

Chapter 1

Introduction

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Chapter 1

Introduction

At the turn of the century, fewer than 5 million American women were older than 50, the average age at which the menopause occurs in this country. 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. In 1991 alone, 1.3 million women turned 50, marking the end of reproductive fertility for those who have not already been rendered sterile as a result of hysterectomy; they join the 35 million other women who have reached the menopause-either surgically or naturally-and who constitute more than one-third of the total female population of the United States (18). With a current life expectancy approaching 80 years, these women can expect to spend more than a third of their life with reduced ovarian hormone levels.

This increasing longevity and the changing demographics noted above will require dramatic changes in the delivery of preventive and clinical health care for women. Women already constitute a significant portion of the practices of many physicians. Indeed, more than 58 percent of the approximately 1.32 billion physician-patient contacts in 1989 were with female patients, and women over the age of 44 accounted for more than 41 percent of these contacts (19).

Furthermore, growing awareness of the role of gender in differential patterns of disease and disability in later life underscores a critical need for gender-specific perspectives in developing research agendas and methodologies. Women constitute approximately 59 percent of the U.S. population aged 65 and older, and about 72 percent of the population aged 85 and older (20). Substantive progress in understanding the etiology and clinical picture of age-related disease among women will require increased sensitivity to their inherent biological and psychosociocultural differences. Such progress is fundamental to accurate diagnosis and effective treatment to reduce morbidity and mortality and maintain the independence of the rapidly growing population of postmenopausal women.

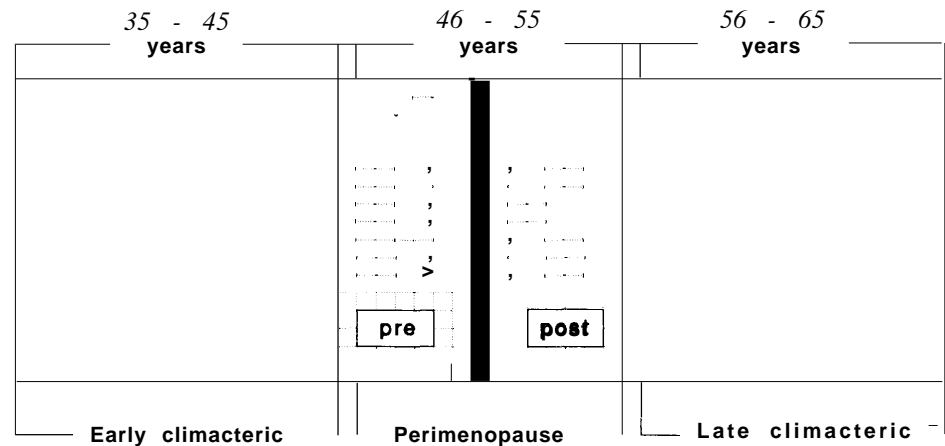
A better understanding of the natural history of the menopause is critical to providing better care. Despite its universality as an event in human

female aging, the menopause and its biology are incompletely understood. Researchers are becoming increasingly convinced, however, that the loss of ovarian hormones plays a significant role in the etiology of age-related pathology in women. Managing diseases and disorders among middle-aged women requires more information to help practitioners differentiate those disorders whose etiologies stem from a cessation of ovarian hormone production (and that are thus potentially treatable by hormone therapy) from those that do not. Only then can misdiagnosis-or dismissal--of the medical complaints of midlife women be prevented.

As the average woman approaches age 50, her ovaries-the primary source of the female hormone estrogen-gradually cease to function as they have since menarche. As follicle depletion occurs in the ovaries, ovarian hormone production slows, and the menstrual cycle typically becomes irregular and finally ceases. For the purposes of this report, the term *menopause* is defined as the final menstrual period that a woman experiences, although *menopause* colloquially describes the transition from the reproductive to the nonreproductive state. The date of the menopause can be accurately pinpointed: It is retrospectively diagnosed after a year with no menstrual periods (9,21). The less frequently used term *climacteric* refers to the phase during which a woman passes from the reproductive to the nonreproductive state. The last few years of the climacteric and the first year after the menopause are the *perimenopause*. The menopause, a single event, is easy to define; the climacteric and perimenopausal periods are much more difficult to quantify and evaluate, particularly from the patient's perspective. The terms *premenopausal* and *postmenopausal* describe, respectively, the state of active ovarian estrogen production and the state of absent ovarian estrogen production (see figure 1-1).

Women whose menses are stopped surgically by removing the ovaries have a sudden and atypical postmenopausal experience. Nevertheless, in studies of the menopause, this group of women is often mistakenly included with those who experience a natural menopause (2,9,12). This report makes an effort to clarify the distinction between natural and surgical menopausal issues whenever they arise.

Figure I-I—The Transition from Reproductive to Nonreproductive Life



NOTE: In this report the perimenopause is defined to be the last few years of the earlyclimacteric and the first year after the menopause.

SOURCE: Adapted from M. Notelovitz, "The Non-Hormonal Management of the Menopause," J.W.W Studd and M.L. Whitehead (eds.), *The Menopause* (Oxford, UK: Blackwell Scientific Publications, 1988).

Few topics in women's medicine today are as fraught with confusion and controversy as the question of appropriate treatments for menopausal symptoms and the prevention of the long-term health outcomes associated with postmenopausal women-osteoporosis and cardiovascular disease. Because decreased estrogen appears to underlie the disturbing symptoms of the menopausal period as well as the susceptibility to bone loss that often leads to osteoporosis, it is not surprising that the administration of estrogen relieves some of these problems.

Since 1937, practitioners have known that estrogen therapy¹ prevents the occurrence of such menopausal symptoms as hot flashes and vaginal dryness (6). The 1960s and early 1970s saw a dramatic increase in retail prescriptions for noncontraceptive estrogens for the treatment of these symptoms. Some attribute the rise in use to the best-selling book *Feminine Forever* by Robert Wilson (22), who claimed that the menopause could be averted and aging allayed with estrogen therapy.

In 1975, however, two case-control studies produced risk estimates that women who used estrogen therapy were four to seven times more likely to develop endometrial cancer than women who did not (8). After further reports of a possible association

between estrogen use and endometrial cancer, sales of estrogen dropped by almost 30 percent (8). The subsequent decline in estrogen prescriptions was followed by a decline in the rate of endometrial cancer.

Women and the medical establishment consequently became more conservative in their use of estrogen. An additional factor in this trend was the fear of increased risk of breast cancer resulting from estrogen use, a fear that has never been satisfactorily resolved. Breast cancer strikes one of every nine women in the United States; it is the second most frequent malignancy among women, constituting 26 percent of all cancers (lung cancer is the most frequent) (1). About 50 percent of breast tumors require estrogen for growth. For some women, increasing the odds of developing breast cancer in any way is unacceptable, and they either refuse estrogen therapy altogether or refuse to comply with prescribed treatment regimens.

In trying to determine the extent of the risk of endometrial cancer associated with estrogen use, researchers found that adding a progestin to estrogen could protect women against endometrial cancer by opposing the effects of the estrogen (hence the terms

¹The use of estrogen for the relief of hot flashes is commonly referred to as estrogen replacement therapy, or ERT. Because some consumer groups oppose the notion that the menopause causes an estrogen deficiency that requires replacement, OTA uses the term *estrogen therapy, or ET*, to describe this practice.



Photo credit: National Cancer Institute

Women are living as much as a third of their life postmenopausally. Decisions about hormone treatment and its effect on subsequent health are based on uncertainty for many women.

opposed and *unopposed estrogen*).² *Estrogen* stimulates the growth of endometrial tissue (the lining of the uterus) while progestins cause shedding of the estrogen-thickened endometrium, lessening the chances that cancer will develop. Progestins have side effects, however, that lead many women to cease therapy. Nevertheless, it has become increasingly more common to prescribe both estrogen and a progestin, or combined hormone therapy, for menopausal women who still have an intact uterus.

Recent studies have shown that estrogen may play a role in preventing cardiovascular disease (3,4,7, 11), which adds a new incentive for prescribing hormones. The effect of progestin on cardiovascular disease prevention, however, is unknown. Since progestins at least partially reverse the favorable

effects of estrogen on circulating cholesterol levels, the addition of a progestin might diminish or completely eradicate the protective effect against cardiovascular disease provided by unopposed estrogen (10).

The debate over hormone therapy—in particular unopposed estrogen—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 (e.g., endometrial cancer) and benefits (e.g., prevention of osteoporosis and cardiovascular disease), as well as unknown outcomes (e.g., risk of breast cancer). The Nurses' Health Study, the largest longitudinal study of women in the world, found an increased risk of breast cancer associated with "current use" of estrogen (5). As with any form of medication, the benefit of relief of symptoms must be weighed against adverse side effects or complications.

ORIGINS AND ORGANIZATION OF THE REPORT

Congressional interest in matters related to the health of women has mounted in the past 5 years. Numerous bills have been introduced (see table 1-1) to address the apparent lack of attention to women's health issues by agencies of the Public Health Service (PHS), in particular, the National Institutes of Health (NIH) and the Food and Drug Administration (FDA). An October 1990 letter to the Office of Technology Assessment (OTA) from Representatives Patricia Schroeder and Olympia Snowe, co-chairs of the Congressional Caucus for Women's Issues, and Senator Brock Adams questioned whether current research programs at NIH and other PHS agencies adequately addressed the menopause. Senator Adams and the caucus requested that OTA study the current state of knowledge regarding the menopause and its management, assess the scope and depth of existing research, and identify those areas

² The addition of a progestin to the estrogen regimen is a practice commonly referred to as hormone replacement therapy, or HRT. For the reasons cited in footnote 1, OTA refers to this form of treatment as *combined hormone therapy*, or CHT. Collectively and generally, the term *hormone therapy* describes either *estrogen* therapy or combined hormone therapy, when a distinction is not necessary.

Table I-I—Women's Health Legislation Introduced in the 102d Congress

Title I—Research

Women's Health Research Act
Clinical Trials Fairness Act
Women's Mental Health Research Act
Women and Alcohol Research Equity Act
Breast Cancer Basic Research Act
Contraception and Infertility Research Centers Act
Sense of Congress Resolution Regarding Contraceptive Research
Women and AIDS Research Initiative Amendments
Ovarian Cancer Research Act
Osteoporosis and Related Bone Disorders Research, Education, and Health Services Act

Title I/-Services

Breast Cancer Treatment Informed Consent Act
Women's Health Care Coverage Expansion Act
The Mickey Leland Adolescent Pregnancy Prevention and Parenthood Act
Adolescent Health Demonstration Projects
COBRA (Consolidated Omnibus Budget Reconciliation Act of 1985) Displaced Family Amendments
Federal Employee Family Building Act

Title I/-Prevention

Medicaid Infant Mortality Amendments
Medicaid Women's Basic Health Coverage Act
Breast Cancer Screening Safety Act of 1991
Medicare Bone Mass Measurement Coverage Act
Women and AIDS Outreach and Prevention Act
Infertility Prevention Act

SOURCE: Congressional Caucus for Women's Issues, 1992.

in need of further attention. Specifically, Congress was interested in hormone therapy—both opposed and unopposed estrogen use—the most common medical treatments for menopausal symptoms. In June 1991, Senator Barbara Mikulski and Representative Henry Waxman endorsed the project and requested that OTA investigate as well the comparative effectiveness of alternatives to hormone therapy for the treatment of menopausal symptoms and postmenopausal disease.

Clearly, widespread interest in understanding sex differences in disease morbidity and mortality exists and could lead to improvements in prevention, treatment, and care for women. Pressure from Congress for action has led to a new NIH initiative to study the effects on women's disease risk of changes in diet and exercise patterns, the use of hormones, and smoking cessation; the study focuses specifically on the risks of cancer, cardiovascular disease, and osteoporosis. Many experts believe that the menopause and the physiological changes that accompany reduced ovarian function play a significant role in the etiology of these diseases.

This report focuses on the menopause as a delineating point in the life of women. Chapter 2 addresses what is known about the factors leading up to and causing the diminishment of ovarian production of estrogen, and how these changes immediately affect the health and well-being of women; it also discusses the long-term health consequences of reduced ovarian estrogen production. Chapter 3 describes the risks and benefits of estrogen therapy (ET) and combined hormone therapy (CHT), the most common treatments for menopausal symptoms. The chapter also presents information about nonhormonal approaches to management of menopausal symptoms and why women choose the treatments they do. The marketing and regulation of the hormones prescribed for menopausal symptoms and prevention of osteoporosis and cardiovascular disease are described in chapter 4, together with what is known about prescribing practices. Chapter 5 sets forth the areas in which research is needed and discusses the role of the Federal Government in addressing those needs. Also included are data on the current Federal investment in research in those areas. Chapter 6 provides a summary and conclusions.

Previous OTA reports on women's health are *Costs and Effectiveness of Screening for Cervical Cancer in the Elderly* (15), *Infertility: Medical and Social Choices* (16), *Breast Cancer Screening for Medicare Beneficiaries* (14), and *Adolescent Health* (13). An additional forthcoming OTA report is an assessment of *Policy Issues in the Prevention and Treatment of Osteoporosis* (17). That report addresses the costs and effectiveness of the use of estrogen for the treatment of osteoporosis.

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