who are seeking treatment and are seen in general clinical practice, and 2) women who are seeking EPT for preventive indications; in particular, osteoporosis prevention and enhancement or maintenance of quality of life (QOL).

The following is my personal analysis of the situation. But first, let me very briefly review the facts we have gleaned from the WHI and the other recently published, randomized studies.

The conjugated equine estrogens (CEE)/medroxyprogesterone acetate (MPA) arm of the WHI has provided profuse data on potential benefits and risks of this drug combination administered to women starting between ages 50 and 79 (mean age 63). The primary endpoint studied was cardiovascular disease and the primary risk factor was breast cancer. The study was not designed as a test of EPT for menopausal symptoms or QOL. Surrogate endpoints were later utilized to determine the latter. Over the course of the study, there was no protective effect against coronary heart disease (CHD), but there were statistically significant increases in stroke and pulmonary embolism. The increase in breast cancer (unweighted hazard ratio, 1.24 [95% confidence interval, 1.02-1.5]) was, interestingly, only significant in women who were prior hormone users (before

entering the study) indicating more than 5 years of use overall. There was a statistically significant reduction in all fractures and in colon cancer. In addition, there was a slight increase in dementia in women starting hormones after age 65. This aspect was not investigated in women commencing EPT when younger than 65.

The most recent NAMS position statement on ET and EPT use in perimenopausal women (the entire statement can be viewed at www.menopause.org) was published in September 2003 and summarized all the data succinctly, provided references and reached the following key conclusions:

1. Primary indication for systemic ET/EPT is treatment of moderate to severe menopause symptoms, or local ET for moderate to severe vulvovaginal symptoms.
2. No EPT regimen should be used for primary or secondary prevention of CHD.
3. EPT is effective in reducing risk for postmenopausal osteoporosis.
4. EPT should not be commenced after age 65 for primary prevention of dementia.
5. Data from WHI and Heart and Estrogen/Progestin Replacement Study (HERS) can be extrapolated with caution only to women younger than age 50, and not at all to women younger than age 40 (with premature menopause).
6. Extended use of ET or EPT is considered acceptable under certain circumstances:
 - symptom relief, particularly after failed attempts to discontinue ET/EPT;
 - treatment of severely symptomatic women at high risk for osteoporotic fractures;
 - prevention of osteoporosis in high-risk women in whom alternate therapies are not appropriate.

Numerous other national and international societies and governmental agencies have weighed in with their own position statements, largely making similar recommendations. In some situations, there have been overreactions to the data. Now we have the latest report from WHI with the data on the terminated ET-only arm, and the ball game changes.

The key results were an increase in stroke similar to what was seen in the EPT arm, but no increase in CHD (and possibly a *protective* effect on CHD when started in younger women, ages 50-59). Moreover, an almost significant *decrease* in breast cancer was seen in the estrogen-treated group by virtually the same margin as EPT increases risk (HR, 0.77; CI, 0.59-1.01). Fracture risk was decreased. These are preliminary results as the study was prematurely terminated. Complete reports for specific diseases will soon be forthcoming once all the data are gathered and adjudicated. Significant areas might become insignificant and vice versa.

But what might all this mean and what are we to recommend to ever more confused patients?

Once again, NAMS is convening a panel of experts and will issue its comprehensive new report at the annual meeting in Washington, DC (October 6-8, 2004).

My personal "take" on this new information is as follows:

1. The WHI populations in the EPT and ET studies were different from one another, especially in body mass index and presence/absence of a uterus. Despite that, there are convincing differences when CEE is administered alone or together with MPA.
2. Unfortunately, more questions are raised than answered:
 - Is the progestin the cause of potential early CHD risk and breast cancer increase?
 - Is continuous progestin the problem?
 - Does the potential decrease in breast cancer on CEE result from a biologic-specific effect (for example, might one of the components in the biologic product CEE have a SERM-like effect) or could this be a class-action effect? Some data might suggest the latter.
 - Can we now reassure younger women on ET that the risk/benefit ratio is in favor of long-term therapy? If so, what would the reasons be for prolonging therapy?
 - Are the increased stroke risk and dementia data due to the prothrombotic effect of ET/EPT?
3. Estrogen-only therapy for symptomatic relief, especially in younger women after hysterectomy and bilateral ovariectomy, has been demonstrated to be remarkably safe. Therefore, the WHI estrogen arm results allow a case to be made for the long-term use of CEE in osteoporosis prevention, at least in such a population.
4. I think it is time for the "hormone evangelists" to stop flogging the dead horse of cardiovascular protection. It is quite clear at this point in time that even if early administration of hormones is shown to have a slight protective effect, behavioral changes (i.e., diet, exercise and smoking cessation) and other pharmacotherapies (i.e., statins, antidiabetic agents and antihypertensives) are far more effective than hormones are ever likely to be.
5. Should the fact that the disease-specific risk/benefit ratio is so finely balanced and that the prevalence of most of these problems increases with age redirect the focus of ET/EPT utilization? That is, when appropriately administered, both the potential benefits and the potential risks of adverse disease outcomes are low. The real question becomes: Does ET/EPT truly enhance QOL over and above the quality of health? In other words, despite the presence of disease or potential handicap, do hormones have a positive impact on aspects of QOL like sense of well-being? Good studies to

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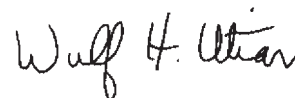
determine whether there is truly a drug effect beyond any placebo response is an area for urgent research.

Significant damage has resulted from the way the WHI results were originally reported. Women have walked away from treatments often necessary for their health and well-being and have lost trust and confidence in their health providers and the care they recommend. Moreover, the public has been further fleeced and insulted by the plethora of snake oil salesmen now marketing a multitude of ineffective placebos for “menopausal symptoms.” Pharmaceutical companies, with huge losses of revenues, have reduced research and development in this crucial area of women’s health care. “Ambulance-chasing” liability lawyers have started class-action law suits with little substance to their charges, adding further burden to our national malpractice crisis. Many medical professionals have lost respect for the WHI writing groups for a perceived bias in the manner in which the data have been written and reported; discussion and conclusions in the published papers often are at variance from the data they report. Clinicians no longer believe epidemiologists and vice versa.

Medical journals like *The New England Journal of Medicine* and the *Journal of the American Medical Association* are perceived by many health professionals to have dropped their peer review standards, to have demonstrated bias in the selection of authors for covering editorials, and to have succumbed to a greater interest in romancing the media rather than meeting their true editorial mission and serving their direct constituency. Some self-proclaimed “medical experts,” hungry for media exposure and career enhancement have, in achieving their “15 minutes of fame,” lost the respect of their colleagues for their ill-informed or poorly considered off-the-cuff sound bites. The media, of course, continue to seek bad news to report, and any positive reports remain deafening by their silence. Take the latest WHI CEE-only arm, for example, which has been given scant attention compared to the EPT arm.

It is clear that, at this time, there have been few winners. My hope is that we can utilize the latest WHI estrogen-only data in a more responsible fashion to truly reopen the debate, reduce the confusion and fear in our real constituency (women with legitimate health concerns and needs) and banish the acrimonious and biased opinions that, until now, have pervaded the subject to the garbage heap of medical history.

NAMS will do its best to achieve this in its next report. Stay posted.



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