Hormone Replacement Therapy: Clinical Trials and Controversy

by Raphael J. Witorsch, Ph.D.

A Brief History of Hormone Replacement Therapy

From adolescence until the fourth decade of life, a monthly pattern of ovarian hormone secretion, referred to as the menstrual cycle, controls the reproductive capacity of the average human female. The ovarian hormones involved in the cycle are estrogen and progestin (generic terms for the specific hormones, estradiol and progesterone, respectively). As women age, the ovary loses the ability to produce estradiol and progesterone in substantial amounts, thus initiating menopause—the absence of menstrual cycles and the loss of the ability to reproduce. Menopause often is associated with a variety of unpleasant symptoms, among them hot flashes, night sweats, vaginal dryness, and a loss of libido. In addition, postmenopausal women are prone to bone fractures resulting from osteoporosis.

In the 1930s, estrogens became available for the treatment of menopausal symptoms, thus initiating the era of hormone replacement therapy (HRT). By the 1960s, estrogen-based HRT became widespread, with approximately 12% of postmenopausal women receiving treatment. Studies in the mid-1970s revealed that estrogen-based HRT was a risk factor for cancer of the uterine lining (endometrium), but the addition of progestin to the regimen diminished this risk. Thus, estrogen + progestin-based HRT became the therapy of choice in older women with intact uteri, whereas estrogen HRT remained the postmenopausal therapy of choice in hysterectomized women. By the early 1980s, estrogen replacement therapy was shown to markedly reduce the risk of hip and wrist fractures in postmenopausal women, consistent with the anti-osteoporotic effects of estrogen found in the laboratory.

Epidemiologic studies of hormonal therapies (postmenopausal and/or contraceptive) have produced conflicting results with regard to other health effects. Some studies have revealed that ovarian hormone therapy is a risk factor for certain cardiovascular diseases (e.g., blood clots, heart attack, and stroke), and others have suggested that estrogen produces beneficial effects on the cardiovascular system (e.g., favorable blood cholesterol profiles). Conflicting data also exist regarding an association between estrogen therapy and breast cancer. In the 1990s, data emerged suggesting other potential benefits of postmenopausal HRT such as protection against Alzheimer's disease, colorectal cancer, and tooth loss.

Postmenopausal HRT has been quite prevalent. About six million women in the United States receive combined hormone postmenopausal HRT, and eight million receive estrogen postmenopausally.[1] A recent survey indicated that 45% of all women born in the United States during the first half of the 20th century have used hormones after menopause for at least one month; 20% of these women have used them for five or more years.[2]

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The Women's Health Initiative

Recent events have shaken the world of HRT. The Women's Health Initiative (WHI), a research effort involving 40 clinical centers supported by the National Institutes of Health (NIH), was undertaken to define the effects of certain therapies and lifestyle practices on a variety of health outcomes in postmenopausal women. From 1993 to 1998, this program recruited almost 162,000 women. Among the

strategies to be examined by the WHI were low-fat diet, calcium, vitamin D supplementation, and postmenopausal HRT. A major component of the WHI involved 16,000 healthy postmenopausal women (aged 50 to 79) in which approximately half of the subjects received Prempro (Wyeth/Ayerst), a widely used estrogen + progestin form of HRT, while the other half—the control group—received a placebo.

The purpose of the study was to evaluate the effects of this form of HRT on the incidence of a variety of health outcomes, namely coronary heart disease (CHD), breast cancer, stroke, blood clots, endometrial cancer, colorectal cancer, hip fracture, and death due to other causes relative to the placebo group. Another outcome was the "global index," which incorporated all of the above endpoints as an overall estimate of the balance of risks and benefits. This study was regarded as the most significant epidemiologic survey to date because of the large number of subjects examined. Furthermore, the design of this study, a randomized controlled clinical trial, is regarded as the "gold standard" of epidemiology. While this trial was conducted, the clinical effects of HRT compared to placebo were monitored semi-annually by an independent data safety and monitoring board (DSMB).

Sponsors of the WHI hoped to resolve some of the uncertainties with regard to the risks and benefits of HRT. In spite of suggestions that HRT could be associated with certain adverse effects, most notably a mild risk of breast cancer, the prevailing view among physicians and their patients receiving postmenopausal hormones was that the treatment was beneficial. Evidence that HRT relieved the discomforts associated with menopause and lowered the risk of osteoporosis was quite compelling, and there was a general belief, despite the lack of consistent evidence, that HRT also reduced the risk of heart attacks.

To the surprise of many, the NIH abruptly terminated the Prempro phase of the WHI trial in July 2002. The study was to have continued through March 2005 with an average treatment duration of 8.5 years; instead, it was halted after 5.2 years. Prempro treatment was associated with the following: increased risk of invasive (but not noninvasive) breast cancer, CHD, stroke, and blood clots; and reduced risk of colorectal cancer and hip fracture. There was no apparent change in endometrial cancer and deaths due to other causes.

The study was halted because of the increased risk of invasive breast cancer and the global index, which reflected a "lack of overall benefit" that was "supportive of a finding of overall harm." Both of these indices had attained a predetermined calculation of risk threshold, prompting the DSMB's recommendation of termination. One HRT trial, which examined the effects of estrogen alone in women without uteri, was not terminated because risk/benefit calculation had not reached this predetermined threshold.

Doctors and patients alike were startled by the NIH action with regard to the Prempro component of the WHI. Physicians were inundated by calls from their patients. Some doctors stopped prescribing estrogen + progestin for postmenopausal HRT, and advised their patients to "live with the symptoms" or seek alternative therapies. Others were skeptical of the data and took more conservative approaches, such as not doing anything or changing to other HRT preparations. A concept emerged—although not universally accepted by the medical profession—that short-term HRT (less then five years) was safe, as compared to longer durations of treatment.

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The Prempro episode also significantly impacted the business and legal world. Prempro sales dropped 50% and Wyeth stock value declined 25%. The situation was described in a *Newsweek* article entitled "The End of the Age of Estrogen"[3] and a *Time* magazine article stated that "taking estrogen and progestin for years in the hope of preventing a heart attack or stroke can no longer be considered a valid medical strategy."[4] The website "Lawyers Weekly USA (The National Newspaper for Small Law Firms)" exhibited the statement "Lawyers Eye Hormone Drug As Possible Mass Tort: Personal injury attorneys are moving quickly to capitalize on a new government study by the WHI showing

that the popular hormone replacement drug Prempro greatly increases the risks of breast cancer, heart attacks, strokes, and blood clots."[5]

The Science of Risk and Causation

Whether these claims will hold up in court is a matter of debate. Most of the increased risks in the WHI trial associated with Prempro are small in magnitude. The risk estimates for CHD (1.29), stroke (1.41), invasive breast cancer (1.26), and global index (1.15) represent increased risks of 29%, 41%, 26%, and 15%, respectively.[6] Furthermore, it is generally agreed that an association between treatment and risk does not necessarily imply that the former "causes" the latter. This is especially true for weak (or quantitatively small) risks because they do not satisfy "strength of association," an important criterion for causation as specified by the noted biostatistician, Sir Austin Bradford Hill.

Epidemiology is an imprecise science. It is virtually impossible to exclude all confounding variables—factors distinct from the one of interest (e.g., treatments, lifestyle habits, living conditions, or genetic predispositions)—that may affect the outcome of the study. Even when these confounders are adjusted for, residual effects of confounders may exist. In the WHI trial, however, the attempt to adjust for such confounding variables was rigorous.

With quantitatively large risks, such as the association between lung cancer and active smoking (estimated to range between 10 and 30), residual-confounding effects may have relatively little impact on the risk estimate. When risks are small (e.g., 2.00 or less), residual-confounding effects could be significant.

Several prominent epidemiologists have expressed serious reservations about the reliability and clinical significance of modestly elevated risks (those below 3.0).[7] On the other hand, it has been suggested that small risks are clinically meaningful if the population involved is quite large (as is the case for HRT).[8] It should be noted that one of the risks associated with Prempro, blood clots, did appear to be higher than the rest of the estimates (2.13).

Another consideration regarding risk and causation is "statistical significance." An epidemiologic study examines a sampling of subjects that presumably represents the entire population of treated and nontreated individuals. A major source of uncertainty in studies of this sort is biological variability. For example, in one sampling of the population a certain percentage of subjects in the placebo group may exhibit breast cancer while the Prempro group may have a different percentage of diseased subjects. Another sampling may produce different percentages of breast cancer for the control and treated groups. Statistics employs probability theory to predict with a *degree of certainty* whether a difference between treatment and control is real or an artifact of chance variation. In science, differences are regarded as "statistically significant" if they achieve a level of certainty of 95% or above. Alternatively, this value can be expressed in inverse terms as a probability due to chance of 1 in 20, or 5% or less.

In the WHI trial, the data are presented as risk estimates accompanied by a range of values in parentheses, namely 1.29 (1.02-1.66) for CHD, 1.41 (1.07-1.88) for stroke, 1.26 (1.00-1.59) for invasive breast cancer, and 1.15 (1.03-1.28) for global index.[9] The numbers in parentheses represent the 95% confidence interval (CI)—the range of values where the true estimate resides with 95% certainty. The width of the 95% CI is an index of the reliability of the calculated risk estimate. The relationship between the lower boundary of the 95% CI to a risk estimate of 1.0, which represents the "null" situation or no risk, indicates whether the elevated risk is statistically significant or not. If this boundary excludes 1.0, the elevated risk estimate is statistically significant. If this boundary includes 1.0, the elevated risk is *not* statistically significant and is suspect.

Using the above criteria, it appears that the risk estimate for invasive breast cancer fails to achieve statistical significance, whereas those of CHD, stroke, and global index were marginally significant (i.e., very close to unity). Statistics, however, are best estimates; even with "safeguards," epidemiologic studies can produce false positives and false negatives.

An estimate of statistical significance also is a function of the statistical methodology used. When the number of comparisons increases in a study, the probability that an outcome is different due to chance alone (or is an artifact of chance) also increases. This occurs because there are more comparisons to be made. To minimize the possibility of false positives, criteria for statistical significance are made more stringent. In the analysis described above, no adjustment was made for multiple comparisons. Such adjustments widen the 95% CI. The study also presents adjusted 95% CI (adjusted for outcome categories and semi-annual monitoring across time). The authors do not consider these adjustments, however, in their conclusions. For CHD, stroke, breast cancer, and global index the lower boundary of the "adjusted" CI incorporate unity. Thus, these risks are no longer statistically significant. Statistical adjustment for multiple comparisons is not, however, a universally accepted procedure.

WISDOM

The Medical Research Council (MRC) of the United Kingdom has been funding WISDOM (Women's International Study of long Duration Oestrogen after Menopause), a trial similar in design to WHI, that also has been examining the health effects of HRT. As of the summer of 2002, the study had enlisted 5000 subjects with the expectation of having a study population of about 22,000 from the United Kingdom, Australia, and New Zealand. The study was to be run until 2016. The independent safety panel and steering committee of WISDOM recommended that the WISDOM study be continued, particularly because of the ambiguity of the WHI findings.[10]

The WISDOM group's major criticism of the WHI trial pertained to the statistical treatment of the data, particularly the failure to adjust for multiple sampling. This omission, according to the WISDOM group, increases "the chances of getting a spurious result."[11] Nevertheless, by October 2002, the MRC halted the WISDOM project—mainly on the basis of slow recruitment of subjects and the expectation that this study would be unlikely to bring a change in medical practice over the next decade. In spite of this action, the safety panel and steering committees within WISDOM concluded that continuation of the trial was both scientifically valid and ethical.

An Uncertain Future for HRT

To date, there are no general guidelines for the continuation of postmenopausal HRT in light of the WHI study, and certain issues remain unresolved unless further research is conducted. For example, Prempro is one of several forms of HRT that vary in specific formulation (types and potencies of estrogens and progestins) and route of administration (e.g., oral, transdermal patch, gels, vaginal creams, and rings). Whether the apparent risks defined by the WHI apply to all forms of HRT is not known.

If HRT eventually is abandoned as the treatment for postmenopausal problems, do suitable alternative treatments exist? Several treatments do exist for the mitigation of osteoporosis but they are not free of contraindications. The efficacy of herbal preparations containing weak estrogenic activity (e.g., phytoestrogens) as suitable alternatives to real estrogens has not been tested rigorously, despite reports of such in the media.

Recent developments suggest that birth control therapy may face the same fate as HRT. Estrogens used for postmenopausal therapy and oral contraception recently were placed on the official list of known human carcinogens under the auspices of the National Toxicology Program.[12] "Known" human carcinogens have such a designation on the basis of "sufficient evidence" as opposed to a lower rating of "reasonably anticipated" human carcinogens, which are categorized as such on the basis of "limited evidence." In January 2003, the Food and Drug Administration ordered that all products containing estrogen or estrogen + progestin drugs for HRT display a boxed warning that use of the product may increase slightly the risk of heart attacks, strokes, blood clots, and breast cancer.[13]

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The actual data that suggest adverse health effects of HRT are not compelling. Most, if not all, of the risk estimates are weak and have marginal—if not questionable—statistical significance. Whether these estimates will hold up in a court of law as the basis of establishing causation, or will stand the test of time in the court of scientific opinion, remains to be determined.

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