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Invited Editorial

The Women's Health Initiative Reports in perspective: facts or fallacies?

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Women's concern about hormone use increased following early termination of the estrogen/progestogen arm of the Women's Health Initiative (WHI) in July 2002[1]. Many women stopped therapy without even discussing it with their physicians; furthermore, many doctors were not sure of how to respond, some even advising their patients to discontinue their hormones. The report of the WHI investigators was pre-empted by a press conference that prejudged the meaning of the data for our patients and us[2]. Media reports glossed over the benefits for bone, decrease in colon cancer, and less deaths in the users than controls to emphasize the risks for breast cancer and cardiovascular disease. It was a classical case of symbolism over substance where hype fomented hysteria. In a recent report, it was estimated that, where there were 91 000 000 new prescriptions for hormone therapy (HT) in the United States in 2001, only 57 000 000 new HRT prescriptions were written in 2003, a 42% decrease[3]. The WHI was thought to be such a well-designed study that it would answer the remaining questions about estrogen use. With its many flaws, the WHI has raised more questions than answers. The information gleaned from multiple studies of so many different hormones and methods of administration for the past 50 years should not be discounted because of a single study, no matter how large, especially when only two different hormone preparations and one method of administration were used (continuous combined).

It is very disappointing that the American authoritative bodies such as the North American Menopause Society (NAMS) and the American College of Obstetricians and Gynecologists (ACOG) have acquiesced to these reports and given them credulity. In the second position paper of NAMS, they recommend that treatment of moderate and severe menopausal symptoms remains the primary indication for systemic estrogen-only therapy (ET) and estrogen–progestogen therapy (EPT)[4]. For moderate to severe symptoms of vulvar and vaginal atrophy such as vaginal dryness, dyspareunia, and atrophic vaginitis, local ET is generally recommended. EPT or ET should not be used for primary or secondary prevention of coronary heart disease or stroke. Use of ET and EPT should be limited to the shortest duration and lower than standard dosages should be considered. With the termination of the estrogen-only arm of the WHI in March 2004, although NAMS issued their statement under the title, 'WHI estrogen-only arm: overall results neutral', they are reviewing this report and not recommending any change in practice beyond those outlined in its 2003 position statement. In so doing, they missed a golden opportunity to at least reassure patients and physicians that, after 7 years of estrogen-only use, there was no increase in cardiovascular events, and emphasize that there was almost a significant decrease in breast cancer in these women, average age of 70 years (relative risk (RR), 0.77; 95% confidence interval (CI), 0.59–1.01). ACOG's news release on March 2, 2004 concurs with the advisory of the National Institutes of Health (NIH) that physicians follow current Food and Drugs Administration (FDA) guidance. The FDA, long biased against estrogen therapy, has approved HT for the relief of menopausal symptoms such as hot

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flushes, and, although effective for prevention of osteoporosis, recommends considering non-estrogen medications first if osteoporosis prevention is the sole reason for using HT. They recommend against its use for prevention of heart disease, and, when using HT, women should do so at the lowest effective dose and for the shortest possible duration for her circumstances. While the International Menopausal Society[5] and the European Menopause and Andropause Society[6] have both issued critiques of the WHI and guidelines for physicians, NAMS has rolled over and played dead.

NAMS should have at least discussed the importance, or lack of it, in the very low hazard ratios between 1 and 2 and the lack of statistical significance in the 95% confidence intervals. The Committee should have clearly indicated and emphasized the differences in previous estrogen study groups and the WHI subjects: menopausal symptoms vs. asymptomatic women; ages 45–55 years (mean, 53 years) vs. ages 50–79 years (mean, 63 years); risks of estrogen deficiency; and that only one method of administration (oral continuous) was used with two different pills. This position statement was a great disservice to the postmenopausal women to whom we are dedicated to help. Furthermore, it did not provide any guidelines for NAMS members, or other practicing physicians for that matter, on what to do for our patients, recommending lower dosages for shorter durations. Disclaimers and qualifying statements all through the report allude to possible differences from earlier estrogen studies with contrary findings; however, they are so worded as to add credibility to WHI findings while denying that any other methodology could possibly be true.

The impact of all this adverse publicity from the continuing WHI reports has caused millions of postmenopausal women to stop their hormones; unknowing physicians are recommending to their patients that they discontinue their hormones, and many women will never start ET/EPT. This may result in many more osteoporotic fractures, cardiovascular diseases, cases of Alzheimer's disease and colorectal cancer, atrophic vaginitis, macular degeneration of the retina, debilitating vasomotor symptoms, and loss of the many other benefits of ET/ERT. The information gleaned from multiple studies of many different hormones and methods of administration for the past 50 years should not be discounted because some epidemiologists will only accept as level I evidence a 'properly randomized, controlled clinical trial'.

As an active NAMS member, long-time researcher in hormone replacement and dedicated advocate of ET/EPT, my major concern is for my own patients; however, I also feel great compassion for the millions of postmenopausal women who will never have the chance to benefit from estrogen therapy. The reply to my critique of the NAMS 2003 Position Statement on the Women' Health Initiative was that my *Letter to the Editor* was an emotional misinterpretation of their statement[7]. It was stated that the Advisory Panel had moved beyond the WHI reports on the terminated HT arm of the study as being the be-all and end-all of the scientific literature. The negative outcomes for individuals who should not have discontinued are yet to be documented, but it was agreed that the level of unnecessary human suffering appears to have been enormous. In a recent report from The National Osteoporosis Risk Assessment, in women who have discontinued HT for less than 5 years, the past-users have almost the same fracture rate (odds ratio (OR), 0.93; 95% CI, 0.63–1.38) as matched never-users[8]. Those women who have discontinued their estrogen for 5 or more years have an excessive risk for hip fracture (OR, 1.65; 95% CI, 1.05–2.59). It was further stated that the panel would continue an unbiased constant review of the literature and that NAMS HT Position Statements are works in progress, so, as evidence accrues, the position will change.

The estrogen-only arm of the Women's Health Initiative was terminated early in February 2004 by the National Institutes of Health, *not* by the Data and Safety Monitoring Board (DSMB), as had been done in July 2002 with the estrogen–progestogen arm[9]. Apparently, there was a debate between the NIH and the DSMB because the global index of risk/benefit was only increased by 1% (hazard ratio (HR) 1.01; 95% CI, 0.91–1.12). It was concluded that the use of conjugated equine estrogens (CEE) increases the risk of stroke, decreases the risk of hip fracture, and does not affect the incidence of coronary heart disease over an average of 6.8 years. It was further concluded that there was a possible reduction in breast cancer risk but that CEE should not be recommended for chronic disease prevention in postmenopausal women. In their discussion about the risk of stroke, they failed to mention that these women were many years postmenopausal, had never used estrogen, and many already had other risk factors for stroke. Table 1 lists the hazard ratios given in the Report.

When stratified by age, some of the risk factors become more obvious, especially for coronary

Table 1 Hazard ratios and 95% confidence intervals for estrogen-only therapy reported by the Women's Health Initiative

	Hazard ratio	*95% confidence interval*
Coronary heart disease	0.91	0.75–1.12
Breast cancer	0.77	0.59–1.01
Stroke	1.39	1.10–1.77
Hip fracture	0.61	0.41–0.91
Colorectal cancer	1.08	0.75–1.15
Dementia	Trend toward increased risk (to be reported separately)	

Table 2 Risk factors of estrogen therapy by age, as reported by the Women's Health Initiative, expressed by hazard ratios (HR) and 95% confidence intervals (CI)

	Coronary heart disease		*Breast cancer*		*Colorectal cancer*	
Age range (years)	*HR*	*95% CI*	*HR*	*95% CI*	*HR*	*95% CI*
50–59	0.56	0.30–1.03	0.72	0.43–1.21	0.59	0.25–1.41
60–69	0.92	0.69–1.23	0.72	0.49–1.07	0.88	0.52–1.48
70–79	1.04	0.75–1.44	0.94	0.56–1.60	2.09	1.08–4.00

heart disease and breast cancer, although, in this arm of the study, there was almost a significantly decreased risk for breast cancer with estrogen use. Almost all of the clinical outcomes increased with each decade of age (Table 2).

The 29% increase in heart disease in the HT users[1], or seven more events per 10 000 women per year, seen mostly in women initiating HT after 70 years of age, is probably true, since this has been shown in the secondary prevention studies such as the Heart and Estrogen/progestin Replacement Study (HERS)[10], and is also biologically explainable (breast cancer is not). Although estrogens have beneficial effects in cardiovascular disease by increasing high density lipoprotein (HDL) cholesterol and decreasing low density lipoprortein (LDL) cholesterol, the major benefit is through direct effects of estrogen upon the coronary arteries. Steroid hormones work through receptors in target tissues. Estrogen increases its receptors in coronary arteries, where progestogens decrease the estrogen receptors, particularly when taken continuously, as they are with continuous combined HT. This may leave less sites for estrogen's beneficial action: increased blood flow, dilation of coronary arteries, reduced vascular resistance, increased endothelial derived relaxing factor (EDRF), inhibition of atherosclerosis progression, and decreased platelet adhesiveness. Progestogens also decrease progesterone receptors in the endometrium, which helps to explain why continuous combined HT is not as endometrial-protective as the sequential therapies (HR, 0.81; 95% CI, 0.48–1.36) or 27 events in the HRT users vs. 31 endometrial cancers in the placebo users during 5.2 years[11].

Not much else is new in the WHI reports. The alleged increased risk in breast cancer in the HT users (HR, 1.26; 95% CI, 1.00–1.59) had been previously reported by the Collaborative Group on Hormonal Factors in Breast Cancer (RR, 1.35; 95% CI, 1.21–1.49) for 5 years or longer, or an excess of two cancers per 1000 women[12]. The lack of protection from Alzheimer's disease when estrogen was not initiated until after age 65 was also demonstrated in the Cache County study[13]. However, if estrogen replacement is given for more than 10 years at menopause transition, there is a 59% reduction in the lifetime risk of Alzheimer's disease (RR, 0.41; 95% CI, 0.17–0.86). Dr Leon Speroff points out that a theme has emerged from the epidemiologic confusion of the past few years: it takes healthy tissue to allow effective response to estrogen and maintenance of health[14]. Experimental evidence indicates that, as cells become involved with atherosclerosis and neurons become affected with the progression of Alzheimer's disease, the beneficial response to estrogen decreases. One area of little controversy is that hormone therapy has a beneficial impact on postmenopausal quality of life. Why did the WHI report no benefit on quality of life? WHI results do not apply to the majority of women prescribed HT because, in the WHI, the average age was 63 years, subjects were 18 years distant from their menopause, and had no significant symptoms.

Older women were chosen who had never used estrogen or had hot flushes so that placebo users would not drop out of the study.

SUMMARY AND CONCLUSIONS

There are no new data in the Women's Health Initiative. The Collaborative Study of Hormone Factors in breast cancer showed a non-significant increased risk after 5 years. HERS showed an increased risk of cardiovascular disease in HT users with previous heart disease. The Cache County study indicated that estrogen therapy initiated after age 60 increased the incidence of Alzheimer's disease. The daily progestogen in the HT users decreased the estrogen receptors in the coronary arteries and minimized the beneficial direct effect of estrogen. It also decreased progesterone receptors in the endometrium, thus making it less endometrial-protective. The WHI was contrary to previous studies of estrogen therapy because women with specific menopausal symptoms were excluded, were older, had never used estrogen and had long-term estrogen deficiency. It takes healthy tissue to allow an effective response to estrogen and maintenance of health. Maximal benefit of HT may require early onset of treatment, near the time of menopause. However, it is never too late to arrest the progression of osteoporosis and decrease the risk of fracture.

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