Hormone Replacement Grows; Some Experts Worried

As the vanguard of baby boomers reaches menopause, gynecologists, internists, and family practitioners are prescribing replacement hormones — principally estrogen and progestins — to a growing number of women. This trend worries some experts, and they are sounding the alarm.

Virtually nobody questions use of HRT (hormone replacement therapy) to relieve the acute symptoms of menopause. What concerns the naysayers is that increasingly the hormones are being prescribed on a long-term, even lifelong, basis, in the unproven hope that they will stave off heart disease and osteoporosis.

Rush to Judgment

"It is disturbing that the medical profession is rushing to judgment," said Jacques Rossouw, M.D., lead project officer of the National Institutes of Health Women’s Health Initiative, which is recruiting women for a clinical trial designed to establish definitively the value of long-term HRT. "Those who believe in evidence-based medicine should be worried about the current trends," he added.

Speaking at a recent meeting of the National Cancer Institute’s advisory board, Rossouw reminded listeners of the swings in popularity that estrogen replacement therapy experienced from the 1960s to the 1990s. ERT use underwent a marked decline after it was observed that women treated with high doses of unopposed estrogens often developed endometrial cancer at a higher than expected rate.

The weight of evidence suggests that hormone replacement might lower overall mortality, chiefly by decreasing the incidence of heart disease, and that it might reduce the incidence of osteoporosis as well. Numerous epidemiologic and basic science studies have demonstrated or suggested that HRT has positive effects on bones and arteries, health and longevity.

But definitive clinical trials have not yet been done. For this reason, Food and Drug Administration approval for estrogen only applies to its use for menopausal symptoms and for established osteoporosis; prophylactic use of HRT is entirely off-label.

Estrogens and progestins produce a panoply of effects. And while most of these, including possible influences on mental acuity and incidence of Alzheimer’s disease, appear to be positive, others — both known and potential — are adverse.

Doctors have learned that the increase in endometrial cancer incidence produced by estrogen can be eliminated by giving the patient progestin along with estrogen. But other hazards cannot be so easily avoided. The greatest concern of physicians is that administration of HRT on a long-term basis may increase a woman’s risk of developing breast cancer.

Considerable indirect evidence links estrogen and breast cancer. For example, several known risk factors for the disease, including early menarche and late menopause, can be explained on the basis of increased exposure to estrogen. Epidemiological studies of HRT have yielded contradictory results, but a
reasonable interpretation of the studies suggests that after several years of replacement therapy, breast cancer risk gradually begins to increase, and that the increase continues for the duration of HRT. This added risk appears to occur regardless of whether estrogen is given alone or with a progestin. In some studies, the increased risk did not occur in women who had stopped taking the hormones; in others the risk appeared to be sustained.

Practicing physicians are aware of the evidence that HRT may protect against heart disease and osteoporosis, as well as the studies suggesting that it may increase the risk of breast cancer. Conscious of the fact that heart disease is the number one killer of older women, and that hundreds of thousands sustain hip and other fractures because of osteoporosis, many doctors have weighed the presumptive risks and benefits and concluded that long-term HRT is often appropriate.

William C. Andrews, M.D., professor emeritus of obstetrics and gynecology at Eastern Virginia Medical School, Norfolk, Va., and immediate past president of the American College of Obstetricians and Gynecologists, is representative of these physicians. He counts lowering the risk of heart disease as the most important reason for a woman to consider lifelong HRT. “Almost half the women in the world die of heart disease, so I think this is an enormous reason to give HRT,” he said. “For anyone who can objectively look at the data, I think it is so consistent. Almost every study has shown protection.” Andrews contrasted these data with those regarding estrogen and breast cancer, where some studies show a relationship, while others find none.

Some researchers argue, however, that observational studies — essentially the only studies that have been done to date on long-term HRT — are inherently unreliable because of the likely presence of confounding factors. “[Such studies furnish] the interesting observations that lead one to think that maybe we should do a trial to find out whether this is true or not, but they in themselves can never prove the

---

Mammography Affected by Hormone Replacement Therapy

The possibility that hormone replacement therapy may increase the risk of breast cancer has created a contentious debate (see story). Added to that has been the fear that estrogen given after menopause may make it more difficult to interpret mammograms properly.

Scientists have known for some time that postmenopausal estrogen therapy increases breast density in a significant proportion of women. They have also shown that increased breast density makes it more difficult to diagnose breast cancer by mammography. For these reasons, it has seemed possible that estrogen replacement therapy might diminish the efficacy of screening mammography, and a report in this issue of the *Journal* (p. 643) lends credence to this concern.

According to the new findings, both the specificity and sensitivity of screening mammography are decreased in women over age 50 who are current users of ERT. Epidemiologist Mary B. Lay, M.D., and her colleagues at the University of Washington, Seattle, studied 8,779 postmenopausal women enrolled in the breast cancer screening program of a health maintenance organization in western Washington. The researchers based their analysis on data gathered from medical and pharmacy records, a self-administered questionnaire, and a regional cancer registry.

Compared with former use and never use of ERT, current use was associated with an increased likelihood of both false-positive and false-negative mammographic readings. The relative risk of a false positive for current users versus never users was about 1.33 (33% increase), and that of a false negative was about 5.23 (423% increase).

The ERT effect found in this study would result in an extra 40 false positives for each 1,000 women screened, the authors note. Decreased specificity of this magnitude would add considerably to the emotional and economic burdens of a screening program. Even more serious, if clinically significant, the reduction in diagnostic sensitivity brought about by ERT could severely compromise the ability of screening mammography programs to reduce mortality from breast cancer.

It is possible that withdrawal of ERT for a short time before a scheduled screening mammogram would increase accuracy of the mammogram’s interpretation, and the authors recommend studies to address this issue.

In an editorial (p. 627) accompanying the Lay article, William Black, M.D., Dartmouth-Hitchcock Medical Center, Lebanon, N.H., and Suzanne Fletcher, M.D., Harvard Medical School, Boston, urge that physicians and patients who are considering beginning or continuing ERT take serious account of the new findings in making their decisions.

—Elaine Blume
And even though the data on long-term HRT suggest a strongly favorable ratio of benefit to risk, experts note that other factors must be taken into account.

"We have many ways to lower risk of heart disease," Meir Stampfer, M.D., told the National Cancer Advisory Board. Stampfer, an epidemiologist at the Harvard School of Public Health in Boston, heads the Nurses' Health Study, which has followed 121,700 female nurses since 1976 and has proved to be an invaluable source of epidemiological data on women. "We have identified many risk factors that are modifiable, and a woman can alter her lifestyle in ways that will very markedly lower her risk of breast cancer. So we cannot simply say, well, because many more women die of heart disease, the benefits outweigh the risks."

Similarly, Stampfer and other researchers point out that several safe and effective interventions are available for prevention of osteoporosis; in 1995 the FDA approved two drugs — calcitonin and alendronate — to treat the disease. It is likely that these drugs will be used for prevention as well.

But proponents of long-term HRT are not easily convinced. Andrews, for example, argues that estrogen has effects on blood vessels and bone that go beyond those that can be produced by other means. He and others believe the beneficial effects of estrogen and alternative interventions may be additive and that it may often be best to employ both.

Another concern of experts is that although much of the data physicians are using to make decisions about long-term HRT come from studies on estrogen alone, thousands of patients are taking both estrogen and progestin. The assumption that data collected on estrogen also apply to the combination therapy is largely that — an assumption — and may or may not prove correct.

Tough Decisions

This apparent split between researchers and practitioners is characteristic of medicine at the cutting edge. Researchers, keenly aware of the limitations of their work and the pitfalls in its interpretation, warn against changing practice until final results are in, and some practitioners heed these warnings.

Others, however, caught between the medical dictum *primum non nocere* (first, do no harm) on the one hand, and reluctance to deprive patients of a promising, if uncertain, new treatment on the other, are prepared to move ahead on the basis of the best available evidence. But members of both groups agree that the patient should take part in the decision.

Sandra Adarnson Fryhofer, M.D., an Atlanta, Ga., internist who serves as chair of the Ad Hoc Committee on Women's Health of the American College of Physicians, stressed this point. "There's no such thing as an average patient," she said. "You have to treat patients as individuals and make a decision together."

— Elaine Blume

---

**Treatment Network Focuses on Pediatric Cancers**

The Pediatric Cancer Network, a new cancer research and treatment network for pediatric cancer patients that intends to change the landscape of managed care, has been unveiled by the Blue Cross/Blue Shield Association.

This model is "focused not on the business of health care but on the philosophy of health care," said Pat Hays, president and CEO of Blue Cross/Blue Shield Association. This network is designed to help wage the war against childhood cancer — the 6th most common chronic childhood illness and the number one disease killer of children.

This progressive managed care model, built on the alliances of many institutions and organizations, was developed by the Blues Network in conjunction with the Pediatric Oncology Group and the Children's Cancer Group, two cooperative clinical trials groups supported by the National Cancer Institute. The Pediatric Cancer Network will coordinate the resources of these organizations to provide rapid access to specialized cancer care, treatment, protocols, and counseling for youngsters diagnosed with cancer.

Hays noted that studies conducted by cooperative group members show...