Although menopause, defined as the last menstrual period, is an integral and normal physiologic event in a woman’s life, it represents a sudden and dramatic change in reproductive capability, health risks, and self-image. The perimenopause (the 3 to 5 years before and after menopause) is characterized by symptoms of estrogen deficiency, such as hot flashes, mood swings, insomnia, and difficulty concentrating. The postmenopausal period is associated with increases in more serious health risks, including osteoporosis, cancer, and cardiovascular disease.

As with many women’s health issues, however, menopause traditionally has been poorly understood. Although publications as early as the sixth century noted the characteristic onset of menopause during a woman’s middle age,1 philosophic explorations frequently lacked such simple acumen. As recently as the latter half of the 20th century, authors set menopause in stark terms, including “the death of womanhood.” Menopause, he said, often destroyed a woman’s “character as well as her health.”

Hormone therapy

The strategy of hormone therapy for menopausal and postmenopausal women was advocated based on a number of unsubstantiated claims. Hormone therapy, noted Wilson and Wilson,3 would prevent menopausal women from becoming “dull and unattractive.” While casting this natural physiologic event in an unscientific and misogynist light, these and other authors also missed the more salient point of hormone therapy, that is, the well-documented reduction of clinically significant early and late symptoms of estrogen deficiency.

The concept of hormone replacement has its roots in the late 19th century, when investigators used ovarian preparations for the treatment of symptoms following female castration.5 The 1899 Merck Manual includes dried ovaries of the cow as a treatment for symptoms of the “climacteric,” or menopause.5 Efforts in the 1920s and 1930s to isolate and synthesize hormones culminated in the production of the first synthetic estrogen in 1938: diethylstilbestrol (DES). Approved for marketing in 1941, DES was widely used during subsequent decades for the prevention of miscarriage. Conjugated equine estrogens (CEE) was approved the next year, and to this day, it is perhaps the most widely used estrogen product.

After the synthesis of DES, CEE, and other reproductive hormones such as progestins, these therapeutic agents found their way into multiple products for a number of indications ranging from birth control pills to the prevention of miscarriage and the treatment of menopausal symptoms.

During decades of widespread hormone therapy, observational studies (usually of retrospective design) suggested that estrogen did address the increased risks following menopause, such as protecting against cardiovascular disease and treating osteoporosis. Estrogen, it appeared, was a “magic bullet” for postmenopausal health risks.

Reports of side effects began to emerge in the literature, receiving the attention of consumer and feminist groups. Subsequent activism by these groups led to congressional hearings in 1968 regarding the possible vascular complications and cancer risks of hormone treatment. As a result, the Food and Drug Administration (FDA) issued warnings regarding the use of hormones, particularly oral contraceptives, which at the time contained larger doses (>50 μg) of synthetic estrogen. Other problems followed, including the discontinued use of DES in 1975 owing to the occurrence of cancers in the daughters of women who took the drug while pregnant.

The use of unopposed estrogen in women with an intact uterus also met with concern, as studies showed that it increased the risk of endometrial cancer in this population. The addition of a progestin to hormone therapy was adopted to reduce this risk.

In the late 1980s, emerging data suggested an additional link between hormone replacement and cancer, this time with breast cancer. In their small series in Sweden, Bergqvist et al6 found a statistically significant increase in the risk of breast cancer after 6 years of estrogen replacement therapy. The Nurses’ Health Study and other later publications supported these findings.7-8

Undertaking the Women’s Health Initiative hormone replacement trial

Even by the 1990s, most data regarding hormone therapy and the risk of cancer...
or cardiovascular disease came from observational studies or small-scale non-randomized clinical trials. Inherent biases in observational studies include selection, prescribing, prevention, compliance, survivor, and prevalence-incidence biases, thus limiting interpretation of their results (Figure). Randomized clinical trials (RCTs), however, are designed to eliminate or significantly reduce these biases, and they represent the “gold standard” of scientific evidence. In the early 1990s, RCTs were initiated to examine the questions surrounding hormone therapy, such as potential reductions in cardiovascular events and risk of fractures and various cancers.

The Heart Estrogen/Progestin Replacement Study\(^7\) (HERS) looked at the concept of secondary prevention or the treatment of women with established cardiovascular disease. The HERS compared use of estrogen plus progestin with placebo in postmenopausal women with preexisting coronary artery disease. This study, however, failed to demonstrate any cardiovascular benefit with hormone therapy in women with established heart disease. Further analysis actually showed an increased risk of an adverse cardiovascular event during the first year of treatment with hormone therapy compared with placebo, though a time-trend analysis suggested some improvement in cardiovascular events with continuing treatment.

Initiated around the same time as the HERS, the Women’s Health Initiative (WHI) hormone replacement trial\(^8\) examined the benefit of primary prevention, that is, the use of estrogen plus progestin in healthy, postmenopausal women. To the surprise of many, the estrogen plus progestin arm of the WHI hormone replacement study was discontinued on the basis of an unfavorable overall risks-to-benefits ratio.

**Comment**

The role of traditional hormone replacement therapy (oral estrogen and progestin) remains controversial as the results of both the discontinued arm of the WHI study and the ongoing estrogen-only arm are analyzed. Clinicians are currently recommending traditional HRT only for short-term use in menopausal women with significant symptoms. They are also emphasizing the importance of adequate informed consent when this therapy is used.

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**References**