Hormone replacement therapy (menopause)

Hormone replacement therapy (HRT) or in Britain, **Hormone therapy** (HT), is a system of medical treatment for surgically menopausal, perimenopausal and to a lesser extent postmenopausal women. It is based on the idea that the treatment may prevent discomfort caused by diminished circulating estrogen and progesterone hormones. It involves the use of one or more of a group of medications designed to artificially boost hormone levels. The main types of hormones involved are estrogens, progesterone or progestins, and sometimes testosterone. It often referred to as "treatment" rather than therapy.

HRT is available in various forms. It generally provides low dosages of one or more estrogens, and often also provides either progesterone or a chemical analogue, called a progestin. Testosterone may also be included. In women who have had a hysterectomy, an estrogen compound is usually given without any progesterone, a therapy referred to as "unopposed estrogen therapy". HRT may be delivered to the body via patches, tablets, creams, troches, IUDs, vaginal rings, gels or, more rarely, by injection. Dosage is often varied cyclically, with estrogens taken daily and progesterone or progestins taken for about two weeks every month or two; a method called "sequentially combined HRT" or scHRT. An alternate method, a constant dosage with both types of hormones taken daily, is called "continuous combined HRT" or ccHRT, and is a more recent innovation. Sometimes an androgen, generally testosterone, is added to treat reduced sexual desire/(libido). It may also treat reduced energy and help reduce osteoporosis after menopause.

HRT is often given as a short-term relief (often one or two years, usually less than five) from menopausal symptoms (hot flashes, irregular menstruation, fat redistribution etc.). Younger women with premature ovarian failure or surgical menopause may use hormone replacement therapy for many years, until the age that natural menopause would be expected to occur.

Attitudes towards HRT changed in 2002 following the announcement by the Women's Health Initiative of the National Institutes of Health that those receiving the treatment (Prempro) in the main part of their study had a larger incidence of breast cancer, heart attacks and strokes. The WHI findings were reconfirmed in a larger national study done in the UK, known as the the Million Women Study. As a result of these findings, the number of women taking hormone treatment dropped by almost half. The *Journal of the American Medical Association* and elsewhere based on these findings warn that women with normal rather than surgical menopause should take prescribed HRT treatment at the lowest feasible dose, for the shortest possible time. For health problems associated with menopause such as osteoporosis (a small percentage of postmenopausal women are at risk of severe bone loss), other life-style changes and/or medications are now recommended.

Types of hormone therapy

Proprietary mixtures of conjugated equine estrogens (CEE) have been a common prescribed form of HRT, as well as progestins that, while not progesterone, approximate its effects. Studies have shown that certain risks are associated with these combinations of progestins and equine estrogens. Because these have been used most commonly and for the longest time, there are many more studies of these forms of hormones than of some of the newer forms with newer delivery systems, and therefore the most is known about these kinds. Whether or not such risks exist with other forms of estrogens and progestins, and other delivery systems, remain to be seen.

Bioidentical forms of human estrogen and progesterone have not been studied very much. This distinction is important, because the adverse biological effects of xenoestrogens and progestins revealed by studies of Premarin and Prempro do not necessarily generalize to supplementation with human forms of estrogen and progesterone. For example, a pilot study reported in *JAMA* by Smith, Heckbert, et al.[1] found clinical evidence that oral conjugated equine estrogens caused clotting, but the other estrogen compound tested in the same study, bioidentical esterified estrogens, does not. Conjugated equine estrogens were found to be associated with increased venous thrombotic risk. In sharp contrast, the study found that users of esterified estrogen had no increase in venous thrombotic risk.

Additionally, the route of administration may be as important as the type of estrogen administered. For example, in a large study published in *The Lancet* Scarabin et al.[2] compared effects of oral vs. transdermal skin patch estrogen (mainly estradiol-17 beta, the "bioidentical" human estrogen) and found that the oral route was associated with a 3-fold

increase in risk of venous clotting disease (thrombophlebitis, pulmonary embolus), whereas the skin patch produced no excess risk. This difference was likely due to the fact that transdermal estrogens are absorbed directly into the bloodstream, while oral estrogens are processed and changed by the liver before release into the blood stream.

Studies finding adverse health effects of equine estrogens and progestins have often been reported, inaccurately, as revealing effects of "estrogen" and "progesterone". It is important to keep this habitual inaccurate generalization in mind in reviewing press reports. On the other hand, creams, gels, etc, containing "bioidentical" hormones custom-prepared by compounding pharmacies are not subject to FDA monitoring or regulation, so that doses delivered and hormone blood levels produced are unpredictable and may be highly variable, and there are fewer large-scale studies of these items.

It has become increasingly clear that oral progestin and equine estrogen pills can increase a number of risks, including the risks of exacerbation of existing liver or gallbladder problems and of dangerous blood clots. Long-term use of equine estrogens probably also increases the risk of breast cancer.[3]. In women with a uterus, therapy with equine estrogen, unopposed by progesterone, is generally acknowledged to increase the risk of uterine cancers in women with intact uterine linings. This proprietary combination can also affect blood triglyceride levels and increase the risk of adverse cardiovascular events. Although HRT with progestins and equine estrogens was once widely thought to promote cardiovascular health in women, on February 4, 2004, the American Heart Association released guidelines stating that it should no longer be considered as an agent to increase heart health or to decrease the chances of cardiovascular disease.

In 2006, results from the large, ongoing, observational Harvard Nurses' study showed that those taking a pill containing a combination of estrogen with methyltestosterone (a synthetic testosterone analogue) had higher risk of breast cancer than those not taking the methyltestosterone. Unfortunately, few or no studies have tested the safety or benefits of human bioidentical testosterone, or of low-dose non-pill administration of testosterone that avoids the first pass through the liver.

Due to the risks and potential problems of progestins and equine estrogens, a number of alternative therapies have been developed, including lifestyle changes, botanical non-hormone drug therapy (phytoestrogens), and bioidentical hormone replacement therapy. To reduce the risk of osteoporosis without hormones, dietary changes that increase calcium uptake, exercise, and drugs such as biphosphates, selective estrogen receptor modulators, or calcitonin have been tried.

HRT has been proven to be more effective than exercise in reversing the effects of aging on muscle. A future aim is to target therapy to molecular mechanisms that work specifically in selected tissues[4]. This can reduce the extent and severity of side effects.

Conjugated equine estrogens

Conjugated equine estrogens contain estrogen molecules conjugated to hydrophilic side groups (e.g. sulfate). They are produced from the urine of pregnant mares, hence the product name Premarin, the most-prescribed form. In the sister product, Prempro, Premarin is combined with a synthetic progestin, medroxyprogesterone acetate. However Premarin, and especially Prempro, are associated with serious health risks.[5]

In January 2003, the FDA required Wyeth to affix a "black box" warning to Prempro, stating

"WARNING

Estrogens and progestins should not be used for the prevention of cardiovascular disease. The Women's Health Initiative (WHI) reported increased risks of myocardial infarction, stroke, invasive breast cancer, pulmonary emboli, and deep vein thrombosis in postmenopausal women during 5 years of treatment with conjugated equine estrogens (0.625 mg) combined with medroxyprogesterone acetate (2.5 mg) relative to placebo (see CLINICAL PHARMACOLOGY, Clinical Studies). Other doses of conjugated estrogens and medroxyprogesterone acetate, and other combinations of estrogens and progestins were not studied in the WHI ... "

Bioidentical hormone replacement therapy

Recently, interest in "bioidentical" hormone replacement therapy (BHRT) has risen. This term is used to refer to HRT formulated to contain the three main naturally occurring human estrogens estradiol, estrone, and estriol, as well as to refer to bioidentical human progesterone and sometimes testosterone. As recently as 2004, before the release of the Women's Health Initiative (WHI) studies referenced below, the relative benefits of bioidentical hormones over xenoestrogens and progestins were regarded as not yet established.[6] BHRT is often delivered via topical administration of a cream or gel solution of the hormones to the skin, reducing concerns about adverse liver effects of oral medications. Larger-scale studies are still needed to confirm the relative benefits and safety noted in pilot trials of Bioidentical hormone replacement compared with equine estrogen and oral progestins. While chemically, these hormones are identical to those found in the human body, they cannot replicate the delivery system of those produced by the human body, nor the amounts. The human body contains over 25 different types of estrogen, and estradiol, estrone, and estriol are merely the three most common types. However, the body is able to convert estrogens into different hormones to a certain extent.

Results of the WHI hormone replacement therapy studies

Clinical medical practice changed rapidly and dramatically with the results of the two parallel WHI studies of postmenopausal HRT. Prior studies were much smaller, and many were studies of women who were electively taking hormones. This self-selected group tended to be composed of women who were more health-conscious, which was a possible factor to explain why these women tended to be healthier than the average. The WHI studies were the first large, double-blind, placebo-controlled clinical trials of HRT in healthy, postmenopausal women. The WHI estrogen-plus-progestin trial and estrogen-alone trial were both halted early (in July 2002 and February 2004 respectively) because preliminary study results indicated that the health risks of the conjugated equine estrogen and progestin exceeded benefits.

The first report on the halted WHI estrogen-plus-progestin study came out in July 2002.[7] It followed over 16 000 women for an average of 5.2 years, half of which taking a placebo, the other half taking a combination of the progestin medroxyprogesterone acetate and conjugated equine estrogens. The study found statistically significant increases in rates of breast cancer, coronary heart disease, strokes and pulmonary emboli. The study also found statistically significant decreases in rates of hip fracture and colorectal cancer. "A year after the study was stopped in 2002, an article was published indicating that estrogen plus progestin also increases the risks of dementia." [1] The conclusion of the study was that the HRT combination presented risks that outweighed its measured benefits. The results were almost universally reported as risks and problems associated with HRT in general, rather than with the specific proprietary combination of conjugated equine estrogen and progestin studied.

The risks of coronary heart disease varied according to age and years since the onset of menopause. Women aged 50 to 59 using HRT showed a small trend towards lower risk of coronary heart disease,[8] as did women who were within five years of the onset of menopause.[9]

The adverse cardiovascular outcomes may only apply to oral dosing with progestin and equine estrogens, while other types of HRT such as topical estradiol and estriol may not produce the same risks. Results from other studies suggest that when estrogen is administered orally, liver function is altered and the risk of blood clots is increased.[10]

The WHI preliminary results in 2004 found a non-significant trend in the estrogen-alone clinical trial towards a reduced risk of breast cancer[11] and a 2006 update concluded that use of estrogen-only HRT for 7 years does not increase the risk of breast cancer in postmenopausal women who have had a hysterectomy.[12] The results of the WHI estrogen-alone trial suggest that the progestin used in the WHI estrogen-plus-progestin trial increased the risk for breast cancer above that associated with estrogen alone.[13]

After the increased clotting found in the first WHI results was reported in 2002, a large number of women who had been taking the proprietary mixtures of equine estrogens and progestins studied (Prempro) ceased filling their prescriptions. The number of Prempro prescriptions filled was abruptly cut almost in half.