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THE WOMEN'S HEALTH INITIATIVE

On 9 July 2002, the announcement of the termination of the estrogen/ progestin (Prempro™) arm of the Women's Health Initiative (WHI) created a frenzy among menopausal women worldwide. For many, there was a belief that this was the first and only study of estrogen use to have been conducted, and that the results showed devastating effects on Prempro users. We as healthcare providers have an obligation to put this study into proper perspective for our patients, and to continue to assess new data as it becomes available in order to care for our patients properly. A brief history of estrogen use will therefore be helpful.

The approval in 1942 of Premarin® (conjugated equine estrogens) for relief of hot flashes radically altered the available options for menopausal women. On its publication in the 1960s, Dr Robert Wilson's tract entitled *Feminine Forever* was received with great enthusiasm. For women, here was the fountain of youth. However, in the 1970s, studies were reported which showed an increased risk of endometrial carcinoma in users of unopposed estrogen. This did not prove to be a major problem, as during the 1980s progestins were introduced to balance out the estrogen.

Unfortunately, progestins were associated with a multitude of problems. With the addition of cyclical progestins, women who were for the most part thrilled to have stopped having menses began to menstruate once more. The alternative of daily progestin administration seemed attractive, but this route also had its difficulties. Many women bled or at least spotted on daily medroxyprogesterone, which was the first progestin to be employed for this purpose. Nonetheless, on its introduction in 1997 Prempro (daily conjugated equine estrogens and daily medroxyprogesterone acetate) was very well received, and the market took off.

No one questioned the efficacy of combination hormone replacement therapy (HRT) for the relief of menopausal symptomatology. However, interesting data began to appear in the 1980s which suggested that women who were taking HRT had a significantly reduced risk of developing coronary artery disease (CAD). Multiple observational studies appeared which showed reductions in myocardial infarctions and in death from the latter in the range of 30-50%. This made intuitive sense, given that CAD is very rare in premenopausal women, and the incidence increases substantially postmenopausally. Epidemiologically, it was also known that women whose ovaries were surgically removed at a very young age showed a significant increase in cardiac disease.

In the 1980s we also began to see the emergence of conflicting data on the incidence of breast cancer in women on long-term estrogen. Although the majority of studies showed no significantly increased risk in women on HRT, a few papers were published that showed an increased incidence of breast cancer

among long-term users.

American women have traditionally had one major fear - that of dying from breast cancer. In a typical poll taken by the Gallup organization in 1994 of women aged 45-65 years, the individuals who were surveyed estimated that 40% of women in the USA die from breast cancer. In fact, that number applies to deaths from CAD, and the actual mortality from breast cancer is around 4%.

Also appearing throughout this timeframe were multiple reports on the efficacy of HRT in the prevention of osteoporosis. As the female life expectancy increased, osteoporosis was emerging as a significant health risk. Statistics began to demonstrate that the mortality from osteoporotic fractures equaled that of breast cancer, and healthcare costs from the morbidities of bone loss escalated.

Thus the stage was set for the WHI. Wyeth Ayerst had requested the new indication from the Food and Drug Administration (FDA) for use of Premarin for the prevention of CAD. The request was denied, The FDA demanded some prospective randomized double-blinded controlled studies to prove this, so in 1993 the National Institutes of Health, with the support of Wyeth Ayerst providing the medications, began the WHI.

Two separate arms of the study were set up. In one arm, postmenopausal women with an intact uterus were randomized to receive either Prempro or placebo in a prospective double-blinded manner. In the other arm, hysterectomized women received either Premarin or placebo. In addition to the major end point of CAD, the investigators were also studying the incidence of breast cancer, stroke, venous thromboembolic disease, osteoporotic fractures and colon cancer.

Concomitantly, Wyeth Ayerst, which was certain of the efficacy of HRT for heart disease, was also sponsoring a trial of HRT for secondary prevention. Women who had documented myocardial infarctions and severe angina were administered Prempro, in an attempt to reduce the incidence of recurrent infarctions. When the results of this trial, known as HERS (Heart and Estrogen/Progestin Replacement Study), were published in 1998 they stunned most healthcare providers. Indeed, not only did Prempro not reduce the incidence of repeat coronary morbidity, but in the first year of administration the risk actually increased.

The American Heart Association and other medical groups soon responded, and HRT was pronounced an inappropriate medication for the prevention of recurrent myocardial infarctions (although if a woman was already on the drug and doing well on it, the recommendation was that it would be medically acceptable to continue its usage).

The stage was then set for 9 July 2002. A news embargo set up by the *Journal of the American Medical Association* was breached, and a story on the WHI appeared throughout the country. The study that had been started in 1993, with the aim of showing that HRT would decrease the incidence of primary heart disease, was stopped prematurely. Women who had been on the study drug Prempro for an average of

5.2 years were showing a statistically significant but only slightly increased risk of developing breast cancer. Furthermore, there was no reduction, and perhaps a slight increase, in CAD.

Although the study showed a modest decrease in hip fractures and colon cancer, the study designers had preset an automatic stop to the study if they perceived any increased risk in breast cancer. Women panicked. Phone lines to medical offices were besieged, and frustratingly for the healthcare providers who had received no advance notice of this event, physicians were bewildered about how to respond to their distraught patients.

Following the announcement that the WHI study had been terminated, healthcare providers tried to reach a consensus over its interpretation. Some of them decided to tell all of their patients to come off HRT. Most healthcare providers, including the writing group for the WHI, conceded that HRT is the most effective therapy for menopausal symptomatology, and agreed to continue the usage of HRT for at least several years. The American College of Obstetricians and Gynecologists, following the WHI announcement, recommended that HRT use be limited to the relief of postmenopausal symptoms, and that its use be withdrawn as soon as possible. The North American Menopause Society (NAMS) reached a similar consensus opinion.

Many gynecologists believe that nothing really happened. Their interpretation of the initial WHI results showed nothing that we did not know previously, and they propose continued usage of HRT as they had planned prior to this date, accompanied by explanations to their patients. At the same meeting of NAMS that issued a statement on stopping the use of HRT, a plenary session on sexual function emphasized the importance of estrogen, and a subsequent session highlighted how important estrogen replacement therapy was for women who were surgically menopausal.

However, on 8 January 2003, almost exactly 6 months after the WHI termination announcement, the FDA pronounced that all estrogen formulations in the USA, including conjugated equine estrogens (Premarin) as well as all others, with or without progestins, should be labeled with a black box warning indicating the WHI findings. The warning would include a statement about the increased risks of breast cancer and cardiovascular disease. The statement would also recommend the use of the lowest dose of estrogen for the shortest possible amount of time for relief of vasomotor symptoms.

HOW CAN THESE DIFFERENT INTERPRETATIONS EXIST?

The increased absolute risks revealed by the WHI study are very small. According to the WHI, Prempro users experienced 38 new cases of breast cancer per 10 000 women per year, compared to 30 new cases in the control group. They also noted a similar increase in cardiovascular disease.

However, many healthcare professionals argue that breast cancer cells are present in the breast for more than 5 years prior to the discovery of the disease, and that hormonal therapy merely promotes their growth, making them detectable (and detected) earlier. They also note that in the WHI study there was

no increased risk of carcinoma *in situ,* which would logically be increased if the hormones were truly carcinogenic.

Many explain the coronary data on the basis of the particular sample. The age of women enrolled in the HERS study was 67 years, whereas in the WHI the average starting age was 63 years. Although the women in the WHI did not have overt CAD, they were an obese cohort, with an average BMI of 28.5 kg/m^2, and 35% were hypertensive. Around 50% were current or previous smokers. Many women's health experts believe that this group most likely had some degree of plaque formation in their coronary arteries due to these risk factors. Thus they believe that the WHI is merely a confirmation of the HERS study, and that it shows no secondary protection for heart disease, but also demonstrates nothing about primary prevention.

All studies of estrogen treatment show an increased incidence of venous thromboembolic events. The range quoted in most studies is a two- to threefold increase. The majority of these events occur during the first 6 months of use, and the WHI study was no exception. Many experts believe that the stroke data, which show a slightly increased risk in HRT users, are a consequence of the thrombogenic potential of estrogen.

WHAT DO WE TELL OUR PATIENTS?

The writing group for the WHI informed us that we should feel confident about using HRT for the relief of menopausal symptoms, and that HRT should be withdrawn when the patient is no longer experiencing significant symptoms. When interviewed, the spokespeople for the group commented that menopausal symptoms lasted for approximately 2 years, and that after this time women should be comfortable when therapy is withdrawn.

The problem is that many women who have been on HRT for a year or two for symptomatic relief are very symptomatic when therapy is withdrawn, and are still suffering from significant hot flashes, insomnia, mood swings, atrophic vaginitis and bladder symptoms. The options available include alternative therapies (both medical and non-medicinal), resumption of HRT, or allowing the patient to continue to suffer. Our orientation is to present how to handle the first and second options, since the authors firmly believe that the third choice is unacceptable.