

LETTERS

Fundamental flaws of the WHI

■ TO THE EDITOR:

In your May issue, the article on hormone replacement therapy ("**Hormone replacement therapy: The right choice for your patient?**," *J Fam Pract* 2005; 54:428) purports to present a knowledgeable discussion of this problem. In fact, Dr Pees does hint at some of the problems with the Women's Health Initiative (WHI), particularly concerning some of the statistical problems and what the study really says. However, this discussion is at a very sophisticated technical level that I believe most of your readers will not appreciate.

Unfortunately, none of your discussions address even more fundamental flaws with the WHI. Dr Pees hints at one of the problems in noting that only 10% of the subjects were in the 50-to-54-year-old age group. In fact, the average age of the subjects was 63.3 years. This is more than 13 years postmenopause for the average woman, which is (or at least used to be) 50 years old. We know that something significant happens physiologically with women postmenopause, and it has been postulated that this change takes place within the first 2 years after menopause. Therefore, we know as a certainty that postmenopausal women are physiologically significantly different from premenopausal women and any study done on these women can only be applied to postmenopausal women. We also know that the incidence of cardiovascular disease and other disease entities accelerates rapidly after menopause. Therefore, postmenopausal women have a high likelihood of having subclinical disease. Based on the aforementioned issues, the WHI cannot be classified as a preventive study and, in fact, because the population used is so significantly different from the premenopausal population, that results from this study cannot be applied to any women who are placed on hormonal therapy at the time of menopause.

It should also be noted that the WHI used a steady-state estrogen and progesterone drug therapy that was not in vogue until approximately 15 years ago. This is significantly different from the cycled hormone replacement therapy prescribed prior to that time and one which many of the previous epidemiological studies are based.

Based on the 2 above methodological fatal flaws in this study, please reveal WHI for what it truly is. Also please refrain from making any statements concerning heart disease based on this study. Only when we have an appropriate study of perimenopausal women (women within the first 2 years of menopause) with a significant arm on cycled hormone therapy can we make any statement concerning the effect on cardiovascular disease any other potentially related disease or symptoms. The "expert panel consensus" released on September 2003 is inappropriate, not based on any evidence, and illustrates the lack of understanding of research design and methodology by the "experts." Our academic rigor needs to improve significantly in the field of medicine.

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■ DR PEES RESPONDS:

Dr Weldy correctly points out some of the shortcomings of the WHI study. Many have speculated that in order to have a protective cardiovascular impact, hormonal therapy needs to be initiated within a critical window. Primate studies have suggested that this critical window is within the first 2 years of reaching menopause. There was a very small component of the women in WHI that fell into this range. The human study to confirm this animal data has not yet been accomplished. Only when such a study has been conducted and appropriately analyzed, can statements be made with respect to preventative cardiovascular health and usage of hormonal therapies. The WHI study population included approximately 1200 women with prior cardiovascular events, further biasing the outcome of this aspect of the study. As with any study, the results can only be applied to individuals that meet the parameters of the study population. To fully

appreciate the absolute risks, one must understand the limitations of the study, the inclusions and exclusions of the study, the absolute numbers, the statistical significance and confidence intervals, and the study populations.

Regarding the estrogen only arm of the study, the impact of estrogen on breast cancer seems to be somewhat clearer. The conclusion of the estrogen only arm did show that estrogen by itself in these dosages did not increase the risk of developing breast cancer. Further, there was the slight suggestion that in the later years of usage, there may be a decrease in the risk of developing breast cancer. However, to make this latter statement, would be incorrect as there is insufficient data to draw this conclusion.

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