

Chapter 6

Conclusions

The menopause is defined as the final menstrual period that a woman experiences. It is a single event, retrospectively diagnosed after a year with no menstrual periods. The period of time preceding a woman's last period and the first year after the menopause constitute the *perimenopause*. After a woman experiences the menopause, she is considered *postmenopausal*. Throughout the perimenopause, ovarian hormone production slows and finally ceases; at the end of this time, the female hormone estrogen is no longer secreted by the ovaries. This loss of ovarian estrogen can produce symptoms such as hot flashes and night sweats and is implicated in the development of osteoporosis and cardiovascular disease. For these reasons, some women and their physicians elect hormone therapy for the treatment of symptoms or the prevention of osteoporosis or cardiovascular disease. If a woman is taking only estrogen (unopposed by a progestin), the therapy is referred to as *estrogen therapy*, or ET. If the woman's ovaries have not been surgically removed, common practice increasingly is to prescribe a progestin in addition to the estrogen. (Estrogen alone increases the risk of endometrial cancer; the addition of a progestin reduces that risk.) Women who take both an estrogen and a progestin are receiving combination therapy, which is commonly referred to as *combined hormone therapy*, or CHT. In CHT, the estrogen is opposed by a progestin. The term *hormone therapy* refers either to ET or CHT.

Many American women now face the question of whether to undergo hormone therapy during the menopause and how long to continue it once it has been elected. Few life events, other than aging, affect as many people as the menopause. In the first decade of the 21st century, more than 21 million women from the baby boom generation will reach the age of 50 and become menopausal. Although universal among women, the menopause is a highly individualized experience: some women may hardly notice it while others maybe disabled by it. Often, physicians treat menopause monolithically, as a threat to health, without any recognition that many women traverse the menopause and enter old age with few medical problems. This clinical variability has contributed to the debate about the

appropriate management of the menopause, as part of the natural process of aging in women. Complicating any decision about using hormones for treatment of the symptoms of menopause (e.g., hot flashes, night sweats) is the issue of hormone therapy and the risks it carries, both increased and decreased, for osteoporosis, heart disease, and cancer.

As long as certain issues remain unaddressed and unanswered, a woman's decision regarding the management of her menopause and the possible reduction of future disease risk must be made under conditions of confusion and uncertainty. Research and time will answer some of the questions raised by current menopause management practices; women today, however, have no choice but to face this conundrum with what is known. This background paper reports on what is known about the menopause, hormone therapy, drug prescribing and review, and research needs. Much research has already been conducted, and more is proposed. Interest in the menopause and in the effects of reduced ovarian hormone levels has accelerated in recent years, producing new data that have yet to be fully analyzed or comprehended. Despite increasing efforts to fully understand the mechanisms of the menopause and its relationship to subsequent disease, many issues remain unresolved or in need of attention. They are summarized here.

DETERMINING THE RELATIONSHIP BETWEEN THE MENOPAUSE AND DISEASES OF AGING

One of the most pressing issues related to the menopause is the lack of knowledge about characteristics of women that place them at higher or lower risk for health problems during the menopause and later in life. A better understanding of the natural history of the menopause is critical. Despite its universality in human female aging, the biology of the menopause is incompletely understood. Substantive progress in understanding the etiology and symptomatology of age-related disease among women requires increased knowledge of their inherent biological and psychosociocultural differences. Such

progress is fundamental to accurate diagnosis and effective treatment to reduce morbidity and mortality and to maintain the independence of the rapidly growing postmenopausal population.

The significance of menopausal symptoms (i.e., hot flashes) to subsequent pathophysiology has never been studied. Undoubtedly, incomplete understanding of ovarian hormone action and of the effects of ovarian hormone levels in nonreproductive target tissues has severely constrained the generation of hypotheses about this relationship. A further complication is the marked interindividual differences among women with respect to the manifestation of menopausal symptoms, as well as to susceptibility to chronic diseases. A major challenge to the prevention of disease in older women lies in exploring the effects of both short- and long-term reductions in ovarian hormones on the development of symptoms and disease. Of particular interest are the effects of reduced levels on the development of diseases that may have along latency period or that are temporally removed from the menopause.

As the proportion of older women in the population continues to grow, the need to focus on the prevention of morbidity and disability increases as well. Such prevention will require an understanding of the potential consequences of modifying lifestyle variables (e.g., nutrition, exercise, smoking cessation) and the identification and use of appropriate intervention strategies (both hormonal and non-hormonal). Identifying appropriate strategies requires substantially improved knowledge of the natural history and sequelae of the menopause, and of the role of exogenous and endogenous estrogens and progesterones in the etiology and prevention of disease.

A more complete understanding of the physiological consequences of reduced ovarian hormone levels requires research protocols and subject selection procedures that can assess the effects of age and type of menopause (natural or surgically induced by bilateral oophorectomy) on intermediate biological variables and, ultimately, on the risk of disease. Sensitivity to the potential role of age and cause of menopause is also important in assessing the effects of hormone therapy: there may be marked differences between younger and older women in tissue-specific responses to hormonal therapy and in the benefits to be realized from such treatment in

oophorectomized women compared with those who experience a natural menopause. Other significant covariates include the time elapsed since the menopause before commencement of hormonal therapy and a woman's prior history of hormone use, especially oral contraceptives.

RANDOMIZED CLINICAL TRIALS ARE NEEDED

Thus far, estrogen therapy is the most efficacious treatment modality for the amelioration of menopausal symptoms and the prevention of osteoporosis. Epidemiologic and animal studies strongly suggest ET has the potential to reduce morbidity and mortality from cardiovascular disease. But in the absence of randomized clinical trials, a definitive, unbiased assessment of the beneficial and adverse effects of estrogen with and without progestin in preventing or ameliorating cardiovascular disease is not possible. Objective evaluation of the risks is likewise precluded. Moreover, there are virtually no studies on the effects of long-term ET with progestin—a treatment regimen sometimes recommended for nonhysterectomized women.

Randomized trials to assess the health effects of hormone therapy must be large enough to detect protective effects against cardiovascular disease and osteoporosis (or fractures); in addition, they must be of long enough duration to detect effects that may occur only after relatively long periods (10 years or more) of use. Both the use of unopposed estrogen and of combination therapy should be assessed to identify any differential protective or risky effect. In addition to cardiovascular disease and osteoporosis, the risk of which may be reduced by hormone use, other outcomes that reportedly increase with hormonal therapy—breast cancer, endometrial and other gynecologic cancers, and cerebrovascular disease—are in need of evaluation. Also worth studying (on the risk side of the benefit-risk ratio) is hysterectomy and the morbidity associated with that procedure.

Disease incidence and mortality should be assessed. Comparisons of total morbidity and total mortality among the treatment groups are important to determine overall risks and benefits. Yet an "overall" comparison is insufficient. Rather, comparisons should be made among various age groups, because the benefit-risk ratio may be quite different at various ages. For example, the major benefits of

hormone therapy may be more substantial for older women, while the major risks may increase for those who are younger; such an outcome would influence one's interpretation of the benefit-risk ratio for hormone therapy. As these results are obtained, it will become possible to calculate the costs of treatment for each group and to compare them with the benefits and risks.

For both cardiovascular disease and osteoporosis, a protective effect of estrogen therapy appears to be related to the duration of use: women may have to take the drugs for relatively long periods (10 to 15 years) to prevent disease. In addition, because the adverse effects of hormone therapy on the risk of breast cancer also may not become apparent until decades later, trials must be of sufficient duration to detect any effects that may occur. A large study of nurses showed that those nurses who had "ever used" hormones were no more likely to develop breast cancer than women who had never used them; "current users," on the other hand, had a higher incidence. These findings are interpreted to mean that hormone therapy accelerates the development of breast cancers in some women and that those cancers are detectable soon after therapy begins. Furthermore, the findings indicated such cancers appear to be less malignant than most breast cancers. The nurses' study, however, was a general investigation into women's health; other studies are needed to examine each of these hypotheses in a more focused way.

Besides the issue of sufficient duration of the research, experimental design must be carefully considered and treatment regimens carefully constructed. Hormone therapy, particularly combination therapy, can have unpleasant side effects. To encourage adherence to combination therapy in study groups will require substantial attention; otherwise poor adherence could diminish the ability of a trial to detect any effects from long durations of use. For these reasons, randomized trials of hormone therapy will be neither easy nor inexpensive to conduct.

Because estrogen and progesterone affect a host of tissues throughout the body, future research should foster an integrated, multidisciplinary approach such as that used in the National Institutes of Health (NIH) current Postmenopausal Estrogen/Progestin Intervention (PEPI) Trial with its multiorgan system evaluation of risk factors and intermedi-

ate points of disease. Randomized **clinical trials of this kind, with their** long-term followup studies and assessments of multiple morbidity and **mortality** endpoints, are crucial to an objective evaluation of risks and benefits. Through the PEPI trial, NIH is investigating the **effects on** intermediate endpoints of different regimens of combined therapy used for 3 years **each**.

REFINING ESTIMATES OF INDIVIDUAL RISKS AND BENEFITS FROM HORMONE THERAPY

If women and their physicians had a better understanding of predictors of risk, they could **make** more informed decisions about interventions related to menopausal symptoms, cardiovascular **disease**, osteoporosis, and gynecologic and breast cancer. **Few** other recently introduced medical interventions **have as great a potential** for affecting morbidity and mortality **as does** hormone therapy. **Some risks are** reduced, **some are** increased, and **some** remain uncertain, and **these** data continue **to be** interpreted differently **by** various scientific, medical, and consumer groups.

Women who seek treatment for menopausal symptoms and the doctors who treat them are more likely to advocate a treatment approach, whereas those who report few symptoms are more sympathetic to the avoidance of medical interventions. The most common diagnosis mentioned in relation to prescription of estrogen is menopausal symptoms. Researchers are becoming increasingly convinced that loss of ovarian hormones plays a significant role in the etiology of age-related pathology in women, yet the relationships are not clear. Although cessation of the menses is not a disease, many researchers and clinicians believe that the resulting decrease in ovarian hormone production can lead to disease in some women, thereby justifying preventive intervention through hormone therapy, either as estrogen alone or in combination with a progestin.

The debate over hormone therapy focuses on whether it should be used to treat menopausal symptoms for a short period of time, thereby reducing any risks associated with long-term treatment, or whether it should also be used to prevent future disease, thereby requiring longer treatment that could increase the risk of cancer.

For most women, the short-term use of hormones has known benefits (e.g., relief of hot flashes) and some known risks (e.g., endometrial cancer); long-term use has known risks (again, endometrial cancer) and benefits (e.g., prevention of osteoporosis and cardiovascular disease), as well as unknown outcomes (e.g., risk of breast cancer). To prevent osteoporosis and cardiovascular disease, estrogen must be taken for long periods of time, possibly until death. The impact of such long-term use is not clear. The effects of adding a progestin to the treatment are even less clear, and in this case, the dilemma is sharper.

Should women be treated with a drug to prevent a disease they might never get? Across-the-board prescriptions for hormone therapy may, in the aggregate, reduce morbidity and mortality. It is a practice that must be questioned, however, when some individuals will be placed at higher risk, even though others benefit. Risks and benefits must be considered individually.

Although the menopause can be expected to occur naturally around age 50, many women, as many as 37 percent, will experience the symptoms of menopause at an earlier age owing to removal of their ovaries through hysterectomy. Oophorectomized women are also at higher risk for diseases of aging such as osteoporosis and cardiovascular disease. In this group of women, appropriate treatment for the severe, sudden symptoms of the menopause following hysterectomy is a critical issue, and not as simple as short-term relief. For many women, the use of estrogen will be an essential postoperative therapy that may have to be continued for 20 to 30 years.

Approximately 15 percent of women who are eligible for hormone therapy are now receiving it. This means 85 percent of eligible women either do not want or need the therapy, or do not know about it. There is little argument about the benefits of estrogen for the alleviation of the most uncomfortable symptoms of the menopause, specifically, hot flashes. Approximately 15 percent of women report symptoms so disruptive that they consider them disabling and consequently seek treatment. Although most women experience hot flashes, most do not seek treatment. There have been no studies to document the number of women who suffer severe symptoms and either do not choose or do not know how to seek treatment.

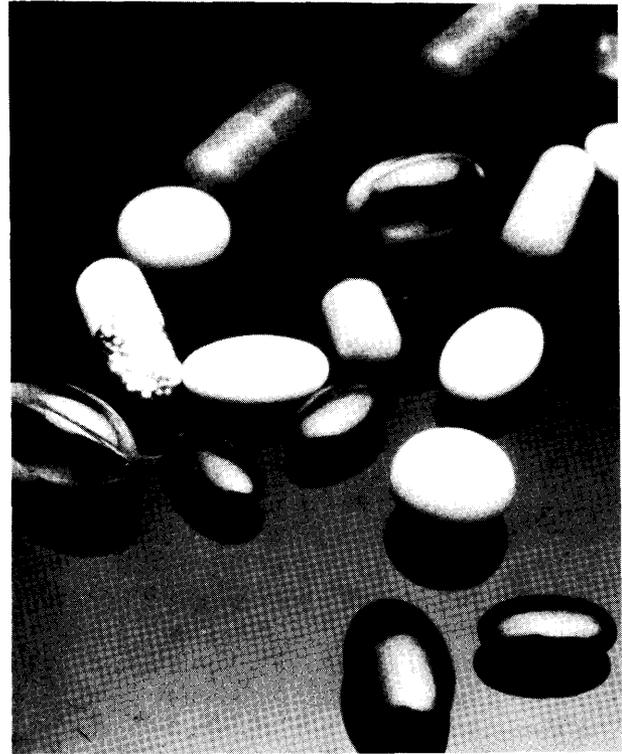


Photo credit: National Cancer Institute

Deciding which therapy to undergo, estrogen or combined, is a sometimes confusing proposition.

There are a number of reasons women may not elect to use hormone therapy. First, it is an optional drug treatment; a woman's life is not immediately threatened if she 'does without it.' Second, women who discontinue hormone therapy after a few years may experience a "rebound effect," or return of symptoms, and bone loss again accelerates. Some women may want to put the experience of hot flashes behind them more quickly by avoiding treatment. Third, side effects such as cramping, water retention, and withdrawal bleeding may be a disincentive to continue or even to seek treatment. Fourth, and perhaps the most critical, in considering long-term use of hormones, women may fear cancer more than heart disease. Discerning how the epidemiologic data refine and define relative versus absolute risk is complex, and interpretation of risks depends on how women define *quality of life* (see box 6-A).

Quality-of-life issues must be decided by each woman. What is a disability to some women maybe merely a nuisance to others. Research has demon-

Box 6-A-Comparing Risks and Benefits

In late 1991, convincing data from the Nurses' Health Study described the apparently protective effect of postmenopausal estrogen replacement therapy in relation to cardiovascular disease. In discussing the findings of the study as they relate to the competing risks and benefits posed by hormone therapy, Lee Goldman and Anna N.A. Tosteson concisely articulated the quandaries of competing risks and benefits:

A fundamental and not widely appreciated principle of epidemiology is that relative risks should not be confused with absolute risks. A twofold increase in the risk of a rare event may not be nearly as important as a 10 percent decrease in the risk of a common event. Consider the following: from the age of 65 through the age of 74, a woman has about a 6 percent risk of dying from ischemic heart disease, a 1 percent risk of dying from breast cancer, a 0.6 percent risk of dying from complications related to a hip fracture, and if her uterus has not been removed, a 0.4 percent risk of dying from endometrial cancer. If the sum of epidemiologic evidence is approximately accurate, what will estrogens do to those 10-year risks? A 60 percent reduction in the risk of hip fracture will lead to an absolute benefit (a 0.36 percent absolute reduction) that is roughly equivalent to the absolute increase (0.30 percent) in the risk of breast cancer attained with a relative increase in that risk by 30 percent. After these two competing factors have canceled each other out what other issues are we left with? First, hip fracture is only one of the many complications of osteoporosis, so there is substantial additional benefit from estrogen in this regard. Second estrogens relieve perimenopausal symptoms, although it is uncertain how women will value this benefit as compared with the inconvenience of estrogen-related bleeding.

Perhaps the most intense debates relate to heart disease and endometrial cancer. A 40 percent reduction in a 6 percent risk of death from ischemic heart disease would result in a substantial benefit (a 2.4 percent absolute reduction in mortality). A sixfold increase in a 0.4 percent risk of death from endometrial carcinoma would result in a nearly equivalent 2.4 percent increase in the absolute risk; however, epidemiologic data suggest that mortality is only about 10 percent as high for endometrial cancer associated with the use of exogenous estrogen as for "naturally occurring" disease, presumably because of earlier detection brought on by symptoms and closer observation. If this much lower risk is the true one, a major reduction in the incidence of ischemic heart disease with postmenopausal estrogen-replacement therapy would greatly outweigh all other effects on life expectancy.

What individual women would do with this type of analysis is not clear. Numerical risks, although quantitatively equal, may be perceived as qualitatively different. In addition, women will make decisions based on their family history (or genetic risk) of disease and their own life experiences (e.g., a friend who dies of breast cancer, an elderly neighbor hospitalized for repeated fractures). Risk assessment, even if sharpened over time, must be considered in the light of risk perception when evaluating the current and future use of hormone therapy by postmenopausal women.

SOURCE: L.Goldman and A.NA. Tosteson, "Uncertainty About Postmenopausal Estrogen: Time for Action Not Debate," *New England Journal of Medicine* 325(11):800-802, 1991.

strated that women give high priority to the short-term impact of hormone therapy on their lives and do not make their decisions based on the risks of morbidity and mortality. In effect, they afford greater weight to considerations of quality of life over quantity of life.

The lack of good data on the use of hormone therapy is a major problem because it confuses any interpretation of risks and benefits. If it is not clear how many women are actually using ET or CHT, projections of risks and benefits are bound to be erroneous. The discrepancy between the stated prescribing philosophies of physicians and the actual use of hormone therapy suggests the menopausal woman may be assuming the role of informed consumer rather than accepting without question the treatments prescribed by her doctor.

CLARITY IN PRESCRIBING PRACTICES AND LABELING

There is no official standard or protocol for administering or prescribing combination therapy. Moreover, no conclusive studies have been performed to indicate which regimen (opposed or unopposed estrogen) is most beneficial. Finally, no studies have been done that meet adequate design, duration, and sample size requirements to determine conclusively the risks and benefits of long-term use of combined therapy.

At present, the Food and Drug Administration (FDA) has approved no combination estrogen and progestin product for sale in the United States, although some are undergoing clinical testing. In contrast, several combination products are available

in Europe. Regimens that prescribe separate estrogen and progestin products are common both here and in Europe. Anecdotal information indicates that as many as 19 different regimens are prescribed in the United States and more than 100 are prescribed in Europe. This variety means that women face a confusing range of options and often conflicting recommendations.

In 1990, total sales of estrogen products were close to \$460 million. Premarin, the top-selling estrogen, is the fourth most prescribed drug in the United States. Estrogen products approved for treatment of the menopause have labeled indications for the treatment of vasomotor symptoms or hot flashes, and Premarin and Estraderm have been approved for the prevention of osteoporosis. None of the progestins used in CHT have been approved by the FDA for treatment of menopausal symptoms, but their use for this purpose is common medical practice. The FDA is considering changes in labeling of the hormones that would reflect the cardioprotective effect of unopposed estrogen use and whether to recommend the use of combined estrogen and progestin therapy for women with intact uteri.

The approval of generic forms of estrogens also remains a topic of debate within the industry and at the FDA. Until the spring of 1991, generic conjugated estrogens were on the market. In that year, however, the FDA withdrew approval for these compounds on the basis of demonstrated bioequivalence.

Although Premarin is relatively inexpensive (approximately \$14 for a month's supply), monitoring programs to screen for cancers of the breast and uterus are not. If hormone therapy is to be widely administered, consideration of costs must include all relevant expenditures.

INVESTIGATING ALTERNATIVES TO HORMONE THERAPY

Estrogen is the most widely used treatment for menopausal symptoms, specifically, for vasomotor symptoms, or hot flashes. But estrogen is contraindicated for a number of women; consequently, they and others seek nonhormonal, nondrug treatments for these symptoms. As with any drug, hormones are not without side effects, a circumstance that may dissuade some women from either starting or maintaining treatment. There is limited research on

alternatives to hormone therapy—i.e., other hormones, nonhormonal drugs, and nondrug products—and large-scale clinical investigation of most of these treatments is nonexistent. Many small-scale studies have been done, however, and evidence shows that these treatments are somewhat successful in remedying hot flashes (although none is as effective as estrogen). Anecdotal evidence indicates that many women try “home remedies” for the alleviation of menopausal complaints. It is not clear how effective these remedies are and if so, for what severity of complaint.

Convincing research into alternatives to hormone therapy is limited. In addition, the true contributions to cardiovascular disease and osteoporosis of such factors as lifestyle—e. g., diet, exercise, smoking—socioeconomic status, race, and genetic predisposition deserve further investigation. Better understanding of these areas could identify more effective alternatives to hormone therapy.

PROFESSIONAL AND PUBLIC EDUCATION

Many studies have shown that women feel disenfranchised from the health care system and contend that providers do not listen to them. They also report having inadequate information on which to base a decision concerning hormone therapy. Patients and health care professionals alike tend to know relatively little about the menopause and about the risks of conditions that may be associated with it. There is no consensus within the medical community about even the definition of the menopause, let alone the risks and benefits associated with hormone therapy, and there is little information about a woman's natural progression through the menopause and the years that follow. Moreover, there is no agreement on what constitutes a “normal” menopause and few conclusive research findings on the normal hormonal changes associated with aging.

Physicians and women need more and better resources to learn about the menopause and hormone therapy. Even the limited information now available is not well distributed to women and their physicians. For example, better informed decisions would flow from more information about the menopause and potential symptoms; about changes in the risks of cancer, heart disease, and osteoporosis that occur after menopause and with increasing age; about the pros and cons of hormone therapy; and about the role

of diet, nutrition, and exercise programs in health promotion and disease prevention.

PROSPECTUS

An enhanced quality of life for older women depends on improvements in early diagnosis, which in turn require the identification of risk factors (some of which are entirely different from those for men) and the development of strategies for prevention and therapy. It also requires objective findings from

well-controlled studies to determine who will benefit and how, for how long a particular intervention (either hormonal or nonhormonal) will be effective, and how such interventions affect different body systems and organs. Better quality of life for women after the menopause also requires increased understanding of women's physiology in general. And it requires the dissemination of badly needed information relating to the menopause to physicians and their patients.