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Reproductive Aging, Nomenclature, Endocrinology, Symptomatology, and Implications

INTRODUCTION

Throughout recorded history, multiple physical and mental conditions have been attributed to menopause. Although medical writers often wrote colorfully in the past, unfortunately they were also less than accurate, unencumbered by scientific information and data, and often approached reproductive aging and menopause as a "disorder" rather than as a normal phase along the continuum of aging. A good example of the stereotypical, inaccurate thinking promulgated over the years is the following statement, which dates back to 1887[1]:

The ovaries, after long years of service, have not the ability of retiring in graceful old age, but become irritated, transmit their irritation to the abdominal ganglia, which in turn transmit the irritation to the brain,

producing disturbances in the cerebral tissue exhibiting themselves in extreme nervousness or in an outburst of actual insanity.

The belief that behavioral disturbances are related to manifestations of the female reproductive system is an ancient one that has persisted to contemporary times. Happenings such as aging-related illness or disability (or even death) in a spouse, relative, or friend; retirement from employment; financial insecurity; the need to provide care for very old parents and relatives; separation from children all likely underlie perceptions that associate the middle years of life with negative experiences, and problems arising from life events have often been erroneously attributed to the menopause.

The scientific study of all aspects of menstruation has been hampered by the overpowering influence of social and cultural beliefs and traditions. Problems arising from life events have often been erroneously attributed to menopause. Regrettably, not just societal perspectives, but also health care providers may be culpable in the perpetuation of this negative narrative of menopause, as only patients with bothersome symptoms come seeking help, with resulting sample bias adding to the distorted understanding of reality. However, robust data from reliable community-based longitudinal studies establish that the increase in most symptoms and problems in middle-aged women reflects social and personal circumstances, not the endocrine events of menopause.[2–11] The variability in menopausal reactions makes the cross-sectional study design particularly unsuitable. Longitudinal studies are better for documenting what is normal and the variations around normal.

It is important to stress the normalcy of reproductive aging, with the final menstrual period (FMP) marking a physiologic watershed between reproductive and postreproductive phases of life. Longitudinal data have identified a relevance of societal, cultural, and personal perspectives for the severity of symptom burden that has long been attributable to reproductive aging in middle-aged women, and that the cessation of menses following menopause had almost no impact on subsequent physical and mental health.[2–12] The Massachusetts Women’s Health Study, a large and comprehensive prospective, longitudinal study of middle-aged women, provides a powerful argument that the menopause is not and should not be viewed as a negative experience by the vast majority of women.[3,12] The cessation of menses was perceived by these women (similarly to women in

other longitudinal studies) as having almost no impact on subsequent physical and mental health. This was reflected by women expressing either positive or neutral feelings about menopause. An exception was the group of women who experienced surgical menopause, but there is good reason to believe that the reasons for the surgical procedure were more important than the cessation of menses.

Changes in menstrual function are not symbols of some ominous "change." There are good physiologic reasons for changing menstrual function, and understanding the physiology will do much to reinforce a healthy, normal attitude. Attitude and expectations about the menopause are very important. Women who have been frequent users of health services and who expect to have difficulty do experience greater symptoms and higher levels of depression.[4,8,9] The symptoms that women report are related to many variables within their lives, and the hormonal change at menopause cannot be held responsible for the common psychosocial and lifestyle problems we all experience. It is important to stress the normalcy of this physiologic event. Menopause is not a disorder or a disease, and postmenopausal hormone therapy should be viewed as a specific strategy for management of symptoms in the short term for many, and as preventive pharmacology in the long term for some.

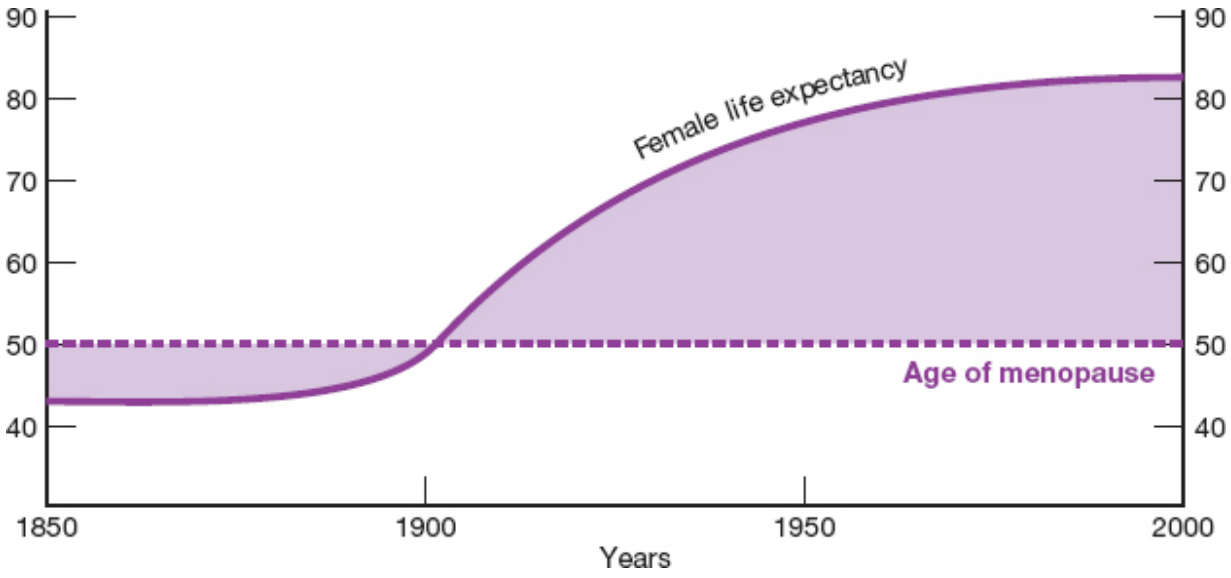


FIGURE 21.1 After Cope E. Physical changes associated with the post-menopausal years. In: Campbell S, ed. *The Management of the Menopause & Post-Menopausal Years*. University Park Press; 1976:33. Copyright © 1976 MTP Press Limited.

It can be further argued that physicians have had a biased (negative) point of view because the majority of women, being healthy and happy, do not seek contact with physicians.[13,14] It is vital, therefore, that clinicians are not only familiar with the facts relative to the menopause but also have an appropriate attitude and philosophy regarding this period of life. Medical intervention at this point of life should be regarded as an opportunity to provide and reinforce a program of preventive health care. The issues of preventive health care for women are familiar ones. They include family planning, cessation of smoking, control of body weight and alcohol consumption, prevention of cardiovascular disease (CVD) and osteoporosis, maintenance of mental well-being (including sexuality), cancer screening, and treatment of urologic problems.

GROWTH OF THE OLDER POPULATION

We are experiencing a relatively new phenomenon: *we can expect to become old.* We are on the verge of becoming a rectangular society in which nearly all individuals survive to advanced age. In 1,000 BC, life expectancy was only 18 years. By 100 BC, the times of Julius Caesar, it had reached 25 years. In 1900, in the United States, life expectancy was only 49 years **(Figure 21.1)**. In 2005, the average life expectancy was 80.7 years for women and 75.4 for men.[15] Today, once you reach age 65, you can expect to reach 83 if you are a man, and if you are a woman, age 85.[16] We can anticipate that eventually, about two-thirds of the population will survive to 85 or more and that more than 90% will live past age 65—this would be the nearly-perfect rectangular society **(Figure 21.2)**.[17,18] Currently, Sweden and Switzerland are closest to this demographic composition.

A good general definition of older adults is individuals aged 65 years and older, although it is not until age 75 that a significant proportion of individuals have an increase in health problems. Today, the older adult population is the largest contributor to illness and human need in the United

States. There are more old people (with their greater needs) than ever before.[19] In 1900, there were approximately 3 million Americans aged 65 years and older (~4% of the total population), and in 2000, there were 35 million (~12% of the total population). By 2030, the older adult population in the United States will reach about 70 million, or about one in five Americans will then be aged 65 years or older.[19] The world's older adult population will become more than doubled from 1998 to 2025, rising from 264 million in 2009 to 416 million in 2050.[20] Population aging must be added to population growth as very important social problems.

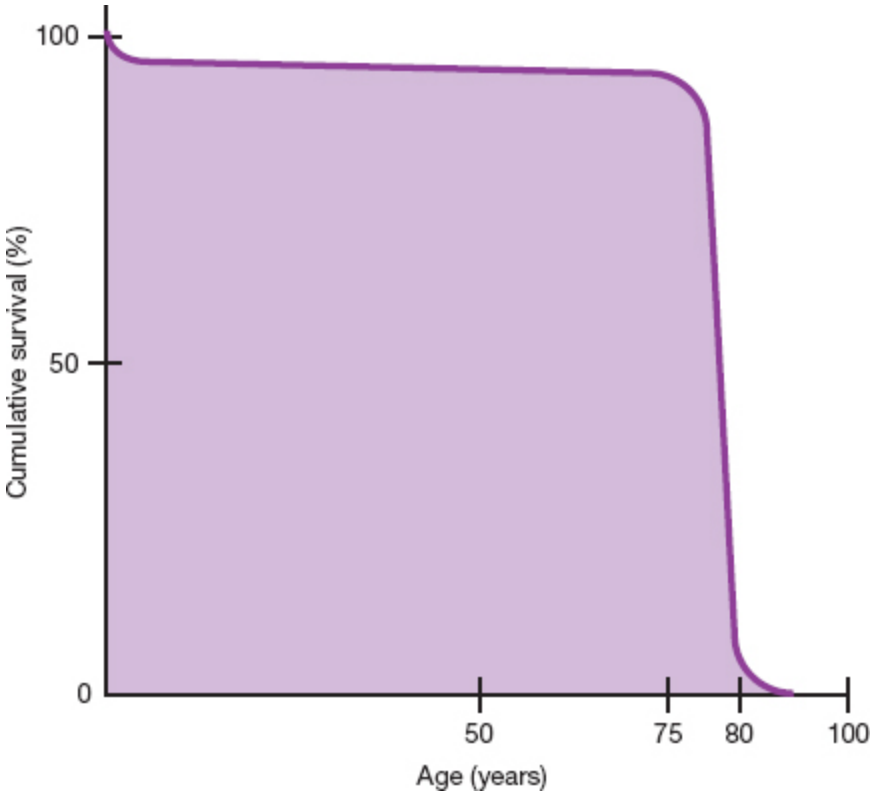


FIGURE 21.2 After Fries JF, Crapo LM. *Vitality and Aging*. W.H. Freeman; 1981.

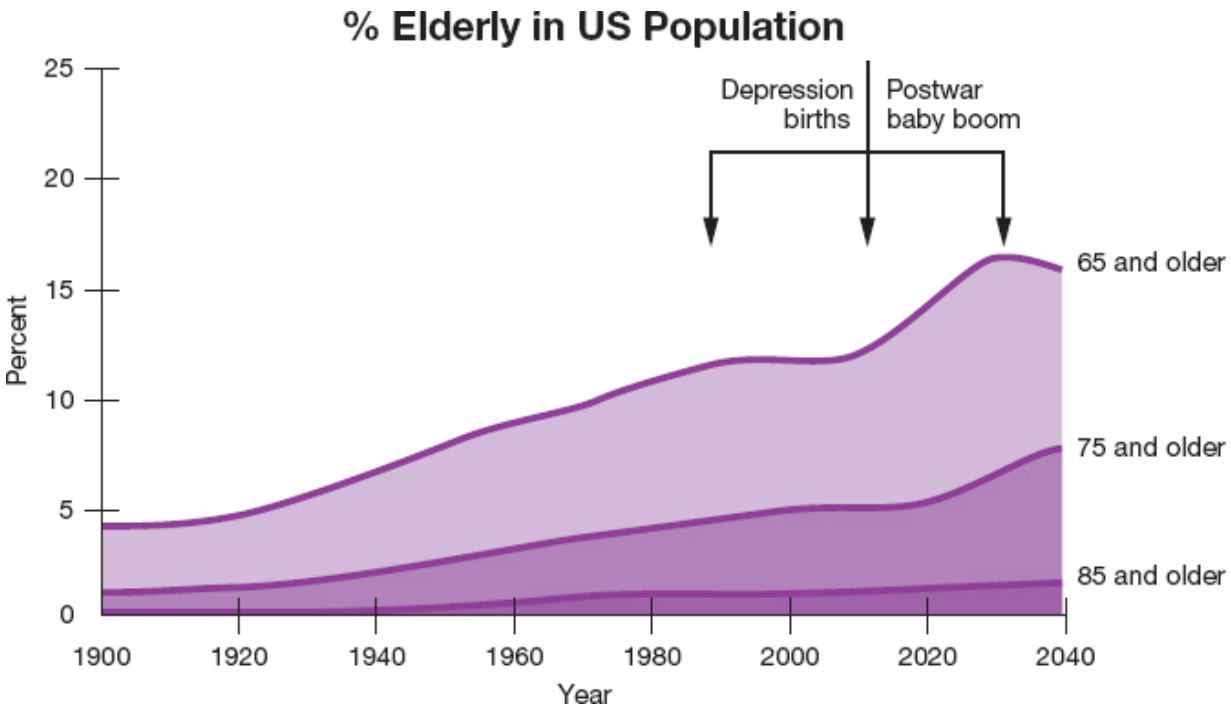


FIGURE 21.3

Two modern phenomena have influenced the rate of change. The first was the post–World War II baby boom (1946–1964) that temporarily postponed the aging of the population, but that is now causing a faster aging of the general population. The second major influence has been the decline in old-age mortality. Our success in postponing death has increased the upper segment of the demographic contour **(Figure 21.3)**. By 2050, the current developed nations will be rectangular societies. China, by 2050, will contain more people over age 65 than the number of people of all ages currently living in the United States **(Table 21.1)**.

This paradigm shift in population demographics is a worldwide development and is not just limited to the affluent societies.[21] The population of the earth will continue to grow until the year 2100 or 2150, when it is expected to stabilize at approximately 11 billion. After 2020, all of this growth will occur in developing countries.[20] In 2000, the poorest countries (located in Africa and Asia) accounted for 87% of the world's population. In 1950, only 40% of people 60 years and older lived in developing countries. By 2050, about 80% will live in those countries, as

fertility in the developing regions is expected to drop from 2.73 children per woman in 2005–2010 to 2.05 by 2050.[20]

GENDER DIFFERENTIAL AND AGING

In aging populations, a gender differential in survival is recognized. In 1900, men over age 65 in the United States outnumbered women by 102 to 100. Now, there are only 70 men for every 100 women over age 65.[22] By age 85, only 39 men are alive for every 100 women. Nearly 90% of White American women can expect to live to age 70. Vital statistics data indicate that this gender difference is similar in both Black and White populations in the United States **(Figure 21.4)**.[23] Approximately 55% of girls, but only 35% of boys, live long enough to celebrate their 85th birthday.[24] One in 5,600 individuals can expect to live to be 100, and women remain uniformly overrepresented in aged populations.[22]

TABLE 21.1 Current World Population Figures

	Births	Deaths	Growth
Year	140,773,000	51,315,000	89,458,000
Month	11,731,080	4,276,250	7,454,834
Week	2,707,173	140,589	245,090
Hour	16,070	5,858	10,212
Minute	268	96	170
Second	4.5	1.6	2.8

From McDevitt TM, Stanecki KA, Way PO. Report WP/98, world population profile: 1998. U.S. Census Bureau; 1999.

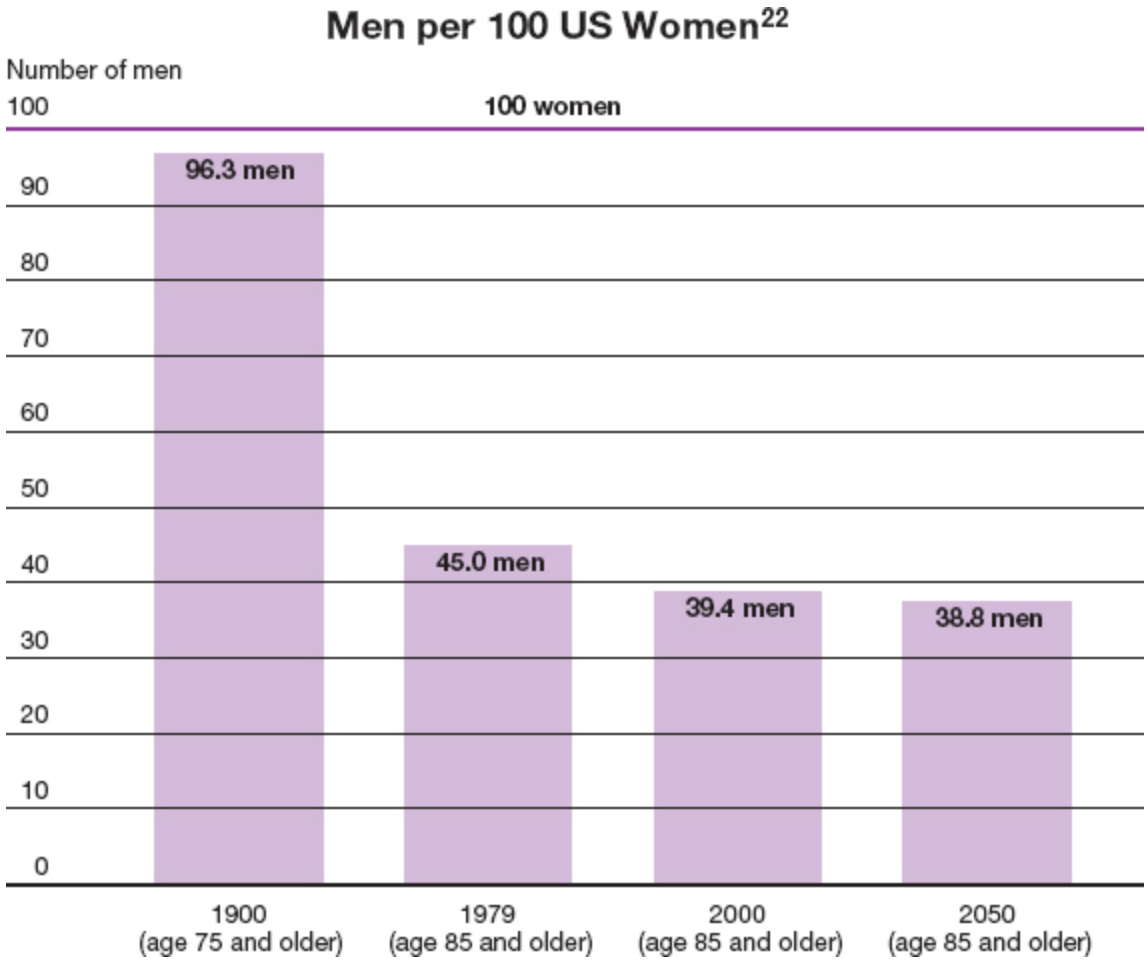


FIGURE 21.4

The 10 leading causes of death in the United States in 2016 were as follows[16]:

1. **Heart disease**
2. **Cancer**
3. **Unintentional injuries**
4. **Chronic lower respiratory diseases**
5. **Stroke**
6. **Alzheimer disease**
7. **Diabetes mellitus**
8. **Influenza and pneumonia**
9. **Kidney diseases**
10. **Suicides**

Men and women reach old age with different prospects for older age, a sex differential that (it can be argued) is due in significant part to the sex-

hormone–induced differences in the cholesterol–lipoprotein profile and other cardiovascular factors and thus the greater incidence of atherosclerosis and earlier death in men. From a public health point of view, the greatest impact on the sex differential in mortality would be gained by concentrating on lifestyle changes designed to diminish atherosclerosis: low-cholesterol diet, no smoking, optimal body weight, and active exercise. The death rate is higher for men at all ages, and therefore women are overrepresented in aging populations **(Table 21.2)**. Coronary heart disease (CHD) accounts for 40% of the mortality difference between men and women. Another one-third is from lung cancer, emphysema, cirrhosis, accidents, and suicides. It is interesting to note that in our society, the mortality difference between men and women is largely a difference in lifestyle. Smoking, drinking, coronary-prone behavior, and accidents account for most of the higher male mortality rate over age 65. It has been estimated that perhaps two-thirds of the difference have been due to cigarettes alone. However, we should emphasize that this is due to a greater prevalence of smoking in men. Women whose smoking patterns are similar to those of men have a similar increased risk of morbidity and mortality.[25]

TABLE 21.2 The US Older Female Population

Age	1990	2000	2010	2020
55–64	10.8 mill. (8.6%)	12.1 mill. (9.0%)	17.1 mill. (12.1%)	19.3 mill. (12.9%)
65–74	10.1 (8.1%)	9.8 (7.3%)	11.0 (7.8%)	15.6 (10.4%)
≥**75**	7.8 (6.2%)	9.3 (7.0%)	9.8 (6.9%)	11.0 (7.3%)
Total	28.7	31.2	37.9	45.9

From McDevitt TM, Stanecki KA, Way PO. Report WP/98, world population profile: 1998. U.S. Census Bureau; 1999.

The mortality sex difference has been decreasing since 1979. The U.S. Census Bureau projects that the difference in life expectancy between men and women will increase until the year 2050 and then level off. In 2050, life expectancy for women will be 82 years and for men, 76.7 years.[26] There

will be 33.4 million women 65 years and older, compared with 22.1 million men.

CHANGING DEMOGRAPHICS AND AGING

In addition to the growing numbers of older adult people, the older population itself is getting older. For example, in 1984, the 65 to 74 age group in the United States was over 7 times larger than in 1900, but the 75 to 84 age group was 11 times larger, and the 85 and older group was 21 times larger. In the 1990s, the population 85 years and older increased by 38%.[22] The most rapid increase is expected between 2010 and 2030 when the post–World War II baby boom generation will be aged 65 years and over. In the next century, the only age groups in the United States expected to experience significant growth will be those past age 55. In this older age group, women will outnumber men by 2.6 to 1. By the year 2040, in the United States, there will be 8 million to 13 million people 85 years of age or older; the estimate varies according to pessimistic to optimistic projections regarding disease prevention and treatment.

Societal norms relating to marriage, partnership, and cohabitation are evolving. Older women are more likely to be left unpartnered due to their male partners' demise compared to older men (22%).[27] Half of men 85 years and older live with their wives, but only 10% of older women live with their husbands.[28] Because the unmarried tend to be more disadvantaged, there will be a need for more services for this segment of the older adult population. Older unmarried people are more vulnerable, demonstrating higher mortality rates and lower life satisfaction. Aging transgender females represent an expanding and uniquely disadvantaged population within aging communities.

The Rectangularization of Life

The lifespan is the biologic limit to life, the maximal obtainable age by a member of a species. The general impression is that the human lifespan is increasing. Actually, lifespan is fixed, and it is a biologic constant for each species.[29] In fact, differences in species' lifespans argue in favor of a

species-specific genetic basis for longevity. If lifespans were not fixed, it would mean an unlimited increase of our older adults. However, a correct analysis of survival reveals that death converges at the same maximal age; what has changed is life expectancy—the number of years of life expected from birth. Life expectancy cannot exceed the lifespan, but it can closely approximate it. Thus, as the number of older people who reach the maximum life expectancy increases, the percentage of a typical life spent in older years will increase **(Figure 21.2)**.

The industrialized world had almost eliminated premature death by reducing the burden of infectious diseases; disorders of the heart and the circulation, cancers, accidents, and suicides were leading causes of death until the world got ensnared in the COVID-19 pandemic. However, despite the havoc caused by the COVID-19 pandemic,[30] the major determinant of life expectancy in the 21st century is chronic disease, affected by genetics, lifestyle, the environment, and aging itself. Even if cancer, diabetes, and all circulatory diseases were eliminated, life expectancy is unlikely to exceed 90 years.[17]

J.F. Fries described three eras in health and disease.[31] The first era existed until sometime in the early 1900s and was characterized by acute infectious diseases. The second era, highlighted by CVD and cancer, is now beginning to fade into the third era, marked by problems of advancing age (fading eyesight and hearing, impaired memory and cognitive function, and decreased strength and reserve). Much of our medical approach is still based on the first era (find the disease and cure it), and we now have conditions that require a combination of medical, psychological, and social approaches. Our focus has been on age-dependent, fatal chronic diseases. The new challenge is with the nonfatal, age-dependent conditions, such as Alzheimer disease, osteoarthritis, osteoporosis, obesity, and incontinence. It can be argued that health programs in the future should be evaluated by their impact on years free of disability, rather than on mortality.

The Concept of the Compression of Morbidity

Chronic illnesses are incremental in nature. The best health strategy is to change the slope, the rate at which illness develops, thus postponing the clinical illness and, if it is postponed long enough, effectively preventing it.

There has been a profound change in public consciousness toward disease. Disease is increasingly seen as something not necessarily best treated by medication or surgery but by prevention.

Preventing illness was expressed by J.F. Fries as the **compression of morbidity**.[29,32] We would live relatively healthy lives and compress our illnesses into a short period of time just before death. Is this change really possible? A good affirmative example is the decrease in atherosclerosis in the United States. Reasons include changes in lifestyle (such as modifications in diet, minimizing the use of saturated fat, and increase in exercise), more effective detection and treatment of hypertension. Health benefits of smoking cessation represent another such example of successfully decreasing health burden through avoidance of toxic exposure **(Figure 21.5)**.

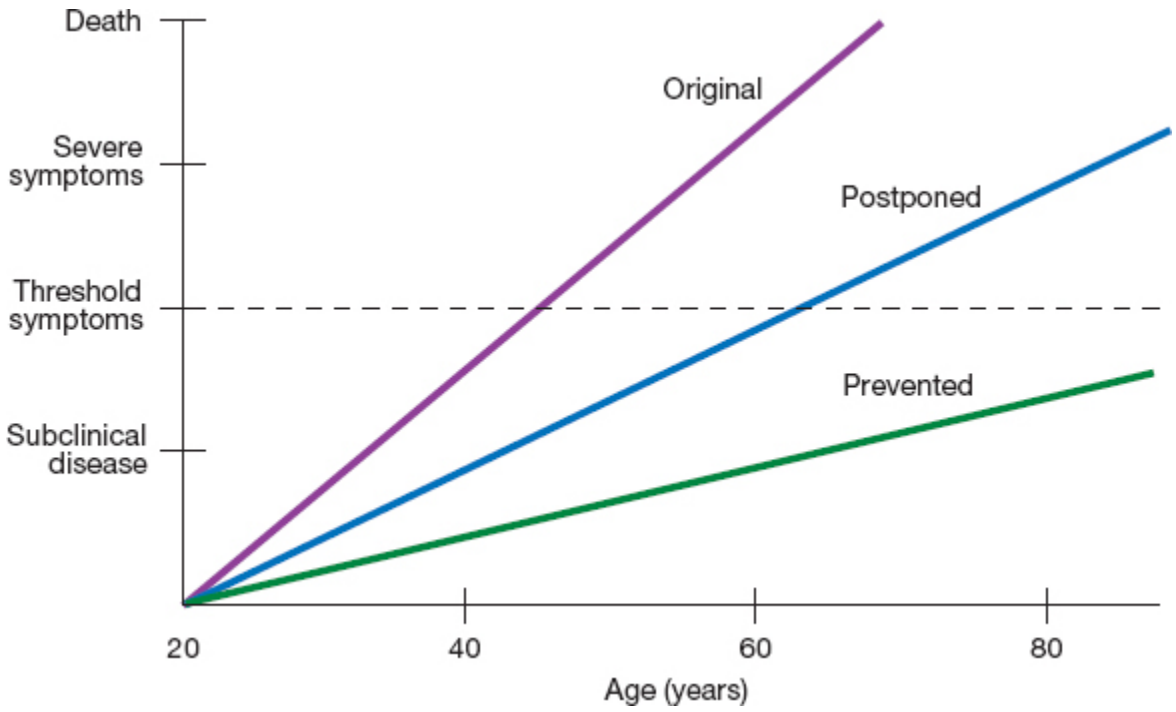


FIGURE 21.5 After Fries JF, Crapo LM. *Vitality and Aging*. W.H. Freeman; 1981.

Tobacco continues to be the single most preventable cause of premature illness and death in the United States. The use of chewing tobacco, pipe smoking, and cigars, and more recent trends of vaping all

contribute significantly to morbidity and mortality. Approximately 35% of people in the United States who have not obtained a high school diploma are smokers, but only 12% of those with higher education are smoking and only 5.7% of those with graduate degrees. Currently, approximately 17.5% of men and 13.5% of women are smokers.[16] It is important to note that smoking has a greater adverse effect on women compared with men.[33] Women who smoke only one to four cigarettes per day have a 2.5-fold increased risk of fatal CHD.[34]

Quitting smoking even after decades of smoking is still beneficial, and these effects can be apparent as early as 1 month after quitting.[35] In the Nurses' Health Study, 61% of the excess risk of CHD mortality and 42% of stroke mortality were eliminated within 5 years after quitting smoking.[36] The improvement in respiratory disease mortality is slower, and a small increased risk of lung cancer mortality persists even after 30 years. However, by 20 years after cessation, all the excess risk of vascular mortality and death due to respiratory diseases other than lung cancer reached the level of a never smoker. Even older patients who already have coronary artery disease have improved survival if they quit smoking.[37] No matter how old you are, if you continue to smoke, you have an increased relative risk of death. However, no matter how old you are, if you quit smoking, your risk of death decreases. Nevertheless, the risk of lung cancer remains elevated even in long-term ex-smokers.[38]

Since 1970, the death rate from CHD has declined approximately 50% in the United States. Between 1973 and 1987, in the United States, cardiovascular mortality declined in nearly every age group. In the combined age groups up to 54 years, cardiovascular mortality decreased to 42% and in people 55 to 84 years old, 33%.[33] Despite our progress, we must continue to exert preventive efforts on the risk factors associated with CVD, especially obesity, hypertension, and lack of physical activity. The effort to improve the quality of life has an important value to society; it will decrease the average number of years that people are disabled, which is a major health and social problem of society. Most significantly, this is a major financial challenge for health care systems and social programs. With evolution toward a rectangular society, the ratio of beneficiaries to taxpayers grows rapidly, jeopardizing the financial support for health and

social programs. Compression of morbidity is at least one attractive solution to this problem.

MENOPAUSE AS AN OPPORTUNITY

Menopause is a normal phase of life, much like puberty. For many women, the cessation of both menstruation and reproductive capacity is a welcome change—no further menses or premenstrual syndrome (PMS) and no need for contraception/concern for conceiving. Clinicians who interact with women at the time of menopause have a wonderful opportunity and, therefore, a significant obligation. Medical intervention at this point of life offers women years of benefit from preventive health care.

While not underrating the importance of good health habits among the young, we would argue that the impact of teaching preventive care is more observable and more tangible at middle age. The prospects of limited mortality and the morbidity of chronic diseases are viewed with belief, understanding, and appreciation during these older years. The chance of illness is higher, but the impact of changes in lifestyle is greater.

Stages of Reproductive Aging—*From Reproductive Years to Perimenopause (Older Terminology) or Menopausal Transition (Newer Term) to Menopause*

In 2001, the Stages of Reproductive Aging Workshop (STRAW) standardized the nomenclature for the stages of the menopausal transition, categorizing the female lifespan into three broad phases: *reproductive* phase, *menopausal transition* phase, and *postmenopausal* phase. Each of the three phases is divided into stages based on clinical (menstrual cycle pattern and symptoms) and biochemical (serum levels of follicle stimulating hormone [FSH] and inhibin B) indices.[39] In 2005, another classification system (PENN-5) was proposed based on analyses of the Penn Ovarian Aging Study. Investigators had noted significant changes in FSH and inhibin B levels in progression to the late premenopause stage that correlated with small alterations in the menstrual cycle and proposed

considering the late reproductive phase as a distinct entity.[40,41] In 2010, at a follow-up workshop ("STRAW + 10"), the original STRAW classification was updated to reflect advances in our understanding of the changes in the hypothalamic–pituitary–ovarian function occurring throughout the continuum of reproductive aging with incorporation of antimüllerian hormone (AMH) levels and ultrasound-based ovarian antral follicle count (AFC) data.[42]

The *menopausal transition* is a finite period of physiologic changes that eventually culminates in reproductive senescence. This phase of life can be associated with unique challenges that can have significant effects on individual women's well-being and on quality of life.[39] A woman is said to have reached *menopause* if she has remained amenorrheic for 12 consecutive months and demonstrates biochemical evidence of hypergonadotropic (elevated FSH and luteinizing hormone [LH] levels) hypogonadism (low estradiol levels). The FMP is identified as stage "0," marking a watershed between reproductive and postreproductive periods of life. The *reproductive* phase itself is broken down into five stages (early [−5], peak [−4], and late [−3]). The *menopause transition* phase is broken down into two stages (early [−2] and late [−1]). The *postmenopause* phase is also divided into two stages (early [+1] and late [+2]).[42] **The FMP thus serves as the reference point for interpretation of the rest of the stages across the three phases of reproductive aging (Figure 21.6)**.

Late Reproductive Stage (STRAW Stage −3, Substages −3b, −3a)

A decline in fecundability is apparent as the earliest hallmark of transition followed by a spectrum of clinically apparent phenomena, such as changes in menstrual cycle pattern. As covert endocrinologic changes set in well before noticeable and clinically apparent features (such as changes in the menstrual cycle length and/or pattern), STRAW +10 divided the late reproductive stage into substages −3b and −3a that reflect the endocrinologic changes that are seen prior to overt clinical manifestations. In stage −3b, the menstrual cycles are relatively unchanged; while serum levels of FSH are in the premenopausal range, levels of AMH and inhibin B are low, as is the AFC.[42] In stage −3a, shortening in the length of menstrual cycles and increases in early follicular FSH levels become noticeable.[42]

Stages	−5	−4	−3b −3a	−2 01	0	+1	+2a	+2b
Phase	*Reproductive*			*Transition*	FMP	*Postmenopause*		
Clinical profile	Fertile	Fertility problems for some	• Fertility problems • Menstrual irregularity • Occasional VMS	• Fertility problems • Menstrual irregularity • VMS are common		• VMS are common • Declining bone density	• Improving VMS in many • Worsening GUSM symptoms • Worsening risk for osteoporosis and cardiovascular disease	
Biochemical finding	• Normal AMH & inhibin • Low FSH	• Normal AMH & inhibin • Low FSH	• Declining AMH • Declining inhibin • Rising FSH	• Low or undetectable AMH & inhibin levels • High FSH		• High FSH • AMH & inhibin undetectable	• Stable FSH • AMH & inhibin undetectable	• Slight decline in FSH • AMH & inhibin undetectable
Ultrasound findings	Adequate AFC >>8		Decline in AFC	Few antral follicles		Occasional antral follicle		

AFC, antral follicle count; AMH, Antimüllerian hormone; FMP, final menstrual period; FSH, Follicle stimulating hormone; GUSM, genitourinary syndrome of menopause; VMS, Vasomotor symptoms.

FIGURE 21.6 Adapted and modified from Harlow SD, Gass M, Hall JE, et al; STRAW + 10 Collaborative Group. Executive summary of the stages of reproductive aging workshop + 10: addressing the unfinished agenda of staging reproductive aging. *Climacteric*. 2012;15(2):105-114.

Early Menopausal Transition (STRAW Stage −2)

This stage is characterized by increasing irregularity of the menstrual cycle length. This irregularity is defined as a recurrence of 7-day difference in cycle length over 10 cycles. This stage is also characterized by variable elevations in early follicular phase FSH levels, with persistently low AMH levels and low AFC.[42]

Late Menopausal Transition (STRAW Stage −1)

The late menopausal transition is characterized by missed menses with periods of amenorrhea lasting at least 60 days. This degree of irregularity in menstrual cycles is due to variability in reproductive hormonal levels and a high incidence of anovulatory cycles. FSH levels are elevated, often to above 25 IU/L. In contrast, AMH and inhibin B levels are often undetectable. Serum levels of LH may still be in the normal premenopausal range. Estradiol levels can vary from low to even high.[43–49] The persistent hypoestrogenemia that is an endocrinologic hallmark of menopause may not be reached until late in this stage prior to the FMP **(Figure 21.7)**. An exaggerated response of the residual ovarian follicles to elevated circulating levels of FSH, and thereby multifollicular recruitment and growth, are mechanisms to explain elevations in estradiol that may be inconsistently

noticeable. The persistent hypoestrogenemia, one of the endocrinologic hallmarks of the menopausal state, may not be reached until late in this stage. This stage can last 1 to 3 years and is when the vasomotor symptoms (VMS), such as hot flushes and night sweats, often begin to occur.[42]

Early Postmenopause (STRAW Stage 1, Substages +1a, +1b, +1c)

In early postmenopause, FSH levels continue to rise, while estradiol levels decline until 2 years after the FMP, after which these hormone levels stabilize. The substages +1a and +1b in early menopause last 1 year each and culminate once fluctuations in FSH levels stabilize. **Stage +1a marks the completion of the 12-month interval required to define the FMP**. This substage also marks the end of the *perimenopause* (ie, the time near menopause, which starts at stage −2 and ends 12 at months following the FMP).[42] Blood levels of FSH and estradiol can continue to fluctuate somewhat during stage +1b. VMS are most common in stages +1a and +1b. It is in stage +1c that the elevated FSH and low estradiol levels become the new normal. This substage can last for up to 3 to 6 years. As such, the entire early postmenopause stage spans a total of 5 to 8 years.[42]

Late Postmenopause (Stage +2)

During this stage, reproductive hormone levels are essentially plateaued and stable. While the burden of VMS eases off for many, physical symptoms attributable to lack of estrogen, such as vaginal dryness and urogenital symptoms, become more prominent at and with progression into this stage. Interestingly, FSH levels may actually decline further with advancing age, although more research is needed to confirm this observation.[42]

THE MENOPAUSAL TRANSITION

There is only one marker, menstrual irregularity, that can be used to objectively define and establish what is called the menopausal transition. This irregularity will be perceived by patients as skipped menstrual periods or longer durations (~40–60 days) between periods.[50] There is no universal pattern; each woman will perceive a change that is her own individual characteristic alteration.

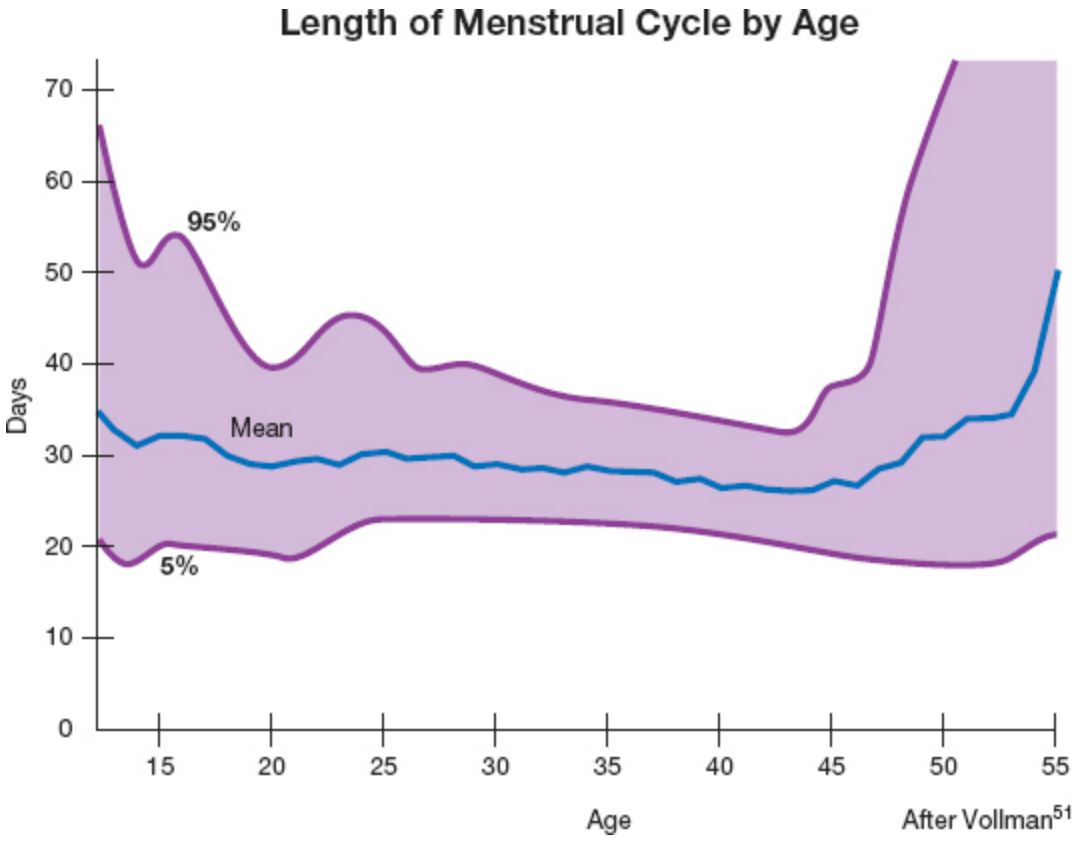


FIGURE 21.7

Menopause is that point in time when permanent cessation of menstruation occurs following the loss of ovarian activity. Menopause is derived from the Greek words *men* (month) and *pausis* (cessation). **Climacteric**, an older, more general, and less precise term, indicates the period of time when a woman passes from the reproductive stage of life through the menopausal transition and the menopause to the postmenopausal years. Climacteric is from the Greek word for ladder. **Perimenopause** is the newer term that includes the years prior to the FMP during which menstrual cycles progress from a regular ovulatory and predictable pattern to irregular and increasingly anovulatory cycles to eventual cessation of menses.[42]

Menstrual cycle length is determined by the rate and quality of follicular growth and development. It is normal for the cycle to vary in individual women. Informative data come from two seminal longitudinal studies (with very similar results): the study of Vollman of more than 30,000 cycles

recorded by 650 women and the study of Treloar of more than 25,000 woman-years in a little over 2,700 women.[51,52] The earlier observations of Vollman and Treloar that documented a normal evolution in length and variation in menstrual cycles were subsequently confirmed by Cole et al[53] **(Figure 21.7)**.

Following the onset of menarche, there is an approximately 2- to 3-year period of relatively longer menstrual cycles at first, after which there is increasing regularity as cycles shorten to reach the usual reproductive age pattern. In the 40s, cycle length may begin to alter again. The highest incidence of anovulatory cycles is under age 20 and over age 40.[54,55] By age 25, over 40% of cycles are between 25 and 28 days in length; from 25 to 35 years, over 60% are between 25 and 28 days. Although a 28-day cycle length is deemed as the standard for normal, overall, only approximately 15% of reproductive age cycles are 28 days in length. Only 0.5% of women experience a cycle less than 21-days long and only 0.9% a cycle greater than 35 days.[56] Most women have cycles that last from 24 to 35 days, but at least 20% of women experience irregular cycles.[57] When women are in their 40s, anovulation becomes more prevalent, and menstrual cycle length increases, beginning 2 to 8 years before menopause.[52] Follicular phase and overall cycle length reach their nadir at approximately age 42. Over the subsequent 8 to 10 years preceding the FMP, average cycle length and variability steadily increase as ovulations become less frequent.[51] Cycles greater than 40 days in length are quite prevalent in the year before menopause and anything exceeding 42 days in length is suggestive of impending FMP within the next 1 to 2 years.[58,59] This period of longer cycles commonly precedes menopause no matter at what age menses cease, whether menopause is early or late.[60] However, the prognostic time frame for FMP may be influenced by factors such as tobacco use, ethnicity (increased time frame in Black women), a history of longer cycles, as well as age at the onset of menopausal transition.[61,62] *The duration of the follicular phase is the major determinant of cycle length*.[63,43] This period of menstrual cycle change prior to FMP is marked by elevated FSH levels and decreased levels of inhibin but normal levels of LH and slightly elevated levels of estradiol.[44–49,64] **Importantly, up to 25% of irregular cycles with intervals of over 50 to 60 days can still be ovulatory, and late perimenopausal women therefore remain at risk for unplanned**

pregnancy despite low fecundability.[65] **Late perimenopausal women remain at risk for unplanned pregnancy.** According to the *Guinness Book of World Records*, a woman from the United Kingdom holds the modern record for the oldest spontaneous pregnancy, conceiving at 59.[66,67]

In the average woman, a decline in fertility begins around ages 37 and 38, and menopause follows approximately 13 years later (average age 51). However, in epidemiologic studies, approximately 10% of women in the general population become menopausal by the age of 45 years.[65,66] While the exact mechanisms underlying spontaneous early menopause (before age 45) remain unclear, and are not generalizable, it is probable that some women are born with a smaller than normal ovarian follicular pool that gets functionally depleted at an earlier age. Menopause occurs when the number of remaining ovarian follicles falls below a critical threshold, about 1,000, regardless of age.

Contrary to older belief (based on a seminal report by Sherman et al in 1976),[61] **estradiol levels do not gradually wane in the years before menopause, but remain in the normal range, and can even be slightly elevated, until about 1 year before follicular growth and development cease.** Sherman et al conducted a small cross-sectional study wherein serum samples were collected over a single menstrual cycle from eight women, aged 46 to 56 years, for the study of reproductive hormones. More recent longitudinal studies of women as they pass through the menopausal transition reveal that estrogen levels do not begin a major decline until about a year before menopause **(Figure 21.8)**.[47,68,69] Indeed, women experiencing the menopausal transition actually have higher overall estrogen levels, a response that is logically explained by an increased ovarian follicular reaction in response to the higher circulating FSH levels during this period.[70] Variability in estrogen levels is characteristic of the menopausal transition, with greater hormonal variability observed in menstrual cycles that display greater irregularity.[71]

As noted, most women experience a 2- to 8-year period of time prior to the FMP when the occurrence of anovulation becomes common.[52] During this time, ovarian follicles continue their rate of loss until the reservoir is finally depleted.[72,73] In a study of human ovaries, the loss that began when the total number of follicles reached approximately 25,000, usually at ages 37 and 38, correlated with a subtle but real increase in FSH and a decrease

in inhibin levels.[74] These changes begin around age 35 but accelerate after 40 and parallel the decline in fecundity that occurs with aging. Aging-related decline in the *quantity* of ovarian follicles is directly related to the rise in FSH levels that occurs with advancing age; this rise in FSH results from reduced secretion of inhibin, a granulosa cell product that exerts important negative feedback on FSH secretion by the pituitary gland. It is possible that both inhibin A and inhibin B may be involved, because luteal phase levels of inhibin A and follicular phase levels of inhibin B decrease with aging and predate the rise in FSH.[75–77] A careful study in Australia, however, indicated that the increase in FSH was correlated only with a decrease in inhibin B, and in response to elevated FSH, estradiol levels increased slightly.[68]

Reproductive Hormone Profile From Menopause Transition (or Perimenopause) Into Menopause
(mean circulating hormone levels)

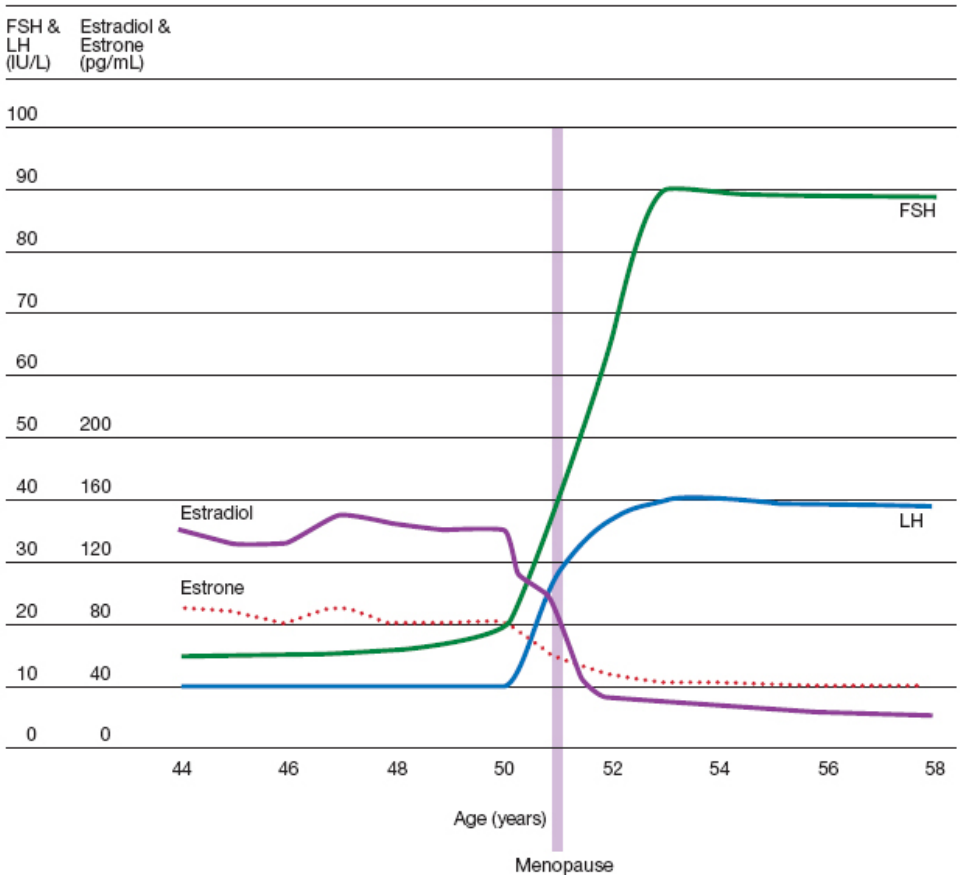


FIGURE 21.8

A decrease in inhibin production by the follicular granulosa cells could reflect a shrinking number of ovarian follicles or a reduced functional capacity of the older follicles or both.[78] **The observation that preovulatory follicular fluid inhibin concentrations are similar in young and older cycling women suggests that the number of remaining follicles is the most important factor.**[79] In the late reproductive stage, driven by higher FSH levels, the process of follicular recruitment and development gets accelerated with resulting shortening of the follicular phase. This accelerated pace of follicular development in the late reproductive stage is reflected in higher estradiol levels being attained earlier in the follicular phase.[80] **Careful studies indicated that the earlier acute rise in estradiol levels results from advanced follicular development at the beginning of the cycle and earlier selection of the dominant follicle.** A rise in estradiol levels earlier in the follicular phase is a recognized hallmark of decreased ovarian reserve. With declining inhibin levels with advancing age, FSH levels start to rise in the late luteal phase of the menstrual cycle. This early rise in FSH initiates early follicular recruitment, accelerates follicular development and earlier selection of a dominant follicle in the succeeding cycle with resulting shortening of the follicular phase and of cycle length.[81,82] Follicular phase and overall cycle length reach their nadir at approximately age 42. Over the subsequent 8 to 10 years preceding the FMP, average cycle length and variability steadily increase as ovulations become less regular and less frequent.[51] The aging-related changes in the endocrine characteristics of the menstrual cycle that result from progressive follicular depletion correlate with a measurable decrease in the ovarian volume and in the number of antral follicles observed by transvaginal ultrasonography during the early follicular phase.[83–89]

The inverse and tight relationship between FSH and inhibin indicates that inhibin is a sensitive marker of ovarian follicular competence and, in turn, that FSH measurement is a reflection of inhibin action.[44,45] The decrease in inhibin secretion by the ovarian follicles begins early (around age 35), but accelerates after age 40, and parallels the decline in fecundity that occurs with aging (as discussed in Chapter 28). **Furthermore, the ineffective ability to achieve suppression of gonadotropins with menopausal hormone therapy is a consequence of the loss of inhibin,**

and for this reason, FSH levels cannot be used to titrate estrogen dosage in menopausal women on standard hormone therapy regimens.

The Michigan Bone Health and Metabolism Study is a longitudinal assessment of the menopausal transition in a cohort of 629 women, initiated in 1992 to 1993. The initial rise in FSH in these women was modest until 7 years prior to menopause but accelerated with an even greater increase in the 2 years before menopause, finally reaching a plateau about a year after menopause.[90] The major decrease in estradiol levels began about 2 years before menopause.[91] Declining levels of inhibin B and AMH reached a low to nondetectable point about 5 years before menopause.[92] Although the inhibin B and AMH results are in agreement with other reports, an exactness of the timing is limited by the fact that the blood samples were obtained from only 50 women in the study. Furthermore, Depmann et al also demonstrated that while AMH can help in predicting impending menopause as it relates to aging, this predictability is far from robust.[93] Nevertheless, the Michigan study confirms the validity of AMH as a marker for residual ovarian follicles, a concept that is referred to as *ovarian reserve*. Unlike inhibin B, AMH is not a participant in the feedback relationship between the ovary and the pituitary gonadotropins; rather, AMH, a product of the granulosa cells, reflects the number of residual follicles awaiting FSH stimulation.[94] **The variability in these hormone measurements from individual to individual, however, precludes the practical use of these biomarkers to predict with accuracy the future date of menopause.**[93]

During the transition or perimenopausal years, circulating FSH may reach postmenopausal levels (>20 IU/L) despite ongoing menstrual cycles; LH levels, however, still remain in the normal premenopausal range. The frequency of anovulatory cycles increases, although occasionally, corpus luteum formation and function occur; the perimenopausal woman is thus not safely beyond the risk of an unplanned and unexpected pregnancy until persistently elevated levels of both FSH (25 IU/L) and LH (30 IU/L) can be demonstrated.[46] However, even under these circumstances, fluctuations can occur, with a transient period of ovarian failure (reflected in amenorrhea, elevated gonadotropins, and low estradiol levels), followed by spontaneous resumption of ovarian function for brief periods.[45] **Because variability is the rule, it would be wise to recommend the use of contraception until**

the postmenopausal stage is definitely established. Several months of amenorrhea together with a persistently elevated FSH level of 40 IU/L or more are reliable signals that menopause is either near or has already happened.[95]

In the longitudinal Massachusetts Women's Health Study, women who reported the onset of menstrual irregularity were considered to be in the perimenopausal period of life.[96] The median age for the onset of this period was 47.5 years. **Only 10% of women ceased menstruating abruptly, with no period of prolonged irregularity.** The menopausal transition from reproductive to postreproductive status was, for most women, approximately 4 years in duration. In the study by Treloar, the average age for entry into the menopausal transition was 45.1, and the age range that included 95% of the women was 39 to 51.[65] The mean duration of the menopausal transition was 5.0 years, with a range of 2 to 8 years **(Table 21.3)**.

Timing of Natural Menopause

Designating the average age of menopause has been somewhat difficult. Based on cross-sectional studies, the median age was estimated to be somewhere between 50 and 52.[97] These studies relied on retrospective memories and the subjective vagaries of the individual being interviewed. Until recently, studies with longitudinal follow-up to observe women and record their experiences as they pass through menopause were hampered by relatively small numbers. The Massachusetts Women's Health Study provides us with data from 2,570 women.[96]

The median age for menopause in the Massachusetts Study was 51.3 years. Only current smoking could be identified as a cause of earlier menopause, a shift of approximately 1.5 years. Those factors that did not affect the age of menopause in this study included the use of oral contraception, socioeconomic status, and marital status. Keep in mind that a **median** age of menopause means that only half the women have reached menopause at this age. In the classic longitudinal study by Treloar, the **average** age of menopause was 50.7 years, and the range that included 95% of the women was 44 to 56 years.[98] In a survey in the Netherlands, the

average age of menopause was 50.2, and in an Italian longitudinal study, it was 50.9 years.[66,99]

TABLE 21.3 The Menopause Transition (or Perimenopause)

Average age of onset: 46 y
Age of onset for 95% of women: 39–51 y
Average duration: 5 y
Duration for 95% of women: 2–8 y

Data from Treloar AE, Boynton RE, Behn BG, Brown BW. Variation of the human menstrual cycle through reproductive life. *Int J Fertil*. 1967;12(1 Pt 2): 77-126; Treloar AE. Menstrual cyclicity and the pre-menopause. *Maturitas*. 1981;3(3-4):249-264; and McKinlay SM, Brambilla DJ, Posner JG. The normal menopause transition. *Maturitas*. 1992;14(2):103-115.

The Study of Women's Health Across the Nation (SWAN) is an ongoing, national study, recording the health of American women of diverse backgrounds as they pass through the perimenopausal transition (http://www.edc.gsph.pitt.edu/swan/). The study began in 1994 in seven research centers and enrolled 3,302 participants with five racial/ethnic groups and a variety of backgrounds for an initial cross-sectional survey. In 1996, these women began a longitudinal, follow-up study with extensive data collection occurring annually.

In the SWAN study, the median age of menopause was 51.4, with an earlier onset associated with current smoking, lower education, and lower socioeconomic status, whereas a later age was associated with parity and prior use of oral contraceptives.[100] In contrast, a Dutch study concluded that prior use of oral contraceptives was associated with earlier (<1 year) menopause.[101] About 1% of women have been reported to experience menopause before the age of 40.[102] The SWAN study reported a similar percentage of 1.1%, with a slightly higher rate in Black and Hispanic women and a lower rate of 0.5% in Chinese women and 0.1% in Japanese women.[103] Hispanic women experienced menopause about 6 months earlier compared with other ethnic groups, whereas Japanese women were about 3 months later.

Two large cohorts of European women reported average ages of menopause in various countries that centered around age 51 years, slightly higher in Northern Europe and slightly lower in Southern Europe.[104] Some countries, like India, report an average age of menopause as much as 5 years earlier.[105] In epidemiologic studies, approximately 10% of women in the general population become menopausal by the age of 45 years.[65,66] Pedigree analysis has revealed that the genetic features of early menopause (age 40–45) and premature ovarian insufficiency (POI) or failure (cessation of ovarian function occurring at an age <40) are similar and suggest a dominant pattern of inheritance through maternal or paternal relatives.[106,107] There are two studies indicating that daughters of mothers with an early menopause (before age 46) also have an early menopause, with up to 15% of women having a first-degree relative with early menopause.[108–111]

There is sufficient evidence to suggest that chronically undernourished women and vegetarians may experience an earlier menopause.[108,112] Because of the contribution of body fat to estrogen production, thinner women experience a slightly earlier menopause.[113] Frequent consumption of alcohol is associated with a later menopause.[109] This is consistent with the reports that women who consume alcohol have higher blood and urinary levels of estrogen.[114–118]

In multiple studies, there has been no correlation between age of menarche and age of menopause, with the exception of one Swedish study concluding that an earlier menarche and earlier menopause go together.[66,98,108,119,120] In most studies, race, parity, and height have no influence on the age of menopause; however, three cross-sectional studies found later menopause to be associated with increasing parity.[66,96,100,108,113] Two studies found that irregular menses among women in their early 40s predict an earlier menopause.[121,122] A French survey detected no influence of heavy physical work on early menopause (before age 45).[123] An earlier menopause has been reported to be associated with living at high altitudes.[124,125] In addition, most intriguingly, an earlier age of menopause has been reported in left-handed women compared with right-handed women.[126,127] Finally, intrauterine growth restriction in late gestation may predispose the affected female progeny to earlier menopause.[128]

It has been suggested, albeit inconsistently, that time to FMP may get accelerated in women undergoing pelvic surgery, wherein ovarian vascular

supply may get compromised, such as following an abdominal hysterectomy. Effects of pelvic surgery on biomarkers of ovarian reserve have been examined, with mixed results. A prospective study could find no elevations of FSH within the first 2 years after surgery.[129–131] Furthermore, in a cross-sectional study assessing ovarian reserve following ovarian cystectomy (for cysts other than endometriomas) and, or salpingectomy, there was no appreciable effect on ovarian reserve.[132]

Multiple studies have consistently documented that an earlier menopause (an average of 1.5 years earlier) is a consequence of smoking. There is a dose–response relationship with the number of cigarettes smoked and the duration of smoking.[133,134] Even former smokers show evidence of an impact.[104]

Unlike the decline in age of menarche that occurred with an improvement in health and living conditions, most historical investigation indicates that the age of menopause has changed little since early Greek times.[135,136] Others (a minority) have disagreed, concluding that the age of menopause did undergo a change, starting with an average age of about 40 years in ancient times, and in Sweden, an increase of about 1 year over a span of 80 years.[120,137] If there has been a change, however, history indicates that it has been minimal. Even in ancient writings, 50 years is not uncommonly cited as the age of menopause.

Sexuality, Aging, and Menopause

Sexuality is behavior that evolves and chances across the lifespan. It begins with birth (maybe before) and ends with death. The notion that sexuality ends with aging is inherently illogical. The need for closeness, caring, and companionship is lifelong. Old people today live longer, are healthier, have more education and leisure time, and have had their consciousness raised in regard to sexuality.

Younger people, especially physicians, underrate the extent of sexual interest in older people. In a random sample of women aged 50 to 82 years in Madison, Wisconsin, nearly one-half of the women reported an ongoing sexual relationship.[138] In the Duke longitudinal study on aging, 70% of men in the 67 to 77 age group were sexually active, and 80% reported continuing sexual interest, while 50% of all older women were still

interested in sex.[139] In the Postmenopausal Estrogen/Progestin Interventions (PEPI) trial, 60% of women 55 to 64 years old were sexually active.[140] In a national sample of American men and women, the prevalence of sexual behavior declined with aging; however, 26% of individuals aged 75 to 85 years were still sexually active.[141] The prevalence of self-reported sexual problems peaks in middle-aged women, sufficient to cause distress in about 22% of US women and about 12% of women aged 45 to 64.[142] Up to 23% of menopausal women are negatively affected by decreased sexual desire.[143]

The decline in sexual activity with aging is influenced by culture and attitudes, as well as by nature and physiology (or hormones). As estradiol regulates serotonergic function, it can affect desire and sexual function.[143] In addition, the discomfort resulting from vaginal dryness and tissue atrophy consequent to low estradiol levels can make coitus unwelcome, even to the point of avoidance. Thus, a significant component of decline in sexual activity in reproductively aging women can be attributed to menopausal symptoms associated with decreasing estrogen levels, a problem that is easily ameliorated by targeted treatment.

There are two main sexual changes in the aging woman. There is a reduction in the rate of production and volume of vaginal lubricating fluid, and there is some loss of vaginal elasticity and thickness of the epithelium. Less vaginal atrophy is noted in sexually active women than in inactive women; presumably, the activity maintains vaginal vasculature and circulation. The spectrum of uncomfortable symptoms that are often described by transitioning and menopausal women with evidence of genital atrophy include a feeling of dryness and tightness, vaginal irritation and burning with penetration, and postcoital spotting and soreness. Given that these symptoms are the direct result of tissue estrogen deprivation, the underlying tissue changes can be effectively prevented by focal estrogen treatment. Systemic estrogen therapy may even have a positive impact on sexuality beyond effects on vaginal tissue.[140] In an ancillary sexual study of the Kronos Early Estrogen Prevention Study (KEEPS)—a randomized, double-blinded, placebo-controlled trial—early menopausal women were randomized to receive either low-dose oral conjugated equine estrogen (CEE) or transdermal estradiol (transdermal E2), over the 4 years of intervention. While both routes of estrogen treatment resulted in an improvement in vaginal dryness and dyspareunia,[143] improvements in libido

and sexual satisfaction were observed only in transdermal E2 users.[143] In an Australian study assessing changes in sexual functioning during the menopausal transition, a correlation with a decline in sexuality was demonstrated with estradiol levels but not with testosterone levels. There are likely many important factors other than hormone levels that are relevant in determining midlife sexual function.[143,144]

Illness and Sex

It is not uncommon to encounter medical or surgical underpinnings to disorders of sexuality. Surgical menopause (removal of both ovaries in premenopausal women) is probably one of the most commonly encountered iatrogenic contributors to altered sexual function in reproductive age women. Remember that vaginal lubrication is an important physiologic sexual response, and, therefore, vaginal dryness is a likely consequence following total hysterectomy even if the premenopausal ovaries are retained. Sexual problems are not limited, however, to surgical procedures and illnesses of the genitalia. Altered self-image such as following vulvectomy or mastectomy can also impact sexual function. However, studies have not found postmenopausal hysterectomy to have a detrimental impact on sexuality.[140,145]

Sexual counseling, to be effective, must be provided to couples both before and after surgery. It is not unexpected that the surgeon may not be fully capable of providing this counseling. A major contribution from an older woman's primary clinician is to arrange for competent and experienced sexual counseling. Unfortunately, most physicians operate on the principle that if no questions are raised, there is no problem. The expert surgeon should be grateful for the help of experts in psychosexual therapy. Seek out the potential for posttreatment sexual morbidity before the surgery. Assess the patient's abilities for coping and her sense of body image. Consider the quality of the patient's relationship, and be sensitive to the absence of a relationship. This entire effort may take some time. The normal state of presurgical anxiety, fear, and denial hampers good communication.

Increasing use of SSRI (selective serotonin reuptake inhibitor) antidepressants is another iatrogenic contributor to female sexual dysfunction that merits attention.[146]

Antihypertensive agents are frequently responsible for male sexual dysfunction, but little information is available regarding female sexual function. Adrenergic blocking agents are especially noted to affect libido and potency in men. Similarly, psychotropic drugs of all categories have been associated with inhibition of sexual function. Finally, one should always suspect alcoholism when patients complain of sexual dysfunction. Androgen treatment for decreased female sexuality is discussed later in this chapter.

The two most important influences on sexual satisfaction in aging couples are the strength of relationship and the physical condition of each partner.[140,141,147] The single most significant determinant of sexual activity for older women is the lack of availability of partners due to divorce or demise as women are outliving men. Given availability of a partner, the same general high or low rate of sexual activity can be maintained throughout life.[4,148] Longitudinal studies indicate that the level of sexual activity is more stable over time than previously suggested.[149–151] Individuals who are sexually active earlier in life continue to be so into old age. However, aging is associated with a decline in sexual function in many women, and this decline has been documented in the years well before the FMP.[152,153]

HORMONE PROFILE OF MENOPAUSAL TRANSITION AND POSTMENOPAUSE

Shortly after menopause, one can safely say that there are no remaining ovarian follicles.[69,154] Eventually, there is a 10 to 20-fold increase in FSH and an approximately 3-fold increase in LH, reaching a maximal level 1 to 3 years after menopause, after which there is a gradual, but slight, decline in both gonadotropins.[155,156] Elevated levels of both FSH and LH at this time in life are conclusive evidence of ovarian failure. FSH levels are higher than LH because LH is cleared from the blood so much faster (initial half-lives are ~20 minutes for LH and 3–4 hours for FSH) and perhaps because there is no specific negative feedback peptide for LH like inhibin. An aging-related decline in the gonadotropin levels in the latter years of postmenopausal life is well described and is believed to reflect aging of the

pituitary gonadotropin–secreting cells, specifically a decrease in the ability to respond to the hypothalamic gonadotropin-releasing hormone (GnRH).

The postmenopausal ovary continues to secrete androgens, primarily androstenedione and testosterone. However, the circulating level of androstenedione after menopause is about one-half that seen prior to menopause.[157] Most of this postmenopausal androstenedione is derived from the adrenal gland, with only a small amount secreted from the ovary, even though androstenedione is the principal steroid secreted by the postmenopausal ovary.[158,159] Dehydroepiandrosterone (DHEA) and its sulfate (DHEA-S), originating in the adrenal gland, decline markedly with aging; in the decade after menopause, the circulating levels of DHEA are approximately 70% less, and levels of DHEA-S are about 74% less than the levels in young adult life.[160,161]

Testosterone production decreases by approximately 25% after menopause, compared to the case in the premenopausal period. The postmenopausal ovary in most, but not all, women secretes more testosterone than the premenopausal ovary, at least in the initial years of the postmenopausal period. With the disappearance of follicles and estrogen, the elevated gonadotropins drive the remaining tissue in the ovary to a level of increased testosterone secretion. The ovarian cells of origin are uncertain; presumably, the steroidogenic tissue is that which has accumulated from ovarian follicles undergoing atresia because stromal cells believed to be of mesenchymal origin lack steroidogenic capability.[162] Suppression of gonadotropins with GnRH agonist or antagonist treatment of postmenopausal women results in a significant decrease in circulating levels of testosterone, indicating a gonadotropin-dependent ovarian origin to circulating testosterone in postmenopausal women.[163–165]

The total amount of testosterone produced after menopause, however, is decreased because the amount of the primary source, peripheral conversion of androstenedione, is reduced. The early postmenopausal circulating level of androstenedione decreases approximately 62% from young adult life.[160] **The menopausal decline in the circulating levels of testosterone is not great, from no change in many women to as much as 15% in others**.[47,156,160,166,167]

In an excellent longitudinal Australian study spanning a period from 5 years before to 7 years after menopause onset, the circulating levels of

testosterone did not change.[161] Indeed, because of a decrease in sex-hormone–binding globulin (SHBG), this Australian study identified an increase in free androgens postmenopause**. Late postmenopause may be considered as a state of relative androgen excess.**

Later in the postmenopausal years, the circulating androgen levels are nearly all, if not all, derived from the adrenal gland. A careful study could detect no circulating androgens in postmenopausal women (averaging 12 years distant from menopause onset) with complete adrenal insufficiency and no intraovarian testosterone or androstenedione.[168]

The circulating estradiol level after menopause is approximately 10 to 20 pg/mL, most of which is derived from peripheral conversion of estrone, which in turn is mainly derived from the peripheral conversion of androstenedione.[157,169,170] The circulating level of estrone in postmenopausal women is higher than that of estradiol, approximately 30 to 70 pg/mL **(Table 21.4)**. The average postmenopausal production rate of estrogen is approximately 45 μg/24 hours, almost all, if not all, being estrogen derived from the peripheral conversion of androgens. The androgen–estrogen ratio changes drastically after menopause because of the more marked decline in estrogen, and an onset of mild hirsutism is common, reflecting this marked shift in the sex hormone ratio. With increasing postmenopausal age, a decrease can be measured in the circulating levels of dehydroepiandrosterone sulfate (DHEA-S) and DHEA, whereas the circulating postmenopausal levels of androstenedione, testosterone, and estrogen remain relatively constant.[156,157]

Estrogen production by the ovaries does not continue beyond the menopause; however, estrogen levels in postmenopausal women can be significant, principally due to the extra glandular conversion of androstenedione and testosterone to estrogen. The clinical impact of this estrogen varies from one postmenopausal woman to another, depending on the degree of extra glandular production, modified by a variety of factors.

The percent conversion of androstenedione to estrogen correlates with body weight. Increased production of estrogen from androstenedione with increasing body weight is probably due to the ability of fat to aromatize androgens. This fact and a decrease in the levels of SHBG (which results in increased free estrogen concentrations) contribute to the well-recognized association between obesity and the development of endometrial cancer.

Body weight, therefore, has a positive correlation with the circulating levels of estrone and estradiol.[157] Aromatization of androgens to estrogens is not limited to adipose tissue, however, because almost every tissue tested has this activity.

TABLE 21.4

Blood Production Rates of Steroids[171]

	Reproductive Age	*Postmenopausal*	*Oophorectomized*
Androstenedione	2–3 mg/d	0.5–1.5 mg/d	0.4–1.2 mg/d
Dehydroepiandrosterone	6–8	1.5–4.0	1.5–4.0
Dehydroepiandrosterone sulfate	8–16	4–9	4–9
Testosterone	0.2–0.25	0.05–0.18	0.02–0.12
Estrogen	0.350	0.045	0.045

Changes in Circulating Hormone Levels at Menopause[47,157,169]

	Premenopause	*Postmenopause*
Estradiol	40–400 pg/mL	10–20 pg/mL
Estrone	30–200 pg/mL	30–70 pg/mL
Testosterone	20–80 ng/dL	15–70 ng/dL
Androstenedione	60–300 ng/dL	30–150 ng/dL

Eventually, the ovarian steroidogenic tissue is exhausted and, despite huge reactive increments in FSH and LH, no further steroidogenesis of importance results from gonadal activity. The postmenopausal ovary weighs less than 10 g, but it can be visualized by ultrasonography.[172] With increasing age, the adrenal contribution of precursors for estrogen production proves inadequate. In this final stage of estrogen availability,

levels are insufficient to sustain secondary sex tissues, such as the genitourinary epithelium **(Figure 21.9)**.

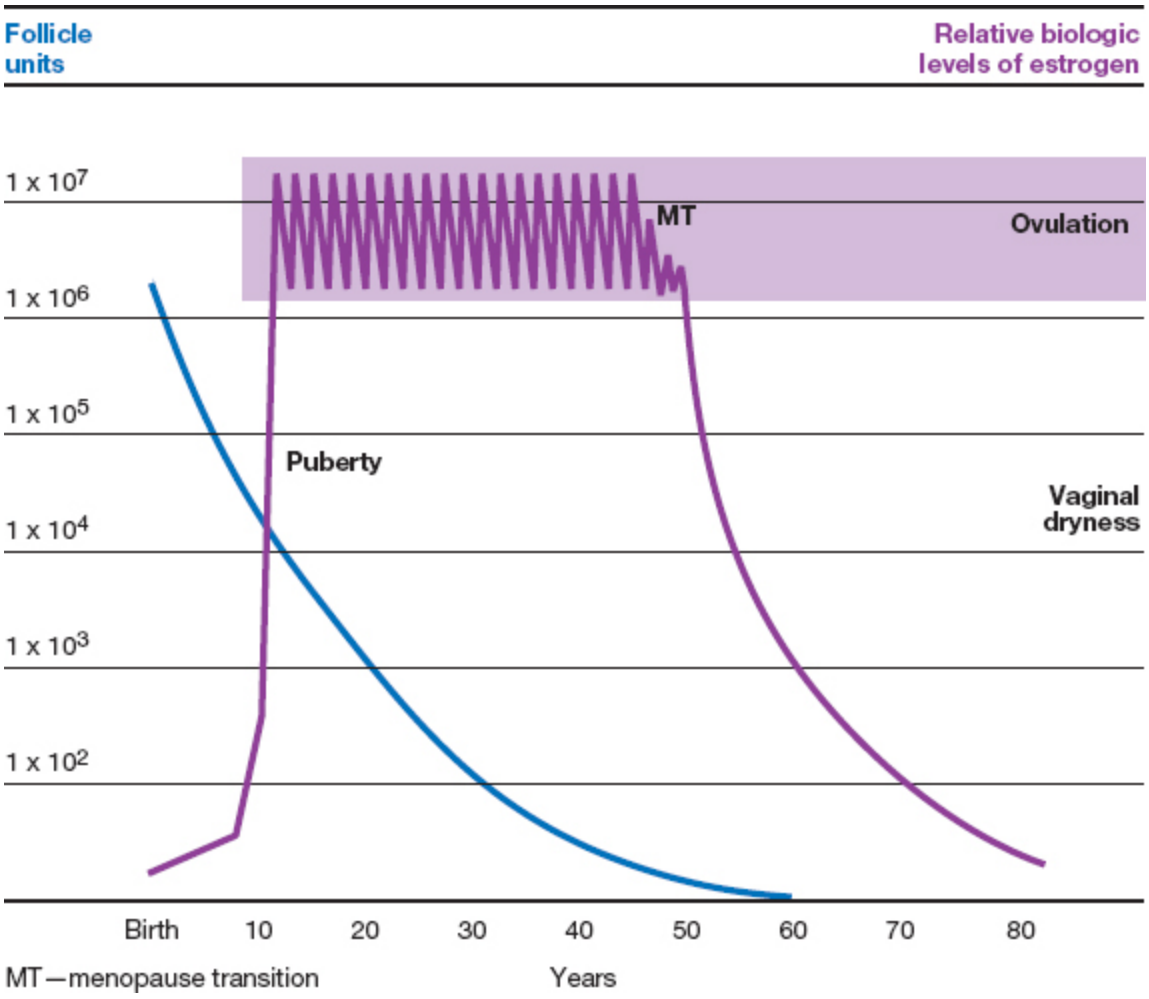


FIGURE 21.9

In summary, the shift in the endocrine milieu from estrogen dominance of premenopause to the hypoestrogenic and relatively hyperandrogenic milieu of postmenopause underlie the common climacteric and menopausal symptoms, which include:

- Disturbances in menstrual pattern, including anovulation and reduced fertility, decreased flow or hypermenorrhea, irregular frequency of menses, and then, ultimately, amenorrhea

- Vasomotor instability (hot flushes and night sweats)
- Symptomatology of the Genito-Urinary Syndrome of Menopause (GUSM) that results from atrophy of the urogenital epithelium consequent to hypoestrogenism; symptoms include vaginal dryness, dyspareunia and pruritus due to vulvar, introital, and vaginal atrophy; general skin atrophy; and urinary difficulties such as urgency and abacterial urethritis and cystitis

A precise understanding of the symptom complex an individual woman may manifest and an individualized approach to quantifying symptom burden as well as health risks must be adopted to arrive at the most optimal approach for symptom control for each individual.

It is helpful to classify the hormonal underpinnings to presenting problems under three distinct categories:

1. **Those associated with relative estrogen excess, such as abnormal uterine bleeding (AUB), endometrial hyperplasia, and endometrial cancer**
2. **Those associated with estrogen deprivation, such as VMS (hot flushes, night sweats), GUSM symptoms, bone loss, osteoporosis, skeletal fragility, and, to some extent, CVD**
3. **Those associated with hormone therapy (discussed in Chapter 22)**

SYMPTOMATOLOGY OF PERIMENOPAUSE AND MENOPAUSE

The period of transition should serve to remind both the patients and the clinicians that this is a time for communication to ensure improvements in patient awareness through education. Certainly, preventive health care education is important throughout life, but at the time of menopause, a review of the major health issues can be especially rewarding. Besides the general issues of good health, attention is appropriately focused on CVD and osteoporosis.

During the transition and early postmenopausal years, in particular, some women may experience significantly bothersome symptoms, whereas others show no reactions or minimal reactions that can go unnoticed. The differences in menopause experience and in the spectrum and severity of symptoms across different cultures are poorly documented, and indeed, it is difficult to do so. Individual reporting is so conditioned by sociocultural

factors that it is hard to determine what is due to biologic versus cultural variability.[173,174] For example, there is no word to describe a “hot flush” in Japanese, Chinese, and Mayan.[175] Nevertheless, there is reason to believe that the nature and prevalence of menopausal symptoms are common to most women and that variations among cultures and within cultures reflect not physiology but differences in attitudes, lifestyles, socioeconomic status, and individual perceptions across societies.[176–181] Hormone levels during the perimenopausal years vary little among different ethnic groups; differences are mainly because of varying body sizes.[182]

Abnormal Uterine Bleeding

The period of transition is characterized by an increasing incidence of anovulatory uterine bleeding. Thus, the late reproductive and early menopausal stages are characterized by longer periods of exposure to unopposed estrogen, of ovarian and extraovarian (from aromatization of androgens) origins. In the SWAN study, about 20% of cycles even early in the menopausal transition were anovulatory, associated with shorter intervals at the beginning of the transition and longer intervals later.[183] Irregular bleeding was most often due to anovulation, whereas heavy menstrual bleeding was associated with obesity and uterine abnormalities. The menopause transition and *early* menopause can thus be considered as times of *relative estrogen excess*. Although the greatest concern emerging from prolonged periods of exposure to estrogen unopposed by progesterone (as occurs during periods of anovulation) is of endometrial neoplasia, the most common tissue finding is that of nonneoplastic tissue displaying estrogen effects unopposed by progesterone.

In addition to the relative excess of estrogen resulting from periods of anovulation, there are four mechanisms that could result in higher endogenous estrogen levels in the perimenopausal and early menopausal women:

1. **Increased precursor androgen (functional endocrine tumors, liver disease, stress)**
2. **Increased aromatization of androgens (obesity, hyperthyroidism, and liver disease)**
3. **Increased direct secretion of estrogen (ovarian tumors)**
4. **Decreased levels of SHBG leading to increased levels of free estrogen**

In any individual woman presenting with AUB, whether perimenopausal or postmenopausal, whether on or off hormone therapy, specific organic causes for AUB (neoplasia, complications of unexpected pregnancy, or bleeding from extrauterine sites) must be ruled out. Additionally, a systematic evaluation should be undertaken that should include careful history taking and physical examination. A transvaginal ultrasound (TVUS) examination should be considered before attempting endometrial sampling for the measurement of endometrial thickness in assessing perimenopausal and postmenopausal AUB to avoid unnecessary endometrial biopsies.[184] **In postmenopausal women with AUB, endometrial biopsy is considered unnecessary when the endometrial thickness on ultrasound is less than 4 mm as the risk of endometrial hyperplasia or cancer in this setting is unlikely**.[185–188] Substantial evidence is, however, lacking to support the application of this criterion to the premenopausal population. **We believe that biopsy is unnecessary in postmenopausal women when the endometrial thickness is 4 mm or less. We further believe that endometrial biopsy is indicated when the clinical history suggests long-term unopposed estrogen exposure (either prolonged periods of oligomenorrhea/amenorrhea or iatrogenic estrogen use) even when the endometrial thickness is "normal" (5–12 mm for premenopausal women). Furthermore, biopsy should be considered when endometrial thickness is persistently greater than 12 mm even in the absence of AUB, even when clinical suspicion of disease is low. Additionally, if AUB persists in postmenopausal women with an EMT <4 mm, an endometrial biopsy should be performed.** An office procedure has been shown to offer tissue yield that is closely comparable to dilation and curettage (D&C) and has an 83% sensitivity for detecting endometrial cancer.

A TVUS study can also help in identifying intracavitary lesions, particularly with intracavitary instillation of saline.[189] Saline infusion sonohysterogram (SHG) can identify intracavitary lesions (ie, polyps and submucosal fibroids) that can be missed on routine 2D TVUS.[189] The sensitivity and specificity of TVUS for identifying intrauterine pathology are 56% to 73%,[190] whereas SHG has a sensitivity of 96% to 100% and a negative predictive value of 94% to 100% in evaluating for uterine pathology.[189] Hysteroscopy has an accuracy of 96% for intracavitary

pathology, with abnormalities seen in about 47% of premenopausal and postmenopausal women with AUB.[157]

If the endometrial assessment is unremarkable but abnormal bleeding persists, then for reasons of both accuracy and cost-effectiveness, the next step should be of endometrial biopsy; when no focal pathology is evident on screening, then it is appropriate for the method of endometrial biopsy to be an office-based procedure. We recommend the use of a plastic endometrial suction device (such as a pipelle) as the procedure is easy to perform, requires no cervical dilation, and is frequently well tolerated and equipment is routinely available even in low-resource settings. An office-based endometrial biopsy has been shown to offer tissue yield that is closely comparable to D&C and has an 83% sensitivity for detecting endometrial cancer. Insertion should first be attempted without the use of a tenaculum. In many patients, this is feasible and avoids the sensation of the tenaculum grasping the cervix. Once the suction is applied, the endometrial cavity should be thoroughly curetted in all directions, just as it would with a sharp curette during a D&C. Although most patients report no problems with cramps or pain, the application of suction in some patients stimulates cramping that usually passes within 5 to 10 minutes. Because cramping can occur, an inhibitor of prostaglandin synthesis given at least 20 minutes before the procedure has been shown to minimize procedure-related discomfort. Less than 10% of postmenopausal women cannot be adequately evaluated by office biopsy. Most commonly, the reason is the inability to negotiate the cervical canal and gain entry into the uterine cavity. In such instances, it is very reasonable to proceed with procedure under anesthesia when a D&C can be performed in the operating room; however, pretreatment with misoprostol or cervical laminaria may allow completion of office endometrial biopsy and thus avoid the need for anesthesia and D&C. We recommend consideration for office hysteroscopy or an SHG prior to proceeding with office endometrial biopsy and undertaking concomitant hysteroscopy at the time of D&C being undertaken for evaluation of AUB,[157] provided access to the equipment is available and the surgeon has the requisite expertise. Following a negative hysteroscopy result, the chance of endometrial cancer diagnosis is 0.4% to 0.5%.[157] If the vulva, vagina, and cervix appear normal on inspection, menopausal bleeding can be assumed to be intrauterine in origin. Confirmation requires

the absence of abnormal cytology on the Pap smear. The principal symptom of endometrial cancer is abnormal vaginal bleeding, but carcinoma will be encountered in patients with bleeding in less than 3% of postmenopausal endometrial biopsies.[191–193] Normal endometrium is found over half the time, polyps in approximately 3%, endometrial hyperplasia about 15% of the time, and atrophic endometrium in the rest of patients with postmenopausal bleeding. Postmenopausal bleeding should always be taken seriously. Approximately 10% of patients who have benign findings at the initial evaluation subsequently develop significant pathology within 2 years.[192] **The persistence of abnormal bleeding demands repeated evaluation.**

Additional procedures to consider include the following:

- **Colposcopy and cervical biopsy** for abnormal cytology or obvious lesions
- **Endocervical assessment** by curettage for abnormal cytology (the endocervix must always be kept in mind as a source for abnormal cytology)

Keep in mind that the pathologic reading, "tissue insufficient for diagnosis," when a patient is on estrogen–progestin treatment, often represents atrophic, decidualized endometrium that yields little to the exploring curette. If the clinician is confident in his or her technique, knowing that a full investigation of the intrauterine cavity has been accomplished, then *as long as the patient's bleeding does not persist*, this reading can be interpreted as comforting and benign, the absence of pathology. Specifically, as long as the clinician is certain that the true uterine cavity was sampled (ie, no false passage or stenotic os encountered), no further testing is indicated unless abnormal bleeding persists and risk factors for neoplasia are present. In the event of continued bleeding or concerning risk factors (ie, long-standing history of unopposed estrogen, obesity, hypertension, diabetes, and nulliparity), consideration for referral to a gynecologic oncologist would be a prudent approach.

In the absence of organic disease, appropriate management of uterine bleeding is dependent on the age of the woman and endometrial tissue findings. In the menopausal woman with AUB associated with evidence of

simple endometrial hyperplasia (uncomplicated by atypia or dysplastic constituents), periodic oral progestin therapy is mandatory (such as 10-mg medroxyprogesterone acetate or 5- to 10-mg norethindrone acetate for 14 days each month). Intrauterine placement of a levonorgestrel intrauterine device (LNG-IUD) is increasingly being utilized as an effective management approach with high regression rates. Higher-dose oral progestins (such as 10- to 20-mg medroxyprogesterone acetate or 10- to 15-mg norethindrone acetate) are always an option and should be considered in the setting of obesity.[194,195] Repeat endometrial sampling should be performed at 3 and 6 months of therapy. Most cases of simple hyperplasia will regress at 6 months; however, if there is no regression at 3 to 6 months, then increasing progestin dose or switching regimen (such as to megestrol acetate in daily doses of 40–80 mg or LNG-IUD) should be considered. Persistence or progression of abnormal endometrium was observed in 28.4% of women with complex hyperplasia and in 26.9% of women with atypical hyperplasia despite treatment with a progestational agent.[196] At least two consecutive repeat negative biopsies should be conducted prior to stopping surveillance.[194] In the absence of any regression after 1 year of progestin therapy, or if there is evidence of progression from simple or complex without atypia to atypical hyperplasia despite progestin therapy, then hysterectomy is indicated and referral to a gynecologic oncologist is strongly advised.[194] Because hyperplasia *with atypia* carries with it a risk of concomitant cancer (even invasive), hysterectomy is the treatment of choice. However, progestational response was better with higher-dosage and longer-duration treatment. If histologic regression is not observed on office biopsy, a D&C should be considered before proceeding with hysterectomy.

Contraception in Perimenopause

Clinicians have often utilized a traditional postmenopausal hormone regimen to treat a woman with the kind of irregular cycles usually experienced in the perimenopausal years. This addition of exogenous estrogen without a contraceptive dose of progestin when a woman is not amenorrheic or experiencing menopausal symptoms is inappropriate and even risky (exposing the endometrium to excessively high levels of

estrogen). **In addition, most importantly, a postmenopausal hormonal regimen does not inhibit ovulation and provide contraception.**[197] The appropriate response is to regulate anovulatory cycles with monthly progestational treatment along with an appropriate contraceptive method or to utilize low-dose estrogen–progestin contraception. An oral contraceptive that contains 20-μg estrogen provides effective contraception, improves menstrual cycle regularity, diminishes bleeding, and relieves menopausal symptoms.[198] Treatment with the transdermal or vaginal method of estrogen–progestin contraception would also be appropriate.

A common clinical dilemma is when to change from estrogen—progestin contraception to postmenopausal hormone therapy. It is important to change because even with the lowest estrogen dose contraceptive available, the estrogen dose is at least 4-fold greater than the standard postmenopausal dose, and with increasing age, the dose-related risks with estrogen become significant. One approach is to start measuring the FSH level annually at 50 years on day six or seven of the placebo week in a standard 3-week regimen (when steroid levels have declined sufficiently to allow FSH to rise). When FSH is greater than 20 IU/L, it is time to change to a postmenopausal hormone program; however, FSH variability indicates this is not always an accurate method, and some women will not have an FSH rise until 2 weeks after the last active pill.[199,200] Women who are dependent on contraceptives to prevent pregnancy can be allowed to enter their mid-50s on low-dose estrogen–progestin contraception and then empirically switched to a postmenopausal hormone regimen. **The empirical approach is necessary with patients using the newer extended-day or continuous dosing regimens of estrogen–progestin contraception.**

Because of the favorable impact of locally released progestin on the endometrium, the LNG-IUD is very effective for the treatment of menorrhagia, as effective as the administration of oral progestins (with less side effects), and compares favorably with endometrial resection or ablation.[201–205] In addition, levonorgestrel IUD is more effective in treating endometrial hyperplasia than oral progesterone.[206–214] The levonorgestrel IUD may be associated with a slight increase in the formation of ovarian cysts, but they are asymptomatic and resolve spontaneously.[215]

Vasomotor Symptoms

The vasomotor flush is viewed as the hallmark of the female climacteric, experienced to some degree by most postmenopausal women. The term “hot flush” or “hot flash” is descriptive of a sudden onset of reddening of the skin over the head, neck, and chest, accompanied by an increase in heart rate and a feeling of intense body heat. The flush sometimes concludes with profuse perspiration. The duration varies from a few seconds to several minutes and, rarely, for an hour. The frequency may be rare to recurrent every few minutes. Flushes are more frequent and severe at night (when a woman is often awakened from sleep) or during times of stress. In a cool environment, hot flushes are fewer, less intense, and shorter in duration compared with a warm environment.[216] Most importantly, hot flushing can affect a woman’s quality of life and interfere with work or recreational activities.

In the longitudinal follow-up of a large number of women, fully 10% of the women experienced hot flushes before menopause, while in other studies as many as 15% to 25% of premenopausal women reported hot flushes.[8,96,217,218] The frequency has been reported to be even higher in premenopausal women diagnosed with PMS.[219] In the Massachusetts Women’s Health Study, the incidence of hot flushes increased from 10% during the premenopausal period to about 50% just after cessation of menses.[96] By approximately 4 years after menopause, the rate of hot flushes declined to 20%. In a community-based Australian survey, 6% of premenopausal women, 26% of perimenopausal women, and 59% of postmenopausal women complained of hot flushing.[220] A large American cross-sectional survey reported that 57% of perimenopausal women and 49% of early postmenopausal women experienced significant hot flushing.[180] Another national survey in the United States reported hot flushing in 79% of perimenopausal women and 65% of postmenopausal women.[221]

In cross-sectional surveys, up to 40% of premenopausal women and 85% of menopausal women report some vasomotor complaints.[218] A longitudinal study in Gothenburg, Sweden, recorded a maximal prevalence of 60% at ages 52 to 54, with a decline to 30% at age 60 and 9% at age 72.[222] In the SWAN study, 57% of perimenopausal women experienced hot

flushing and about 50% after menopause up to age 55.[223] There is no difference in the prevalence of vasomotor complaints in US surveys of Black and White women.[224,225] Overweight women report more hot flushing, perhaps reflecting the effect of body fat causing a higher core body temperature.[180,182,226] Exact estimates on prevalence are hampered by inconsistencies and differences in methodologies, cultures, and definitions.[227] The prevalence in different societies is influenced by personal and social attitudes, individual psychological and physical health, familiarity with the portrayal of menopausal issues in the literature and media, ethnic variation, different diets, and dissimilar living conditions; however, accounting for cultural differences, the overall prevalence and experience are similar throughout the world.[228,229]

Although the flush can occur in the premenopause, it is a major feature of the menopause transition and postmenopause, peaking in the first year after the last menses, lasting in 50% of women for 4 to 5 years, but in some (as many as 25%) for longer than 5 years, and even up to 15 years in 10% (Table 21.5).[230] In an excellent Australian longitudinal cohort study, the average duration of VMS was 5.2 years (with a range of 2–10 years) in nonusers of hormone therapy and slightly longer, 5.5 years, in hormone users.[231] In the SWAN cohort, the median total duration of VMS was 7.4 years. Women who were premenopausal or early perimenopausal at first reporting of frequent symptoms experienced the longest duration (median, >11.8 years) and post-FMP persistence (median, 9.4 years), whereas women who first experienced VMS after onset of menopause had the shortest total duration of symptoms (median, 3.4 years).[232]

TABLE 21.5 The Hot Flush

Premenopausal	10–25% of women
Perimenopausal	60%
Postmenopausal:	
No flushes	15–25%

Daily flushing	15–25%
Duration	1–2 y average: 15–20% 5 or more years: 25%
Other causes	Psychosomatic Stress Thyroid disease Subacute, chronic infections Pheochromocytoma Carcinoid Leukemia Cancer

The physiology of the hot flush is not entirely understood. In recent years, a pivotal role of the hypothalamic KNDy (Kisspeptin Neurokinin B, Dynorphin) neurons has been identified in driving the thermoregulatory response to estrogen deprivation.[233,234] Studies suggest that women with hot flushes have a more narrow zone of temperature regulation and that, therefore, smaller changes in core body temperature produce compensatory responses, such as shivering or flushing.[235] MRI scanning of the brain during hot flushing indicates widely distributed cortical activation rather than a precise location.[236]

Hot flushes are definitely brought about by a decline in estrogen; however, not all hot flushes are due to estrogen deficiency. Flushes and sweating can be secondary to diseases, including pheochromocytoma, carcinoid, leukemias, pancreatic tumors, and thyroid abnormalities.[237] **When the clinical situation is not clear and obvious, estrogen deficiency as the cause of hot flushes should be documented by elevated levels of FSH.**

The correlation between the onset of flushes and estrogen reduction is clinically supported by the effectiveness of estrogen therapy and the absence of flushes in hypoestrogenic states, such as gonadal dysgenesis. Only after estrogen is administered and withdrawn do hypogonadal women experience the hot flush. Although the clinical impression that premenopausal surgical castrates suffer more severe vasomotor reactions is

widely held, this was not borne out in the only objective study ever performed.[238]

The hot flush is the most common problem of the peri and early postmenopausal period. The flush is accompanied by a discrete and reliable pattern of physiologic changes.[235,239] The flush coincides with a surge of LH (not FSH) and is preceded by a subjective prodromal awareness that a flush is beginning. This aura is followed by measurable increased heat over the entire body surface. A flush is triggered by a small elevation in core body temperature. The body surface experiences an increase in temperature, accompanied by changes in skin conductance, and then the flush is followed by a fall in core temperature—all of which can be objectively measured. In short, the flush is not a release of accumulated body heat but a sudden inappropriate excitation of heat release mechanisms. Its relationship to the LH surge and temperature change within the brain is not understood. The observation that flushes occur after hypophysectomy indicates that the mechanism is not dependent on or due directly to LH release. In other words, the same brain event that causes flushes also stimulates GnRH secretion and elevates LH. It is now understood that estrogen exerts suppressive effects on the hypothalamic KNDy neurons, which in turn directly modulate the thermoregulatory center. The loss of estrogen results in activation of the KNDy neurons and consequent release of neurotransmitters that increase neuronal and autonomic activity with resetting of the thermoregulatory center and episodic activation of heat dissipation cascade, resulting in the vasomotor episode of the flash **(Figure 21.10)**.[233,234,240]

Premenopausal women experiencing hot flushes should be screened for thyroid disease and other illnesses. A comprehensive review of all possible causes is available.[241] Clinicians should be sensitive to the possibility of an underlying emotional problem. Looking beyond the presenting symptoms into the patient’s life is an important service to the patient and her family that will eventually be appreciated. This is far more difficult than simply prescribing estrogen, but confronting problems is the only way of reaching some resolution.

A striking and consistent finding in most studies dealing with menopause and hormonal therapy is a marked placebo response (at least 51% in the first weeks of treatment)[242] in a variety of symptoms, including

flushing. In a randomized, placebo-controlled English study of women being treated with estrogen implants and requesting repeat implants, there was no difference in outcome in terms of psychological and physical symptoms on comparing the women who received an active implant to those receiving a placebo.[243]

A significant clinical problem encountered in our referral practice is the following scenario: a woman will occasionally undergo an apparently beneficial response to estrogen, only to have the response wear off in several months despite ongoing use of prescribed hormonal regimen. Rather than continuously increasing the estrogen dose, it is important to consider altering the mode of delivery (ie, switching from oral to transdermal) or timing of medication (ie, if administering orally, consider twice-daily dosing if giving estradiol as opposed to CEE). Importantly, uncommon differential diagnoses, such as pheochromocytoma or carcinoid, must be entertained when encountering recalcitrant VMS that remain unresponsive to increasing doses of estrogen therapy. Additionally, a careful inquiry must be undertaken to search for underlying psychosocial problems. To help persuade a patient that her symptoms are not due to low levels of estrogen, we find it very helpful and convincing to measure the patient’s blood level of estradiol and share the result with her.

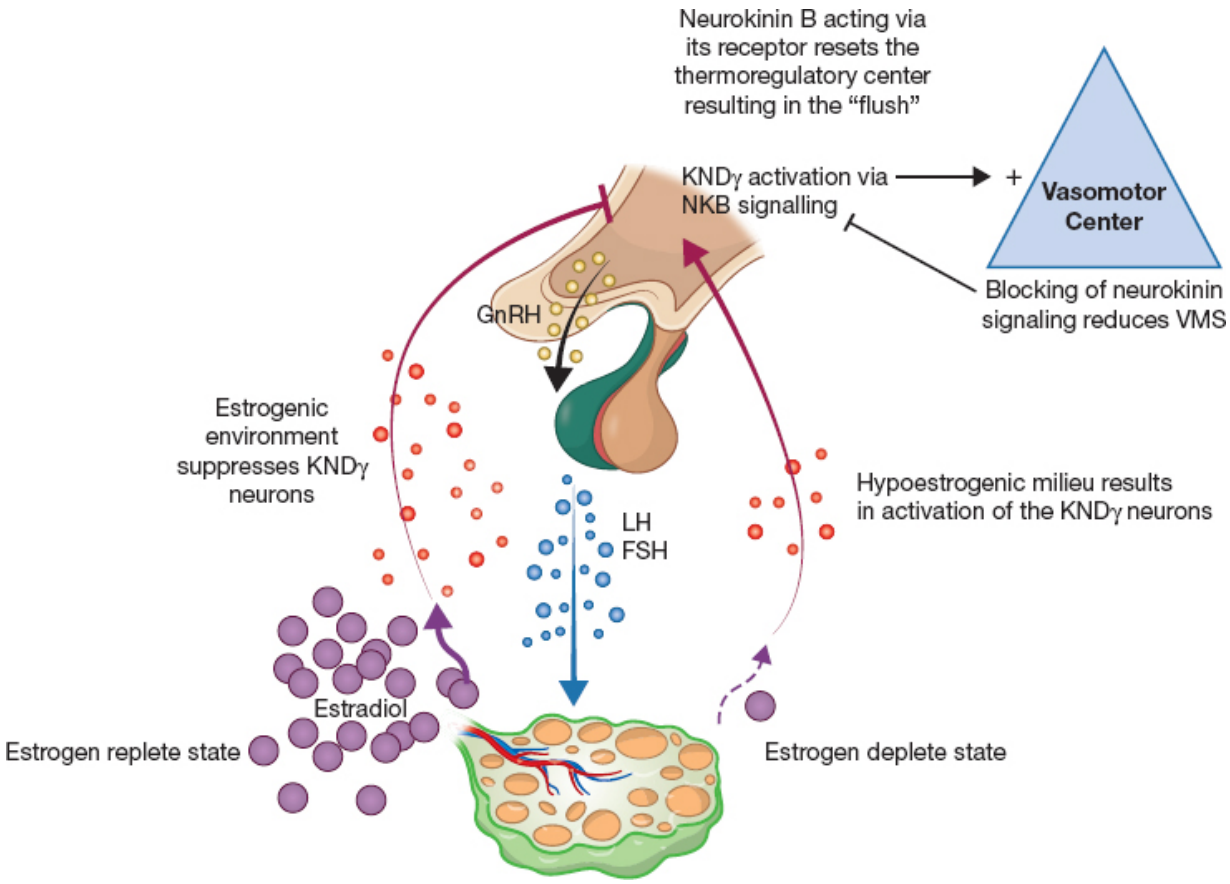


FIGURE 21.10

The Genitourinary Syndrome of Menopause

Although vaginal dryness may be experienced during the perimenopause, symptoms such as those of vaginitis, pruritus, dyspareunia, and frequent urinary tract infections, which are attributable to atrophy of vaginal mucosal surfaces, worsen as women advance into postmenopausal years and can contribute to worsening quality of life.[244]

Urethritis with dysuria, urgency incontinence, and urinary frequency are results of mucosal thinning of the urethra and bladder.[245] Recurrent urinary tract infections are effectively prevented by postmenopausal intravaginal estrogen treatment.[245] However, certain anatomic conditions, such as vaginal tissue relaxation with cystocele, rectocele, uterine prolapse, and vulvar dystrophies, that are common accompaniments to aging are not a consequence of estrogen deprivation.

Deprived of estrogen, the vagina loses collagen, adipose tissue, and the ability to retain water. As the vaginal walls shrink, the rugae flatten and disappear. The surface epithelium loses its outer fibrous layer and thins to a few layers of cells, markedly reducing the ratio of superficial to basal cells. As a result, the vaginal surface is left friable, prone to bleeding with minimal trauma. While these changes are occurring, the blood vessels in the vaginal walls narrow, and secretions from sebaceous glands diminish. Over time, the vagina itself contracts and loses flexibility, while the labia minora become paler and smaller. In addition, pH becomes more alkaline, making the vaginal environment less hospitable to lactobacilli and more susceptible to infection by urogenital and fecal pathogens. **Measuring pH is a simple way to determine estrogen's influence or absence. A pH greater than 4.5 is almost always observed with estrogen deficiency.**[246,247] Infecting organisms can ascend into the urinary system to cause urethritis, urinary tract infections, and cystitis.

Dyspareunia, sometimes with postcoital bleeding, is the inevitable consequence of a severely atrophied vagina with scant lubrication. Even for women who are not sexually active, atrophic vaginitis can cause itching, irritation, and burning. These symptoms often go unmentioned, and it is important to inspect for signs of vaginal atrophy even in the absence of complaints. Dyspareunia or vaginal discomfort seldom brings older women to see their gynecologists. A basic reluctance to discuss sexual behavior still permeates society, and per the literature summary from the North American Menopause Society (NAMS), anywhere between one-third and three-fourths of women who experience symptoms of estrogen deprivation do not discuss this with providers, while another one-third desire the providers to start the discussion (NAMS).

Objective measurements have demonstrated that vaginal factors that influence the enjoyment of sexual intercourse can be maintained by appropriate targeted treatment; until recently, only estrogen-based therapy was available to effectively address symptoms of vaginal atrophy, but now a postmenopausal woman can choose from a finite variety of hormonal and nonhormonal treatment options, which are further discussed in Chapter 22.[248] Both patient and clinician should be aware that a significant response can be expected by 1 month but that it can take a longer time to fully restore wellness of the genitourinary tract (6–12 months), and clinicians and

patients should not be discouraged by an apparent lack of immediate response. Vaginal dryness is worse with use of aromatase inhibitors commonly utilized as adjuvant therapy for postmenopausal breast cancer and as chemoprophylaxis. Sexual activity by itself supports the circulatory response of the vaginal tissues and can itself improve vaginal tissue elasticity, stretchability as well as mucosal integrity as well as enhances the therapeutic effects of estrogen. Therefore, sexually active older women have less atrophy of the vagina, even without estrogen.

Although it is argued that genuine stress incontinence is not affected by treatment with estrogen, others contend that estrogen treatment improves or cures stress incontinence in over 50% of patients due to a direct effect on the urethral mucosa.[249–251] A metaanalysis concluded that improvement was reported only in nonrandomized studies.[252] Two randomized trials dedicated to this clinical problem failed to demonstrate a beneficial effect of estrogen treatment.[253,254] Most cases of urinary leakage in older women are due to a mixed problem with a significant component of urge incontinence, which, unlike stress incontinence, may be improved by estrogen therapy. However, the Heart and Estrogen–Progestin Replacement Study (HERS) randomized trial indicated a worsening of incontinence with hormone therapy for both urge and stress incontinence, and the Nurses' Health Study reported a small increase in incontinence in hormone users.[255,256] In the SWAN study, only 15% of incontinent women reported a worsening of urinary incontinence during the menopausal transition, largely because of weight gain.[257] The majority of incontinent women experienced either no change or an improvement. The SWAN study results imply that urinary incontinence is not a major symptom of menopause and the perimenopausal transition.[257,258] In contrast, a Cochrane review from 2012 found that compared to placebo, women who received vaginal estrogen-based therapy for incontinence noted an improvement in symptoms.[259] Interestingly, in trials using oral estrogen, women reported worsening of urinary symptoms.[260] **Overall, data suggest that new-onset urinary incontinence at midlife is not a consequence of hormonal changes and, therefore, is not likely to be impacted with the use of estrogen.**

A decline in skin collagen content, elasticity, and skin thickness that occurs with aging can be considerably avoided by postmenopausal estrogen therapy.[261–265] The effect of estrogen on collagen is evident in both bone and

skin; bone mass and collagen decline in parallel after menopause, and estrogen treatment reduces collagen turnover and improves collagen quality.[266,267] Several studies demonstrated not only an increase in facial skin thickness but also an improvement in wrinkles, dryness, elasticity, and thickness with hormone therapy.[268–271] Smoking is a major risk factor for facial skin wrinkling, and hormone therapy cannot diminish its negative impact.[272] In a 1-year clinical trial, hormone therapy did not improve skin wrinkling already present.[271]

One of the features of aging in men and women is a steady reduction in muscular strength. Many factors affect this decline, including height, weight, and level of physical activity. Women currently using estrogen have been reported to demonstrate a lesser decline in muscular strength, although at least one study could detect no impact of estrogen.[273–278] This is an important issue because of the potential protective consequences against fractures, as well as a benefit due to the ability to maintain vigorous physical exercise.

Sexuality, Aging, and Menopause

Sexuality is behavior that evolves and chances across the lifespan. It begins with birth (maybe before) and ends with death. The notion that sexuality ends with aging is inherently illogical. The need for closeness, caring, and companionship is lifelong. Old people today live longer, are healthier, have more education and leisure time, and have had their consciousness raised in regard to sexuality.

Younger people, especially physicians, underrate the extent of sexual interest in older people. In a random sample of women aged 50 to 82 in Madison, Wisconsin, nearly one-half of the women reported an ongoing sexual relationship.[138] In the Duke longitudinal study on aging, 70% of men in the 67 to 77 age group were sexually active, and 80% reported continuing sexual interest, while 50% of all older women were still interested in sex.[139] In the PEPI trial, 60% of women 55 to 64 years old were sexually active.[140] In a national sample of American men and women, the prevalence of sexual behavior declined with aging; however, 26% of individuals aged 75 to 85 years were still sexually active.[141] The prevalence of self-reported sexual problems peaks in middle-aged women, sufficient to

cause distress in about 22% of US women and about 12% of women aged 45 to 64.[142] Up to 23% of menopausal women are negatively affected by decreased sexual desire.[143]

The decline in sexual activity with aging is influenced by culture and attitudes, as well as by nature and physiology (or hormones). As estradiol regulates serotonergic function, it can affect desire and sexual function.[143] In addition, the discomfort resulting from vaginal dryness and tissue atrophy consequent to low estradiol levels can make coitus unwelcome, even to the point of avoidance. Thus, a significant component of decline in sexual activity in reproductively aging women can be attributed to menopausal symptoms associated with decreasing estrogen levels, a problem that is easily ameliorated by targeted treatment.

There are two main sexual changes in the aging woman. There is a reduction in the rate of production and volume of vaginal lubricating fluid, and there is some loss of vaginal elasticity and thickness of the epithelium. Less vaginal atrophy is noted in sexually active women than in inactive women; presumably, the activity maintains vaginal vasculature and circulation. The spectrum of uncomfortable symptoms that are often described by transitioning and menopausal women with evidence of genital atrophy include a feeling of dryness and tightness, vaginal irritation and burning with penetration, and postcoital spotting and soreness. Given that these symptoms are the direct result of tissue estrogen deprivation, the underlying tissue changes can be effectively prevented by focal estrogen treatment. Systemic estrogen therapy may even have a positive impact on sexuality beyond effects on vaginal tissue.[140] In an ancillary sexual study of the KEEPS—a randomized, double-blinded, placebo-controlled trial—early menopausal women were randomized to receive either low-dose oral CEE or transdermal estradiol (transdermal E2), over the 4 years of intervention. While both routes of estrogen treatment resulted in an improvement in vaginal dryness and dyspareunia,[143] improvements in libido and sexual satisfaction were observed only in transdermal E2 users.[143] In an Australian study assessing changes in sexual functioning during the menopausal transition, a correlation with a decline in sexuality was demonstrated with estradiol levels but not with testosterone levels. There are likely many important factors other than hormone levels that are relevant in determining midlife sexual function.[143,144]

Illness and Sex

It is not uncommon to encounter medical or surgical underpinnings to disorders of sexuality. Surgical menopause (removal of both ovaries in premenopausal women) is probably one of the most commonly encountered iatrogenic contributors to altered sexual function. Remember that vaginal lubrication is an important physiologic sexual response, and therefore, vaginal dryness is a likely consequence following total hysterectomy even if the premenopausal ovaries are retained. Sexual problems are not limited, however, to surgical procedures and illnesses of the genitalia. Altered self-image such as following vulvectomy or mastectomy can also impact sexual function. However, studies have not found postmenopausal hysterectomy to have a detrimental impact on sexuality.[140,145]

Sexual counseling, to be effective, must be provided to couples both before and after surgery. It is not unexpected that the surgeon may not be fully capable of providing this counseling. A major contribution from an older woman's primary clinician is to arrange for competent and experienced sexual counseling. Unfortunately, most physicians operate on the principle that if no questions are raised, there is no problem. The expert surgeon should be grateful for the help of experts in psychosexual therapy. Seek out the potential for posttreatment sexual morbidity before the surgery. Assess the patient's abilities for coping and her sense of body image. Consider the quality of the patient's relationship, and be sensitive to the absence of a relationship. This entire effort may take some time. The normal state of presurgical anxiety, fear, and denial hampers good communication.

Increasing use of SSRI antidepressants is another iatrogenic contributor to female sexual dysfunction that merits attention.[146]

Antihypertensive agents are frequently responsible for male sexual dysfunction, but little information is available regarding female sexual function. Adrenergic blocking agents are especially noted to affect libido and potency in men. Similarly, psychotropic drugs of all categories have been associated with inhibition of sexual function. Finally, one should always suspect alcoholism when patients complain of sexual dysfunction. Androgen treatment for decreased female sexuality is discussed later in this chapter.

The two most important influences on sexual satisfaction in aging couples are the strength of relationship and the physical condition of each partner.[140,141,147] The single most significant determinant of sexual activity for older women is the lack of availability of partners due to divorce or demise as women are outliving men. Given availability of a partner, the same general high or low rate of sexual activity can be maintained throughout life.[4,148] Longitudinal studies indicate that the level of sexual activity is more stable over time than previously suggested.[149–151] Individuals who are sexually active earlier in life continue to be sexually active into old age. However, aging is associated with a decline in sexual function in many women, and this decline has been documented in the years well before the FMP.[152,153]

Mental Health, Perimenopause, and Menopause

The view that menopause has a deleterious effect on mental health or induces psychiatric disorders (involutional melancholia) is not supported in the psychiatric literature or in surveys of the general population, and this belief has been abandoned.[217,218,279,280] Indeed, depression is less common among middle-aged women, and the menopause cannot be linked as causative to psychological distress.[2–8,281,282] The longitudinal study of premenopausal women indicates that hysterectomy with or without oophorectomy is not associated with a negative psychological impact among middle-aged women.[283,284] Longitudinal data from the Massachusetts Women's Health Study document that menopause is not associated with an increased risk of depression.[282] Although women are more likely to experience depression than men, this sex difference begins in early adolescence, not at menopause.[285]

The U.S. National Health Examination Follow-up Study includes both longitudinal and cross-sectional assessments of a nationally representative sample of women. This study has found no evidence linking either natural or surgical menopause to psychological distress.[284] Indeed, the only longitudinal change was a slight decline in the prevalence of depression as women aged through the menopausal transition. Results in this study were the same in estrogen users and nonusers.

A negative view of mental health at the time of menopause is not justified; many of the problems reported at menopause are due to life events.[10,11,286,287] Thus, there are problems encountered in the perimenopausal transition and early postmenopause that are seen frequently, but their causal relation with estrogen is unlikely. These problems include fatigue, nervousness, headaches, insomnia, depression, irritability, and palpitations. Indeed, at this stage of life, both men and women express a multitude of complaints that do not reveal a gender difference that could be explained by a hormonal cause.[288,289] Nevertheless, midlife women report complaints more often than men,[289] perhaps reflecting the generally negative perceptions and connotations our cultures and societies have attributed to menopause.

Sleep disturbances are a common complaint during the menopausal transition and in early postmenopausal years.[290] Difficulties with falling asleep and with staying asleep, sleep interruptions, and early awakenings are all more often encountered during menopausal transition and postmenopause than during the reproductive stage of aging. Disordered sleep itself can negatively affect health outcomes, including risk of depression.[290] While hormonal changes can affect sleep, it has been difficult to establish the extent to which hormonal changes contribute to poor sleep. Several epidemiologic studies have demonstrated that men and women, on entering midlife, experience poor sleep quality.[291] Increased nighttime awakening and an overall loss of total sleep time are common in women in the menopausal transition and postmenopause.[291–294] Perhaps not surprisingly, nocturnal VMS (hot flushes and night sweats) likely contribute to sleep disturbances.[291] The underlying body temperature dysregulation and stress activation during episodes of vasomotor phenomenon are detrimental to sleep.[291] Studies assessing correlation between VMS and sleep patterns on polysomnography, however, are conflicting, suggesting the existence of unidentified confounders.[291]

The high prevalence of sleep issues during the menopausal transition and postmenopause has been suggested to contribute to depressive symptoms and to an overall decline in the quality of life.[292–294] Two longitudinal cohort studies assessed the new onset of depressive symptoms and disorders during the menopausal transition. The Penn Ovarian Aging Study followed for over 8 years 436 women with no history of depression

and correlated hormonal changes with the onset of depressed mood.[295] Fifty percent of the women developed an increase in measures of depression, and 26% met the criteria for a clinical diagnosis of depressive disorder. Using the women as their own controls, the depression group was 2.5 times more likely to develop clinical depression comparing status during the perimenopausal transition to the premenopausal state. These symptoms during the perimenopausal transition were associated with greater variability (but no average differences) in estradiol levels. These data suggest that fluctuations of estradiol can be an important destabilizing factor.

The Harvard Study of Moods and Cycles is a prospective cohort of women with and without histories of depression.[296] In the women who entered the menopausal transition, the risk of new depression was almost doubled compared with premenopausal women, from 9.5% to 16.6%, and this risk was linked to the presence of VMS. Importantly, a statistically significant increase in risk of new depressive symptoms was present only in women with a history of adverse life events (the events are not defined or specified in the report). Also of note, 83% of the women experienced no mood changes.

The SWAN study reported similar results. A first episode of depression in perimenopausal women was linked to poor physical health, anxiety disorders, stressful life events, and hot flushing.[297]

Additional studies have shed further light on the role of VMS, sleep disturbances, and depressive symptoms. In a pooled analysis of eight studies from the InterLACE consortium, it was found that sleep difficulties related to VMS explained to a large extent the relationship between VMS and depressed mood.[293] Interestingly, the OR of depressed mood associated with often/severe VMS was not significant when adjusted for baseline sleep disturbances at baseline.[293] However, having an often/severe depressed mood remained associated with subsequent risk of VMS.[293] Alternatively, using the SWAN cohort, a study by Kravitz et al noted that while sleep disturbances increased across the menopausal transition, they did not necessarily worsen over time.[298] It is important to note, however, that VMS were significantly associated with the number of sleep disturbances experienced throughout the menopausal transition.[298]

This area of concern has been very difficult to study. Inconsistent results can reflect variations in study designs, selection of subjects, methods used to measure mood, and the definition of menopausal status. **However, the best reports provide reliable evidence that there may be a vulnerable population of women who do experience depression during menopause, and thus, the most important question is how to identify these women.**

Unfortunately, identifying this specific subset of women has been difficult. Depressive mood changes are influenced by numerous factors, including body weight, smoking, PMS (discussed in Chapter 14), employment, and marital status. **PMS during reproductive years is a strong predictor of depressive symptoms arising in the menopausal transition.**

The most important questions are whether truly normal women experience an increase in depression during the menopausal transition and whether there are subtle or even clinically apparent psychological problems that identify a susceptible subgroup. In a cross-sectional analysis of the SWAN cohort, it was found that only 5% of women were affected with the "triad" of depressed mood, disturbed sleep, and sexual problems, suggesting that perhaps there is a susceptible group of women predisposed to psychological consequences in menopause.[299] Cohort studies support the argument that there is a vulnerable group of women who are at risk for experiencing new-onset depressive symptoms during the menopausal transition. Existing data are consistent with the idea that fluctuations in reproductive hormone levels appear to relate to mood symptoms during the period of menopause transition; however, it is impossible to know if this is a true cause-and-effect relationship. Until such a cause-and-effect relationship is elucidated, current efforts should focus on identifying and treating menopausal women suffering from sleep disturbances related to VMS. Therefore, focusing on a part of this "triad" by improving sleep quality through the reduction of VMS has been successful in improving the quality of life. In a pooled analysis of individual participant data from four randomized, control trials (RCTs) assessing the effect of various interventions for insomnia related to VMS, cognitive behavioral therapy (CBT) was most successful in reducing insomnia symptoms.[294] Exercise, venlafaxine, escitalopram, yoga, and estradiol were also effective but less so when compared to CBT.[294] One recent small RCT suggested that the

prophylactic use of hormone therapy in women around their FMP may help reduce depressive events. However, they did not assess for previous history of depression and noted a more pronounced effect when patients had more stressful life events in the year of treatment and when hormones were started closer to their FMP.[300]

In summary, most women (over 85%) experience the menopausal transition without mood difficulties. Some, however, are at greater risk of new-onset depressive symptoms, and this is probably enhanced by hormonal variations and VMS. This "vulnerable" population is likely derived from a group of premenopausal women with underlying psychological underpinnings. Although it can be hypothesized that the perimenopausal hormone milieu makes an individual less able to deal with adverse events in life, concrete data to support this concept are lacking.

Attempts to study the effects of estrogen on these problems have been hampered by the subjectivity of the complaints (high placebo responses) and the "domino effect" of what a reduction of hot flushes does toward improvement in sleep quality and this correlation to depression. Using a double-blind crossover prospective study format, Campbell and Whitehead concluded that many symptomatic "improvements" ascribed to estrogen therapy result from relief of hot flushes—a "domino" effect, which has been corroborated by several other studies.[152,301,302] In fact, many studies have demonstrated the positive impacts of estrogen therapy on sleep quality, time to sleep, increase in rapid eye movement (REM) time, even in asymptomatic women.[303–309] Studies that have been controlled for menopausal symptoms conclude that mood is greatly affected by VMS and sleep disturbances, besides reflecting life problems.[152,302]

Selection bias is problematic when analyzing the interplay between psychosomatic and VMS. A study of 2,001 Australian women aged 45 to 55 years focused on the utilization of the health care system by women in the perimenopausal period of life.[13] Users of the health care system in this age group were frequent previous users of health care, were less healthy, and had more psychosomatic symptoms and vasomotor reactions.[13] These women were more likely to have had a significant previous adverse health history, including a prior history of premenstrual complaints. This study emphasized that perimenopausal women who seek health care help are

different from those who do not seek help, and they often embrace hormone therapy in the hope that it will solve their problems. Similar findings have been reported in a cohort of British women.[310] It is this population that is seen most often, producing biased opinions among clinicians regarding menopause. We must be careful not to generalize to the entire female population the behavior experienced by a few. Most importantly, menopausal women who present to clinicians often end up being treated with estrogen inappropriately and unnecessarily. Nevertheless, it is well established that a woman's quality of life is disrupted by VMS and that estrogen therapy provides impressive improvement.[311–313] Patients are grateful to be the recipients of this "domino" effect.

The Women's Health Initiative (WHI; discussed in Chapter 22 under the section "Menopausal Hormone Therapy") concluded that estrogen–progestin therapy had no beneficial impact on health-related quality of life.[314] However, only 12.7% of the participants had moderate to severe VMS at entry to the study, and the symptom burden in this population can be questioned because the participants were willing to take placebo medication. The overall baseline quality of life in this study was relatively high, and the study participants were older (the average number of years distant from menopause was 12+). This randomized, clinical trial did not study the appropriate population of women in order to assess the effect of hormone therapy on measures of quality of life.

The Women's International Study of Long Duration Oestrogen after the Menopause (WISDOM) trial was a randomized, controlled trial in the United Kingdom, Australia, and New Zealand of 3,721 women aged 50 to 69 treated with either combined 0.625-mg conjugated estrogens to 2.5/5.0 mg medroxyprogesterone or placebo.[315] The original plan was to randomize 22,300 women to the study that would last 10 years. The study was canceled in October 2002 in reaction to the initial reports from the WHI. Unfortunately, the premature cancellation precludes the possibility of any long-term data from WISDOM. In the 2,130 women who completed 1 year, there were statistically significant improvements in the treated women in the categories of vasomotor, sexual, and sleep symptoms. Treated women reported a reduction in aching joints and muscles, night sweats, insomnia, and vaginal dryness. The treated group reported more breast tenderness, but the percentages were notably low (16% in the treated group and 7% in the

placebo group), with minimal side effects. In contrast, no differences in depression, anxiety, quality of life, or self-esteem were noted between hormone therapy or placebo. Similar results with VMS, sleep, and joint complaints were actually reported by the WHI, but with a smaller difference between treated and placebo groups. The most important point of these trials (WISDOM, WHI, and HERS; discussed further in Chapter 22) were all similar in that they all enrolled postmenopausal women heavily tilted toward older asymptomatic women. The authors acknowledged that younger, symptomatic women may have benefit from hormone therapy not seen in an older, asymptomatic population.[315]

It is a simple and logical conclusion that hormone therapy in a younger, symptomatic group of postmenopausal women would produce greater quality of life benefits than that quantified in the clinical trials. All three clinical trials, therefore, underestimated the beneficial impact because of age and symptom status of their participants. However, in the WISDOM trial, even older postmenopausal women who were symptomatic benefited from hormone therapy. Age should not be the sole guiding factor in decision-making.

Emotional stability during the perimenopausal period can be disrupted by poor sleep patterns. Hot flushing does have an adverse impact on the quality of sleep.[303–305] Estrogen therapy improves the quality of sleep, decreasing the time to onset of sleep and increasing the REM sleep time.[306,307,311] In the SWAN study, one-third of the women reported sleep problems, even without hot flushes or night sweats, and the prevalence of VMS was associated with an increased risk of sleep disturbances; hormone therapy improved sleep quality.[308,309] Perhaps flushing may be insufficient to awaken a woman but sufficient to affect the quality of sleep, thereby diminishing the ability to handle the next day’s problems and stresses. An improvement in sleeping with estrogen treatment can even be documented in postmenopausal women who are reportedly asymptomatic.[307]

Thus, the overall “quality of life” reported by women can be improved by better sleep and alleviation of hot flushing. However, it is still uncertain whether estrogen treatment has an additional direct pharmacologic antidepressant effect or whether the mood response is totally an indirect benefit of relief from physical symptoms and, consequently, improved sleep. Although multiple studies have seen improvement of depressive

symptoms with hormone therapy with an antidepressant, another cohort study saw no benefit with the use of estrogen therapy.[316–321] Utilizing various assessment tools for measuring depression, improvements with estrogen treatment were recorded in oophorectomized women.[316,317] In the large prospective cohort study of the Rancho Bernardo retirement community, no benefit could be detected in measures of depression in current users of postmenopausal estrogen compared with untreated women.[322] Indeed, treated women had higher depressive symptom scores, presumably reflecting treatment selection bias; symptomatic and depressed women seek hormone therapy. Others report that estrogen therapy has a more powerful impact on women's well-being beyond the relief of symptoms such as hot flushes.[311,318,319] In older depressed women, improvements in response to fluoxetine were enhanced by the addition of estrogen therapy.[320] In a 12-week, randomized, placebo-controlled trial of 55 perimenopausal women with clinically significant major depression, estradiol treatment with the 100 mg transdermal method significantly improved mood.[323] A similar American short-term study of 34 perimenopausal women with both major and minor depressions treated with 50 mg estradiol transdermally demonstrated improvements independently of an effect on VMS.[321] Overall, these small clinical trials argue that estrogen treatment is beneficial as an adjunct for the treatment of clinical depression. This conclusion is supported by the successful treatment of postpartum depression with estradiol treatment.[324,325]

The most common cause of mood problems is preexisting depression,[9,326] but there does exist a small population of women whose moods are sensitive to hormonal changes.[9,326,327] In the American SWAN study, the prevalence of mood changes increased from premenopause to early menopause, from about 10% to about 16.5%.[326] There are three possible explanations: (1) the decline in estrogen at menopause affects neurotransmitters that regulate mood; (2) mood is adversely affected by VMS (domino theory); and (3) mood is affected by the vicissitudes of life that are commonly prevalent around menopause. Some would argue that these mood swings are in response to the hormonal fluctuations that occur during the perimenopausal years. These fluctuations do indeed occur,[70] but whether they cause any symptoms remains to be determined. It seems logical that individuals with mood problems can reflect all these

mechanisms. The menopause transition is full of confounders for depression, such as poor sleep/dyspareunia/vaginal dryness due to estrogen deprivation, and life factors with decreasing personal or partner physical well-being. Thus, it is important to consider all potential contributing factors of depression when treating an individual with peri/postmenopause. **Although the literature has seemed convoluted and is fraught with selection and recall bias, as well as a variety of potential outcomes, existing data have led to a consensus, endorsed by the NAMS, that it does appear that the menopause transition is a time when women are more susceptible to depressive symptoms or a major depressive episode. However, this is more likely in women who have preexisting depression or in those whose moods are sensitive to hormonal changes (such as those with a history of PMS).**[9,326]

Cognition, Dementia, Aging, and Menopause

Cognitive decline and dementia are recognized accompaniments to aging. The role and relevance of female hormones and their deprivation post-menopause has been examined in multiple observational studies as well as in a few RCTs.[328] Depending on the method of assessment, evidence for the beneficial effects of estrogen on cognition can be found in the literature, especially in the domain of verbal memory.[329,330] However, the effects in healthy women are not impressive and perhaps of little clinical value. A short-term study failed to document an objective improvement in memory, although a slight improvement in mood was recorded.[331] Another short-term (3 months) randomized, double-blind study could detect no improvement in cognitive performance compared with placebo treatment.[332] The Melbourne Women's Midlife Health Project could not document an effect on verbal memory during the menopausal transition.[333] A longitudinal study in Chicago could not detect a cognitive decline through menopause, as assessed by working memory and perceptual speed.[334] The KEEPS cognitive and affective study was an ancillary study to the KEEPS (discussed in more detail in Chapter 22) that had examined cognitive effects of menopausal hormone therapy when initiated within 3 years of onset of menopause. The parent KEEPS trial examined the *timing hypothesis* from the perspective of CVD, whereas the cognitive ancillary study examined the

timing hypothesis from the perspective of cognition and mood.[335] In KEEPS, postmenopausal women within 3 years of the FMP were randomized to oral versus transdermal estrogen versus placebo and were followed for 4 years. The primary outcomes for the cognitive and affective ancillary study included the Modified Mini-Mental State Examination, verbal learning/memory, auditory attention/working memory, visual attention/executive function, speeded language/mental flexibility, and a mood measure (Profile of Mood States).[335] KEEPS cognitive study failed to demonstrate any neuroprotective effects of menopausal hormone therapy on the studied cognitive outcomes.

Unlike natural menopause, estrogen treatment of women immediately after bilateral oophorectomy was associated with improvement in certain, but not all, specific tests of memory, and healthy postmenopausal women taking estrogen scored higher on tests of immediate and delayed recall.[336–338] In a case-control study of women aged 55 to 93 years, estrogen users had better recall of proper names but no improvement in word recall.[339] Women in the Baltimore Longitudinal Study of Aging who were using estrogen performed better in tests of visual learning and memory.[339–342] In a New York City cohort of women, the use of estrogen was associated with better performance in tests of cognition, and better performance in verbal memory, but the cohort in the Study of Osteoporotic Fractures demonstrated no effect of estrogen use on the age-related decline in cognition.[342,343] In Connecticut, a randomized, placebo-controlled trial demonstrated better reading ability and verbal memory in the estrogen-treated group of postmenopausal women.[344] Perhaps a lack of agreement is due to the variability in test vehicles and the specific aspects of memory function studied. Furthermore, there is impressive individual variability, and when differences have been observed, they have not been large and perhaps of little clinical importance. In addition, any beneficial effects may be attenuated by progestational agents.[330]

Another possibility for the variable effects of estrogen treatment on cognition is the variability among women in endogenous estrogen levels. Using sensitive assays for free, non–protein-bound estradiol and bioavailable (loosely bound) estradiol, cognitive decline occurred at a greater rate in women with low estradiol levels.[345] Studies of cognition may have to differentiate between low- and high-risk women according to

endogenous, biologically active estradiol levels. Similarly, a beneficial effect on cognitive decline has been observed only in women negative for the gene associated with Alzheimer disease, *APOE-ε4*, which encodes the ε4 allele of the glycoprotein known as apolipoprotein E, which has, as one of its functions, the shuttling of lipids during neuronal repair.[346]

Up to 3 times as many women as men develop Alzheimer disease. Estrogen is capable of protecting central nervous system function by means of multiple mechanisms. For example, estrogen protects against neuronal cytotoxicity induced by oxidation; estrogen reduces the serum concentration of amyloid P component (the glycoprotein found in Alzheimer amyloid plaques); and estrogen increases synapses and neuronal growth, especially dendritic spine density.[347–349] Estrogen protects against the cerebrovascular toxicity exerted by amyloid peptides and promotes synaptic formation and neuronal growth and survival.[350–352] Progestational agents do not exert similar actions.

Case-control and cohort findings indicated that Alzheimer disease and related dementia occurred less frequently (perhaps as much as 60% less) in estrogen users, and the effect was greater with increasing dose and duration of use.[353–355] In the Baltimore Longitudinal Study of Aging (a prospective cohort), the risk of Alzheimer disease was 54% reduced; in a cohort in New York City, the risk was reduced 60%; and in the Italian Longitudinal Study of Aging, the risk was 72% reduced in estrogen users.[356–358] The findings are not uniformly positive; a case-control study with accurate information on clinical diagnoses and estrogen use from the UK General Practice Research Database could detect no impact of estrogen treatment on the risk of developing Alzheimer disease, but the number of estrogen users was very small.[359]

The short-term administration of unopposed estrogen to patients with Alzheimer disease (secondary prevention) has been reported to improve cognitive performance but mostly to have no effect.[360–365] The administration of combinations of estrogen and progestin has also failed to demonstrate a beneficial impact in Alzheimer disease.[366] The presence of estrogen therapy has been reported to enhance the beneficial response to tacrine in women with Alzheimer disease,[365] but overall, the evidence is consistent with a failure of estrogen to influence already existing Alzheimer disease or other forms of dementia.[367]

Although observational data support a primary preventive effect of estrogens, this impression remains unproven by RCT data. In a prospective cohort study of women living in Cache County, Utah,[368] hormone therapy provided about a 41% reduced risk of developing Alzheimer with any use and an 83% reduction with 10 or more years of use. This cohort also demonstrated improved cognition in estrogen users.[369] Similarly, other studies have shown a dose and duration dependent relationship between estrogen and Alzheimer disease prevention, with a 54% to 72% reduction in Alzheimer disease with the use of estrogen.[353–359] This same reduction, however, was not seen in a small UK study. Most importantly, if women had initiated hormone therapy within a period that encompassed 10 years before the development of clinical symptoms, there was no effect. The Utah study strongly suggested that hormone therapy must be used for a significant duration of time very early in the postmenopausal period to reduce the risk of Alzheimer disease. As neurons become changed by the pathology of dementia, they lose their ability to respond.[298] Similarly, a beneficial effect of hormone therapy on cognitive decline was observed only in women negative for *APOE-ε4*, the gene associated with Alzheimer disease.[346] Divergently, in a subsample of 61 recently menopausal women who had enrolled in the KEEPS RCT (further discussed in Chapter 22), the effect of hormone therapy on β-amyloid protein deposition was studied using positron emission tomography (PET) scan. While there were no differences in baseline characteristics of the subjects, carriers of the *APOE-ε4* allele on transdermal estradiol had evidence of reduced β-amyloid protein deposition on PET scan.[370] While the sample size is small, KEEPS and other studies' data suggest that as the neurons change, they lose their ability to respond favorably to estrogen, known as the timing hypothesis.

The importance of timing is supported by findings from the WHI. Women aged 65 years or older who were treated with either estrogen alone or combined estrogen–progestin had an increased risk of impaired cognition and of dementia.[371–373] In a subset of these women, MRI scans demonstrated greater brain atrophy in the women receiving hormone therapy.[374] The mechanism for this adverse effect of hormonal therapy in old women may be a neurotoxic action because the WHI study with MRI scanning could not detect an increase in ischemic brain lesions.[375] Smaller MRI studies of

younger women treated with hormone therapy found beneficial trophic changes in brain morphology, associated with improved cognition.[376–378] The mechanism seems to differ by route and formulation of hormone regimen.[370]

The theme that emerges is that maintenance of health in target organs by estrogen requires normal tissue, a principle of timing that will also be discussed further in the hormone therapy chapter (Chapter 22). Following the failure of secondary prevention trials to demonstrate a beneficial impact of hormone therapy on coronary disease in older women, it is increasingly argued that estrogen only exerts positive effects in healthy cardiovascular endothelium. A similar argument is made for brain tissue, focusing on biochemical and signaling pathways that do not show improvement with estrogen therapy when they are already compromised with disease.[379] The requirement for normal tissue, at least in the heart and in the brain, would explain the beneficial effects in studies of primary prevention and the lack of effect in secondary prevention trials.

CARDIOVASCULAR DISEASE, AGING, AND MENOPAUSE

Diseases of the heart are the leading cause of death for women in the United States, followed by cerebrovascular disease and malignant neoplasms. In 2016, one in four female deaths was from CHD compared with one in eight women who develop breast cancer.[380] More female deaths in 2016 were caused by CVD than the combined total from cancer, chronic lower respiratory disease, Alzheimer disease, accidents, and diabetes mellitus.

Most CVD results from atherosclerosis in major vessels. Risk factors for CHD are the same for men and women: family history of CVD, high blood pressure, smoking, diabetes mellitus, an abnormal cholesterol/lipoprotein profile, and obesity **(Table 21.6)**. However, when controlling for these risk factors, men prior to age 40 have a risk of developing CHD twice that of women. With increasing age, this advantage is gradually lost, and CVD becomes the leading cause of death for both older women and men.

TABLE 21.6 The Optimal Cholesterol/Lipoprotein Profile	
Total cholesterol	<200 mg/dL
High-density lipoprotein (HDL) cholesterol	>50 mg/dL
Low-density lipoprotein (LDL) cholesterol	<100 mg/dL
Triglycerides	<150 mg/dL

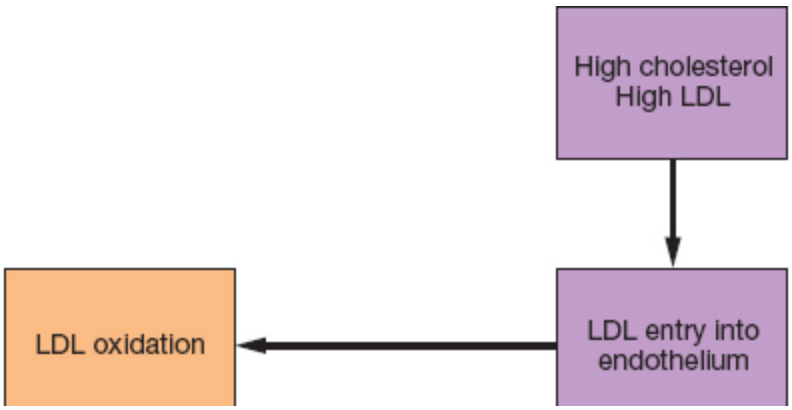
CVD, especially atherosclerosis, is a consequence of multiple metabolic changes that interact with each other:

- Adverse changes in the circulating lipid–lipoprotein profile.
- Oxidation of low-density lipoprotein (LDL), producing a modified LDL that is chemotactic for circulating monocytes and inhibits macrophage motility, trapping then in the intima, which causes cell injury and death in the endothelium.
- Endothelial injury and dysfunction affecting nitric oxide and prostacyclin production.
- Macrophage migration and functions, influenced by growth factors and cytokines.
- Proliferation and migration of smooth muscle cells also influenced by growth factors and cytokines; these cells become the dominant cell type and the source of the connective tissue matrix in the atherosclerotic lesion, the fibrous plaque.
- Vasoconstriction and thrombogenic events.
- Remodeling of coronary arteries. An artery is able to respond to a developing atherosclerotic plaque by increasing its overall diameter in an attempt to maintain flow.[381]

The mechanism of this adaptive remodeling is not known, but the extent of this process does affect the risk of occlusion and infarction.

There is an established sequence of events leading to atherosclerosis **(Figure 21.11)**. The process starts with endothelial dysfunction that leads to the fatty streak in arterial vessels, the precursor to clinically significant

lesions. The fatty streak lesion, therefore, antedates the fibrous plaque, developing under the endothelial surface and dominated by fat-laden macrophages (the foam cells). The damaged endothelium expresses cytokines, adhesion molecules, and other inflammatory agents that are involved in the formation of atherosclerotic plaques. The formation of a plaque is initiated by the aggregation and adherence of circulating monocytes (macrophages) to a site on the arterial endothelium, stimulating an inflammatory response. When the monocytes penetrate through the endothelium and enter the intima, they become loaded with lipids and converted to foam cells. Modification of LDL, especially oxidation, is crucial in this conversion of monocytes to foam cells. The adherence of monocytes to endothelium can be induced by elevated cholesterol and LDL cholesterol in the circulation. Most of the cholesterol that accumulates in atherosclerotic plaques is derived from circulating LDL cholesterol. As plaques become significant in size, they are prone to instability, rupturing, and creating a prothrombotic state. Matrix metalloproteinase enzymes are secreted by inflammatory cells and smooth muscle cells. These enzymes digest the proteins in the fibrous cap of an atherosclerotic plaque, making the plaque unstable and predisposed to rupture. **Estrogen induces matrix metalloproteinase production or activity, which digests the fibrous cap of a plaque, exposing the underlying thrombogenic collagen, and this is believed to be the mechanism involved in the adverse thrombotic effects of estrogen in the presence of established atherosclerosis.**[382] **In addition, 27-hydroxycholesterol, a cholesterol metabolite elevated in atherosclerotic lesions, competitively antagonizes estrogen receptor activity in cardiovascular epithelium.**[383]



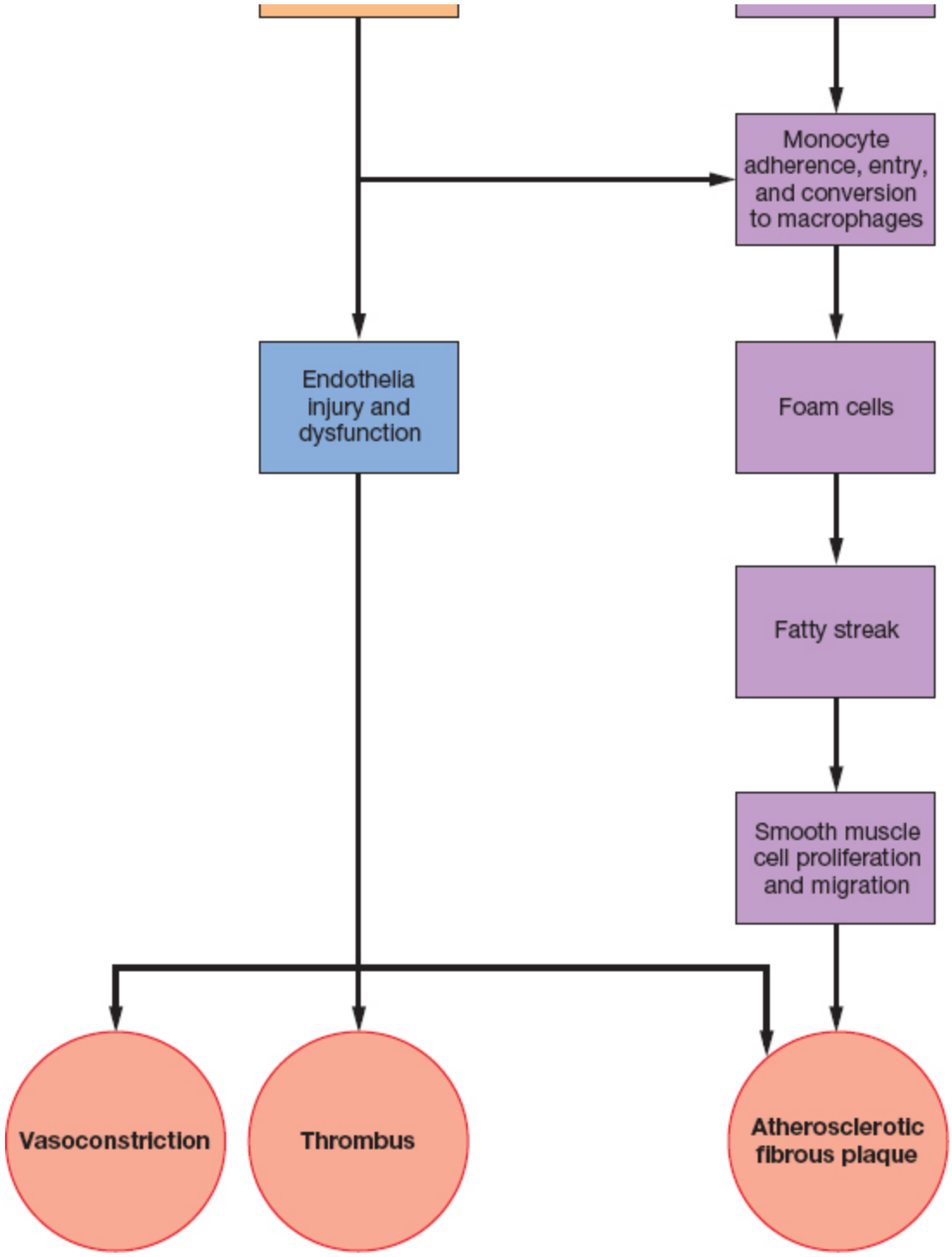


FIGURE 21.11

During the reproductive years, women are “protected” from CHD. Women lag men in the incidence of CHD by 10 years, and for myocardial

infarction and sudden death, women have a 20-year advantage. The reasons for this are complex, but a significant contribution to this protection can be assigned to the higher high-density lipoprotein (HDL) levels in younger women, an effect of estrogen and lower levels of testosterone. Throughout adulthood, the blood HDL cholesterol level is about 10 mg/dL higher in women, and this difference continues through the postmenopausal years. Total and LDL cholesterol levels are lower in premenopausal women than in men, although the levels gradually increase with aging and after menopause they rise rapidly.[384–388] After menopause, the risk of CHD doubles for women as the atherogenic lipids at about age 60 reach levels greater than those in men. These changes can be favorably reduced by dietary modifications.[389,390] Of course, These lipid changes *at* menopause (whether natural or surgical) can be reversed with estrogen treatment.[391]

Prospective studies have documented the strong association between total cholesterol and CHD in women, although CHD risk appears at higher total cholesterol levels for women than for men.[392,393] Women with total cholesterol concentrations greater than 265 mg/dL have rates of CHD 3 times that of women with lower levels. Even in older women, a high total cholesterol remains a significant predictor of heart disease, but the strength of association between the cholesterol level and CVD decreases with aging, and by age 80, the cost and benefits may not justify cholesterol intervention.[394] This is the reason for ceasing lipoprotein screening after age 75 in patients with normal lipids. However, this decision should be individualized, taking into account the vigor and health of the patient.

The strongest predictor of CHD in women is a low HDL cholesterol.[392,393,395] The average HDL cholesterol in women is approximately 55 to 60 mg/dL. A decrease in HDL cholesterol of 10 mg/dL increases CHD risk by 40% to 50%. In women (and men) who had normal total cholesterol and LDL cholesterol levels, but low HDL cholesterol levels, treatment with lovastatin can reduce the risk of an acute major coronary event by approximately 37%.[396] High HDL cholesterol levels are uncommon in women with CHD, but even women with high levels do develop CHD.[397] **Because of the increased risk of CHD observed in individuals with low HDL, it is appropriate to be concerned when HDL cholesterol levels are less than 50 mg/dL.** It should be emphasized that modest elevations in blood pressure markedly increase the overall

cardiovascular risk associated with an elevated LDL cholesterol or a low HDL cholesterol.

Keep in mind that low HDL cholesterol levels are a component of the metabolic syndrome related to insulin resistance. The metabolic syndrome is partly a result of heredity but is also strongly influenced by obesity and physical inactivity. In the United States, the overall estimated prevalence of the metabolic syndrome is 24%, higher in women (40% by age 60) and increasing with age.[398] The prevalence increases with increasing body weight, from about 5% in individuals with normal weight to 60% in men and women with obesity, and the prevalence is highest in Mexican Americans and lowest in Blacks.[399]

Metabolic Syndrome and Cardiovascular Disease

As defined by the National Heart, Lung, and Blood Institute and the American Heart Association, a diagnosis of metabolic syndrome requires the presence of any three of the following five clinical characteristics[400]:

1. **Increased waist circumference (>88 cm for women in the United States)**
2. **Increased blood pressure (≥130 mm Hg systolic; ≥85 mm Hg diastolic) or receiving medication for hypertension**
3. **Increased triglycerides (≥150 mg/dL) or receiving medication for hypertriglyceridemia**
4. **Decreased HDL cholesterol (<50 mg/dL) or receiving medication for reduced HDL**
5. **Increased fasting glucose (≥100 mg/dL) or receiving medication for hyperglycemia**

An increasing prevalence of metabolic syndrome during the menopausal transition is correlated with increasing androgen dominance that is also associated with truncal obesity, hypertension, and disorders of lipid/carbohydrate metabolism.[401,402] Adiposity of the trunk is a risk factor for CHD in women and is associated with a relatively androgenic hormonal state, as well as hypertension, and disorders of lipid and carbohydrate metabolism [403] Central fat distribution in women is positively correlated with increases in total cholesterol, triglycerides, and LDL cholesterol and negatively correlated with HDL cholesterol.[404] The atherogenic lipid profile associated with abdominal adiposity is at least partly mediated through an interplay with insulin and estrogen.[405] It is worth noting that there is a strong correlation between the magnitude of the worsening in

cardiovascular risk factors (lipid and lipoprotein changes, blood pressure, and insulin levels) and the amount of weight gained during the menopausal transition. Thus, weight gain and lowering LDL to less than 100 mg/dL with cholesterol-lowering drugs (statins) in the presence of CHD is an important part of preventive health care.[406–409] Attention to weight gain during middle age is one of the most important components of good preventive health care. However, **weight gain at menopause is not just an effect of hormonal changes but rather a reflection of aging-related alterations in metabolism as well as changes in diet and exercise that accompany aging.**[406]

Current recommendations regarding the optimal cholesterol/lipoprotein profile are more aggressive, urging more intensive treatment aimed at lowering LDL cholesterol levels; in the presence of CHD, the goal is to lower LDL cholesterol to less than 100 mg/dL.[407] Cholesterol-lowering drugs, specifically the statin family, have been repeatedly demonstrated in clinical trials to effect a marked reduction in the risk of clinical cardiovascular events in both men and women.[408,409]

Triglycerides are also an important risk factor for CHD in women but are most commonly encountered in individuals with the metabolic syndrome.[407] If the triglyceride level is greater than 400 mg/dL and the HDL cholesterol is less than 50 mg/dL, the risk of heart disease is substantially increased. Patients with an elevated triglyceride level and a positive family history for heart disease most likely have an autosomal dominant disorder classified as familial combined hyperlipidemia. This disorder accounts for most myocardial infarctions in women under 40 years old. Triglyceride levels of 150 to 200 mg/dL are considered borderline elevated. Triglyceride levels can be elevated because of obesity, smoking, and lack of exercise. Weight loss alone can return elevated triglyceride levels to normal.

Observational studies and clinical trials indicate that the major determinants of blood lipid levels are the same for both sexes. A diet high in saturated fatty acids and dietary cholesterol unfavorably increases blood lipids. Excess caloric intake and obesity decrease HDL cholesterol and increase total cholesterol, LDL cholesterol, and triglycerides. Smoking also decreases HDL cholesterol (and also produces lower estrogen levels and an earlier age at menopause). Genetic defects of receptor-mediated

cholesterol uptake account for only a small percentage of hyperlipidemia in men and women. There is also evidence that men and women who had impaired fetal growth have increased levels of cholesterol and LDL cholesterol in middle age.[410] The speculation is that impaired liver growth in utero produces a permanent adverse change in cholesterol and lipoprotein metabolism.[410] Reduced fetal growth also leads in adulthood to insulin resistance and lower HDL cholesterol levels, most severe in those who become obese.[411] **However, obesity or weight gain, tobacco use, and other social risk factors noted at menopause is not an effect of menopausal hormonal changes but rather a reflection of aging-related alterations in lifestyle.**[406]

C-Reactive Protein and Cardiovascular Disease

The immune system (monocytes, cytokines, and cell adhesion molecules) and inflammatory processes both play an active role in the process of atherosis.[412] Studies indicate that C-reactive protein (CRP) is a marker of cardiovascular risk in both men and women.[413–415] This risk is limited, however, to arterial disease; CRP levels are not linked to venous thrombosis or pulmonary embolus.[413] CRP predicts an increased risk of cardiovascular events even in individuals who have normal lipid levels, and, therefore, it is argued that both CRP and lipid profiles should be used for screening purposes.[415,416] CRP is a protein synthesized in the liver and atherosclerotic arteries and was given its name because it reacts with the C-polysaccharide of *Streptococcus pneumoniae*. Thus, the circulating level of CRP increases in response to various inflammatory stimuli but, specifically, bacterial infections and chronic inflammatory conditions such as systemic lupus erythematosus (SLE). Sensitive assays now detect small increases associated with low-grade inflammation in the vascular system.

Increased levels of CRP in patients with angina predict poor outcome, an increase in the relative risk of a coronary event. Prospective studies have documented an increased risk of cardiovascular events in patients without known CVD who have high CRP levels, an association that is even greater in smokers.[417] Higher mean levels are found in both men and women who subsequently have myocardial infarctions. Stroke and peripheral vascular disease are also increased in men with higher CRP levels, and in women,

CRP is also elevated in stroke.[418] In a metaanalysis of 14 prospective studies, individuals with CRP levels in the top third compared with individuals in the bottom third had a 2-fold increase in relative risk for CHD.[419] Thus, CRP levels have predictive value in both healthy individuals and individuals with cardiac disease. In addition, statin treatment lowers CRP levels,[420] and evidence indicates that statins and aspirin achieve greater benefits in individuals with high CRP levels.[413,420,421]

In general, studies have indicated that oral estrogen treatment (with or without progestin) increases CRP levels and raloxifene does not. In a double-blind, randomized trial, menopausal hormone therapy and raloxifene equally lowered homocysteine levels (a marker for vascular risk), but estrogen–progestin treatment increased CRP levels, whereas raloxifene had no effect.[422] These results were duplicated in a Dutch randomized study.[423,424] Tibolone (discussed later in Chapter 22 under the section "Menopausal Hormone Therapy") increases CRP levels to the same degree as oral estrogen therapy.[425] A cross-sectional study found higher levels of CRP in healthy postmenopausal women using hormone therapy.[424] In the PEPI randomized trial, hormone therapy increased CRP levels, but the levels of E-selectin, another marker of inflammation, were reduced.[426]

Estrogen-induced increase in CRP levels may be due to the known stimulant effects of estrogen on hepatic synthesis of proteins, especially because of the first-pass phenomenon with oral administration. For this reason, transdermal estrogen treatment does not change CRP level.[425,427,428] Studies on multiple inflammatory markers report that oral estrogen therapy increases only CRP, the only marker synthesized in the liver. In fact, oral hormone therapy, while increasing CRP, reduces the circulating levels of other inflammatory markers (E-selectin, intercellular adhesion molecule-1, vascular cell adhesion molecule-1, monocyte chemoattractant protein-1, and tumor necrosis factor-α), with inconsistent effects on interleukin-6 (IL-6).[429,430] **Most importantly, it is not certain that the decrease in CRP levels with statins and the increase with estrogen are actually instrumental in clinical outcomes or reflect other effects. Thus, raising or lowering CRP levels will not necessarily increase and decrease the risk of clinical disease. A study from the WHI confirmed the correlation between baseline levels of CRP and an elevated risk of CHD, but the increase in CRP induced by oral hormone therapy did**

not further increase this risk![431] The uncertainties and questions regarding the clinical relevance of CRP levels make it premature to conclude that changes in CRP levels with hormone therapy have any direct clinical consequence. This does not detract, however, from the utility of CRP levels in quantifying the overall risk of CVD in an individual patient.

Lipoprotein(a) and Cardiovascular Disease

Lp(a) is composed of two parts, a lipoprotein particle that is similar to LDL and a glycoprotein component that resembles a clotting protein. Lp(a) is an independent risk factor for CHD. Menopausal hormone therapy has been associated with a reduction in circulating Lp(a) levels.[432] Unlike other markers, the levels of Lp(a) are unaffected by lifestyle, and no clinical use has been established for Lp(a) measurements as a screening tool.

Sex Steroids and Cardiovascular Disease

As noted earlier, the leading cause of death among women continues to be CHD. Coronary atherosclerosis is a lifelong process that varies in its slope of development according to the presence or absence of risk factors. The landmark Pathobiological Determinants of Atherosclerosis in Youth (PDAY) study documented the presence of fatty streaks in adolescents and an increasing prevalence with increasing age.[433] The PDAY study further established that abnormal lipid profiles early in life are a major factor in determining the extent and age of onset of atherosclerosis.[434] It is important for clinicians caring for women to appreciate the importance of premenopausal atherosclerosis and to understand that appropriate medical interventions can reduce the risk of later clinical events. Because atherosclerosis begins early in life, it is logical to conclude that the postmenopausal risk of coronary clinical events is influenced by the degree of coronary artery atherosclerosis already present at the time of menopause.

Women with POI (older terminology is “premature or primary ovarian failure, or POF”) are at increased risk for CVD.[435] In other words, there is an inverse relationship between the risk of CVD and the age of menopause.[436] Endothelial function in women with POI is impaired, as measured by dilation of the brachial artery in response to blood flow, a

response known to be mediated by estrogen-modulated endothelial nitric oxide.[437,438] This association between endothelial dysfunction and hypoestrogenemia is reinforced by the observation that endothelial dysfunction in women with POI was improved by hormone therapy.[437]

An important contribution to the gender difference in CVD prevalence and age of onset is the favorable effect of estrogen on important endothelial events. Vasodilatory and antithrombotic activities can be attributed to endothelial production of nitric oxide and prostacyclin, a process favorably influenced by estrogen. Hypercholesterolemia adversely affects this important endothelial process, and estrogen protects this important endothelial function in the presence of hypercholesterolemia.[439] Estrogen inhibits the oxidation of LDL and also protects against the toxic effects of oxidized LDL on the endothelium. Women in the SWAN study who complained of hot flushing had more evidence of subclinical CVD, such as aortic calcification, compared to those without hot flushes.[440]

A Chinese comparison study concluded that Chinese men and women with angiographically determined coronary artery disease differ in the circulating sex steroid hormone milieu, compared with age-matched healthy individuals.[441] Straightforward reasoning has led investigators to connect the different prevalence of coronary artery disease in men and women to the obvious differences in circulating sex steroids determined by the testicles and ovaries. The newly appreciated importance of estrogen in the premenopausal years has added strength to this connection. For many years, it has generally been believed that higher estrogen exposure in women protects against coronary artery disease and that the difference in coronary artery disease prevalence between men and women diminishes after menopause because of the loss of estrogen. At the heart of the matter is the gonadal difference between men and women.

Acute coronary events in premenopausal women occur more frequently when estrogen levels are the lowest during the menstrual cycle.[442] In the national SWAN study, cardiovascular risk factors were more favorable in women with higher levels of estrogen and less favorable in women with longer menstrual cycles.[443] This was supported in the WISE (Women's Ischemia Syndrome Evaluation), a study of premenopausal women undergoing coronary angiography for suspected myocardial infarction, where coronary artery disease was more prevalent in those women who had

low estrogen levels because of hypothalamic suppression.[444] These findings are similar to the pioneering studies in monkeys that demonstrated acceleration of atherosclerosis in animals with low estrogen because of stress-induced hypothalamic suppression, an effect that could be prevented by oral contraceptive treatment.[445–447] Postmenopausal women studied with coronary angiography in the WISE study who had used oral contraceptives in the past had less coronary artery disease.[448] Even amenorrheic athletes in good physical condition have demonstrated endothelial dysfunction, a condition that responded favorably to estrogen-containing oral contraceptives, further highlighting the beneficial impact estrogen has on CVD throughout a woman's life.[449,450]

A recent secondary analysis of data from the previously mentioned KEEPS looked at the deposition of fat around the heart and risk for coronary artery disease in relation to both use of and route of hormone therapy compared to placebo. Of 727 recently menopausal women enrolled in the KEEPS RCT, 474 (mean age: 52.7 (SD 2.6)) underwent chest computed tomography-based heart fat quantification at baseline and at 48 months; authors compared association between pericardiac and epicardial adipose tissue (PAT) with coronary artery calcification (CAC) score, a primary endpoint in KEEPS. In comparison to those randomized to placebo, women who received oral CEE over the 48-month duration of KEEPS were significantly less likely to have any increase in PAT (odds ratio was 0.62 [95% CI, 0.40–0.97]; $P = 0.03$). Not only was there no evidence of attenuation in PAT accrual in women receiving transdermal estrogen, but an interaction was also observed between route of hormone therapy and the relationship between changes in PAT and progression in CAC ($P = 0.02$) such that increases in PAT were associated with CAC increases only in the transdermal 17β-estradiol group.[451] This same group, in a separate analysis on the KEEPS cohort, also noted that in contrast to transdermal estradiol, use of oral CEE slowed the progression of atherosclerosis as assessed by carotid intima-media thickness (CIMT).[452] However, the authors conclude that more research is required to better understand the mechanism that would explain the observed differential in CIMT progression between the two hormone therapy interventions as it is unclear if the beneficial effect resulted from the route of hormone administration or the type of estrogen formulation (CEE vs 17β estradiol).

Depression is a recognized risk factor for heart disease, but its contribution to premenopausal atherosclerosis is just beginning to be appreciated. Premenopausal monkeys that exhibit depressive behavior (induced by their lower social rank in a colony of animals) develop a more adverse lipid profile and an increasing degree of atherosclerosis when fed atherogenic diets.[453] Premenopausal women with a history of recurrent depression and without known coronary disease are more likely to have coronary and aortic calcification, a marker for early atherosclerosis.[454] The SWAN study found more aortic calcification in Black women with depressive symptoms, although an association between coronary calcification and depression in Black or White women could not be detected.[455]

Thus, hypoestrogenemia in the premenopausal years, whatever the cause, can increase the progression of atherosclerosis. This would include suppressed ovarian function associated with stress, depression, or intense athletic activity. The progressively deleterious effects of hypoestrogenemia include endothelial dysfunction, lower levels of HDL cholesterol, an increase in central obesity, and possibly depression. **In monkeys and in women, lipid effects account for only 25% to 30% of the atheroprotective effects of estrogens.**[456,457]

A Chinese comparison study concluded that Chinese men and women with angiographically determined coronary artery disease differ in the circulating sex steroid hormone milieu compared with age-matched healthy individuals.[441] Straightforward reasoning has led investigators to connect the different prevalence of coronary artery disease in men and women to the obvious differences in circulating sex steroids determined by the testicles and ovaries. Thus, it is the gonadal difference between men and women that creates the differences in coronary artery disease. The newly appreciated importance of estrogen in the premenopausal years has added strength to this connection and encourages the thought process that estrogen inhibits atherosclerosis by multiple mechanisms.[458]

A vast literature has documented multiple mechanisms favorably influenced by estrogen that would inhibit the development of atherosclerosis.[458] Clinicians tend to view testosterone as an estrogen opponent, and this is supported, for example, by studies such as lipid responses to testosterone that move in opposite directions to those of

estrogen.[459] Both beneficial and detrimental vascular actions of testosterone have been described in in vitro and animal studies.

Clinical studies in women have, in general, supported an association between hyperandrogenism and an increased risk for CVD. The lipid and lipoprotein profile in androgenized women with polycystic ovaries (who are also exposed to relatively lower estrogen levels over time) is similar to the male pattern with higher levels of cholesterol, triglycerides, and LDL cholesterol, and lower levels of HDL cholesterol, and this abnormal pattern is independent of body weight.[460–465] An adverse lipid and lipoprotein profile is a distinguishing feature of these patients even when body mass index (BMI), insulin, and age are controlled in case-control studies.[465] Subclinical atherosclerosis can be demonstrated by carotid ultrasonography to be prevalent in premenopausal women with a history of anovulation and polycystic ovaries.[466] In women undergoing coronary angiography, the prevalence of polycystic ovaries is increased, and women with polycystic ovaries have more extensive coronary atherosclerosis.[467] In the Nurses' Health Study, women with very irregular cycles compared to women with regular cycles had an adjusted increased risk of CHD.[468] **Thus, anovulatory women with polycystic ovaries develop risk factors for atherosclerosis and ultimately clinical disease comparable with that found in older postmenopausal women.**

Given the variability in circulating sex steroid levels between individuals, between sexes, and within individuals, we should not be surprised that random blood sampling does not always document meaningful differences in blood levels of gonadal steroids in men and women with coronary artery disease. Nevertheless, some cross-sectional and prospective cohort studies have documented lower circulating testosterone levels in men with coronary artery disease and higher levels in men with a reduced risk of metabolic syndrome.[469,470] A prospective cohort study determined that lower testosterone levels were associated with an increased risk of developing metabolic syndrome in men.[471] Men with heart failure demonstrate improvements in symptoms and functional capacity when treated with testosterone.[472]

In healthy postmenopausal women, higher androgen levels are associated with increased metabolic markers for the risk of coronary artery disease, and increasing testosterone levels during the perimenopausal

transition correlated with an increasing prevalence of metabolic syndrome in the SWAN study.[401,473,474] Higher testosterone levels, *although still in the normal range*, have also been found to correlate with a reduction in atherosclerosis progression in naturally postmenopausal women.[475,476] **In summary, existing data suggest that higher testosterone levels within the normal physiologic range may be protective against atherosclerosis (perhaps by target tissue aromatization to estrogens), whereas elevated androgen levels above the normal range, such as in anovulatory women with polycystic ovaries, are atherogenic.**

The important studies in women and monkeys reviewed previously indicate that there exists an innate trajectory of atherosis for each individual that can be modulated by various risk factors and that the slope of this process determines the age of onset for clinical events, providing an opportunity for primary prevention.[477] The contribution of premenopausal atherosclerosis to the development of clinical events highlights the important role for clinicians in aggressively promoting preventive interventions that can favorably change the slope of progression of atherosclerosis. An important risk factor is exposure to protective levels of estrogen at all stages of life. Conditions associated with hypoestrogenemia during the premenopausal years, therefore, require evaluation and treatment. There are many causes of hypoestrogenemia, and the treatments will vary according to the etiology. When indicated, appropriate hormone treatment can reduce the risk of CVD later in life. In addition, appropriate interventions in insulin-resistant women with the metabolic abnormalities associated with polycystic ovaries can reduce the risks of both CVD and diabetes mellitus.

A logical continuum of this reasoning is that hormone therapy in the perimenopausal and early postmenopausal years may and can offer some level of primary prevention of clinical coronary disease; conversely, initiating hormone therapy for the first time in older women who are well into the postmenopausal period when atherosclerotic processes may have already been initiated may increase their risk for CHD, particularly so in the first year of hormone use.[478] **The “timing hypothesis” proposes that adequate estrogen exposure prior to the onset of clinical events provides protection against CVD (discussed in further detail in Chapter 22).** A metaanalysis of 23 randomized hormone therapy trials

concluded that hormone treatment reduced the risk of CHD events in younger women compared with older women (10 or more years since menopause or >60 years of age).[479] This is a conclusion that is less firm now than when first proposed because most of these trials were not designed to measure an endpoint of CVD. However, another metaanalysis by the same authors concluded that hormone therapy reduced overall mortality in women with an average age of less than 60.[480]

Cardiovascular Disease and Vasomotor Symptoms[440,478,481–483]

A relationship between severity and frequency of VMS and risk of CVD was observed in the ongoing longitudinal SWAN cohort (Study of Women's Health Across the Nation). Similar findings were observed in MsHeart/MsBrain studies that objectively affirmed VMS burden and imaging-based evidence of vascular detriment in association with severity of vasomotor burden. These observational studies have identified frequent and severe VMS as a risk for CVD and vascular health. Worsening lipid profile, inflammatory milieu, higher blood pressure indices, and evidence of subclinical CVD have been observed in association with greater vasomotor symptomatology.

Cardiovascular Disease, Aging, and Menopause: Concluding Thoughts

In the last 30 years, mortality from CHD has declined substantially in the United States. Improvements in medical and surgical care can account for some of this decline, but 60% to 70% of the improvement is due to timely implementation of preventive measures. Excellent data from epidemiologic studies and clinical trials demonstrate substantial contributions from strategies such as smoking cessation, blood pressure reduction, and lowering of cholesterol toward a documented decline in stroke and heart disease–related morbidity and mortality.[484–486] The most effective means to lower CHD in a population is through primary prevention, especially smoking cessation and body weight reduction. While physiologic levels of estrogen are clearly relevant for maintenance of cardiovascular health, however, the impact of exogenous estrogen on cardiovascular risk in aging postmenopausal women who are remote from the FMP is not clearly

delineated and may even be detrimental.[487] When attempting to understand the role of estrogens on cardiovascular risk, it is important to distinguish between endogenous and exogenous estrogens. In addition, more recent work has begun assessing the role of additional reproductive hormones (ie, FSH) as well as the relevance of vasomotor instability in itself as predictors of cardiovascular risk.[487] While the loss of premenopausal estradiol levels is believed to contribute to the escalation in CVD in postmenopausal years, the bulk of existing clinical data are "associative." Appropriately designed studies are needed to better understand the spectrum of players (hormonal and nonhormonal) that may be relevant as causative to the processes that result in risk escalation for CVD as women progress along the stages of reproductive aging.[487]

Special Patient Populations

Human Immunodeficiency Virus and Menopause[488–491]

There are accruing data analyzing an interplay between chronic infection with human immunodeficiency virus (HIV) with age at natural menopause and menopausal symptomatology. With improved survivorship secondary to effective antiretroviral therapy, HIV-infected women are increasingly surviving into postmenopausal stage of life. An increasing number of observational studies are showing earlier age at menopause and greater menopausal symptom burden in the HIV-infected populations.[488,489] In a 2021 systematic review of eight studies, five showed an earlier age of menopause, between the ages of 46 to 50 versus 47 to 51, in HIV positive versus negative women.[490] Additionally, increased rates of POI and early menopause (2.3–35% and 14.6–27.9%, respectively) were noted in HIV-infected populations. However, study flaws were noted such as the lack of an HIV-negative control.[490] A correlation between low CD4 counts (<200 cells/mm^3, 200–500 cells/mm^3, and >500 cells/mm^3) and decreasing age of FMP has been inconsistently recognized (Imai). Lastly, there are conflicting results concerning a potentially decreased response to antiretroviral treatment with increasing age. The authors noted that these studies did not consider important variables that impact menopause, such as drug use, social/economical/educational factors, and race.[488] Additionally, a metaanalysis in 2019 noted a 1.7 increased odds ratio of amenorrhea in

women living with HIV. Given the adverse impacts of hypoestrogenemia on long-term bone, heart, and brain health, this remains a vulnerable population that requires additional care to identify those at risk early in the menopausal journey so as to allow opportunities for timely initiation of preventive strategies toward safeguarding overall health.[491]

Primary (or Premature) Ovarian Insufficiency (POI)

POI is distinct from age-appropriate natural menopause, in that onset of ovarian insufficiency occurs before age 40, and is discussed in detail in Chapter 10. While the endocrinology and the symptomatology of POI are similar to that of natural menopause, the course and pathophysiology of POI differ from natural menopause in many respects. Ovaries of women with POI demonstrate residual dormant ovarian follicles in a higher density than seen in naturally menopausal women. Unlike natural menopause, episodic resumption of ovarian follicular growth can be seen in up to 10% of women with POI, and spontaneous conceptions have also been described.

Diminished or Poor Ovarian Reserve[492–494]—A Distinct Phase in Paradigm of Reproductive Aging?

Diminished ovarian reserve (DOR) or poor ovarian reserve (POR) is a distinct clinical entity that relates to infertility. Unlike POI, women with DOR or POR are deemed premenopausal in experiencing regular menstrual cycles despite biochemical evidence of impending ovarian insufficiency (elevated FSH and low to undetectable AMH levels). Therefore, based on menstrual cyclicity alone, one would assume that appropriate levels of reproductive hormones are present and thus protective for general well-being, and for skeletal and cardiovascular health, in particular. However, does the reduced oocyte supply impact age at menopause or long-term health risks? One cross-sectional study of 89 premenopausal women with 28 patients with DOR attempted to answer this question by analyzing data on quality of life and bone health. Upregulation of bone turnover markers, lesser bone mass, and an increase in sleep disturbances and sexual dissatisfaction were observed in reproductive age women with DOR compared to those with normal ovarian reserve.[492] Others compared cardiovascular risk markers in DOR versus normal ovarian reserve patients

and identified worse cardiovascular and metabolic indices (insulin resistance; higher CRP, triglyceride, and LDL levels; and lower HDL levels) in women with DOR.[493,494] The literature around POR and age at menopause is even more sparse. One small, single site retrospective cohort study saw an increased risk of premature and early menopause (3% vs 0%; 11% vs 3%, respectively) in infertile women who underwent artificial reproductive techniques and who were classified as POR versus those with normal ovarian reserve.[495] Although more studies are needed to validate these observations, preliminary data are concerning that women with DOR/POR may represent a subgroup who may be susceptible to early deterioration in aging associated cardiovascular and skeletal indices and may hence be at an exaggerated lifetime risk for skeletal fragility and CVD.

In summary, in women, well-defined stages delineate the trajectory of reproductive aging, each with defined norms. Menopause marks an end to the reproductive stage of life. While age-appropriate menopause is a normal phenomenon, this phase of life can be burdensome for some symptomatic women. When menopause is early (before age 45) or premature (before age 40), or sudden (such as following surgical removal of both ovaries), not only can the symptom burden be more troublesome, but, additionally, these women may be at an exaggerated lifetime risk for chronic disorders such as CVD and osteoporosis. The symptoms frequently seen and related to decreasing ovarian follicular competence as women transition from premenopause into perimenopause and then postmenopausal stages of life that is characterized by estrogen loss include:

- Disturbances in menstrual pattern, including anovulation and reduced fertility, AUB, and, ultimately, amenorrhea
- Vasomotor instability (hot flushes and sweats)
- Atrophic conditions: atrophy of the vaginal epithelium; formation of urethral caruncles; dyspareunia and pruritus due to vulvar, introital, and vaginal atrophy; general skin atrophy; and urinary difficulties such as urgency and abacterial urethritis and cystitis
- Health problems secondary to long-term deprivation of estrogen, including osteoporosis and CVD

- There is a lack of knowledge concerning long-term health consequences in special patient populations, such as those with HIV, DOR, and POR.

Preventive Health Screening of Healthy Perimenopausal Women

The most important contribution a clinician can provide to the perimenopausal woman is the awareness and the knowledge that is required to allow aging women to make timely lifestyle and indicated therapeutic choices. This early educational process will help to build a solid relationship with patients, a relationship they will want to continue as they age.

PERIMENOPAUSE AND MENOPAUSE TIMING AS AN OPPORTUNITY

Preventive intervention during the perimenopausal and early menopausal years has three major goals. The overall objective is to demystify reproductive aging and ensure that phases of menopause transition and postmenopause are approached as physiology and not pathology. The overarching goal is to optimize mental, physical, and social well-being. A specific goal is to detect as early as possible any of the major chronic diseases, including hypertension, heart disease, diabetes mellitus, and cancer, as well as impairments of vision, hearing, and teeth. Finally, the clinician should help symptomatic women to smoothly traverse the menopausal period of life. Preventive health care and management of the later reproductive years give clinicians an excellent opportunity to function as a woman's primary care provider.

Given that the leading causes of death in the United States are due to chronic diseases that are influenced by age and lifestyle factors, the period of menopausal transition offers unique opportunities to the aging women as well as their health providers to proactively initiate preventive strategies toward improving quality of life as well as long-term health through medical intervention and counseling.

While not underrating the importance of good health habits among the young, we would argue that the impact of teaching preventive care

is more observable and more tangible at middle age. The prospects of mortality and the morbidity of chronic diseases are viewed with belief, understanding, and appreciation during these older years. The chance of illness is higher, but the impact of changes in lifestyle is greater.

The following recommendations are derived from our own clinical experience:

- Provide reassurance that reproductive aging is a normal phenomenon and not a disorder.
- Provide guidance and education to facilitate a patient's decision-making.
- Provide time and an appropriate location for sensitive and uninterrupted discussions.
- Use educational materials but also explain them using your own words.
- Involve family members.
- Be accessible and encourage communication. Consider designating a member of your staff as the menopause resource person.
- Be involved in community and hospital educational programs for the public.
- Use an effective, well-trained counselor for patients who need in-depth help in coping with life's trials and tribulations.

Key Points

- Regardless of chronologic age, women should undergo annual medical evaluations that should include a thorough medical history and a thoughtful risk quantification based on personal and family histories as well as physical examination.
- Annual visits should include assessment of vitals (blood pressure and pulse), body weight and BMI, breast and pelvic examinations, and screening for sexually transmitted infections when appropriate. Thyroid function (TSH) should be assessed in the 40s and annually beginning at age 60.
- Annual screening mammography should begin at age 40 (discussed in Chapter 16).
- At each visit, appropriate testing is scheduled for specific chronic conditions, indicated immunizations are provided, and counseling for changing nutritional needs; physical

activities; injury prevention; occupational, sexual, marital, and parental problems; urinary function; and use of tobacco, alcohol, and drugs.

- For low-risk individuals without a family history of colon cancer, screening colonoscopy is recommended starting at age 50 and then every 10 years through age 75.[496]

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22

Managing Menopausal Symptoms

AN OVERVIEW

There is little question that estrogen is the most effective of available remedies for women who suffer from bothersome vasomotor symptoms (VMS) such as hot flushes and night sweats or from consequences of atrophy of reproductive tract tissues. However, in the 1990s, the focus of postmenopausal hormone therapy (HT) changed from short-term use for menopausal symptoms to long-term utilization as a preventive strategy against various diseases, including cardiovascular disease (CVD), dementia, and osteoporosis. This was due to biologic plausibility and observational data. The skeletal benefits in preventing osteoporosis are clear. However, long-term use of HT for the sole purpose of targeting CVD and dementia was challenged by a sequence of seminal clinical trials, with Women's Health Initiative (WHI) being at the forefront. Not only did the clinical trial data indicate that HT did not protect against CVD, nor mitigate the risk of aging-related dementia, but, on the contrary, raised concerns regarding the potential for harm as evident in an increased risk of thrombotic phenomenon, stroke, and breast cancer in women who initiated HT that was

over 10 years from menopause. In addition, the Women's Health Initiative Memory Study (WHIMS) noted the incidence of cognitive deterioration was higher in the hormone-using postmenopausal women compared to placebo. The ensuing decades following publication of WHI findings witnessed passionate and widespread quests attempting to unravel potential mechanisms that could explain HT-related harm; for a brief period, the field of menopause was rendered complex and decision-making by clinicians and patients very difficult. In this section, we offer a comprehensive review of the literature, including more recent data and analyses, to help serve as a guide for the practicing clinician caring for postmenopausal women.

MENOPAUSAL HORMONE THERAPY

History[1–4]

The existence of hormones was unknown 200 years ago. In the last half of the 19th century, a scattering of chemists and physiologists began to produce hormonally active extracts from glands, bile, and urine of animals. Adventurous clinicians used these extracts to treat patients—for example, supplying thyroid hormone to treat severely hypothyroid individuals—and the specialty of endocrinology was born. The word "endocrine" was adopted to designate the "glands of internal secretion," the multiple sources of hormones.

Charles-Édouard Brown-Séquard, the son of a French woman and an American sea captain, was born on the island of Mauritius. Speaking fluent English and French, he practiced medicine and lectured in London and New York before settling in Paris. Brown-Séquard reported in 1889 that he was rejuvenated by the self-administration of extracts from dog testicles, most likely a placebo effect considering the scant amount of testosterone he could have extracted using his aqueous method, and he suggested that ovarian extracts would have the same revitalizing effect in women. Initial efforts to treat women around the end of the 19th century were largely unsuccessful, but in 1897, ovarian extract was reported to be effective for menopausal hot flushing.[5]

The first American attempt to treat menopausal symptoms is attributed to E.L. Severinghaus and J. Evans of Madison, Wisconsin, who administered a derivative from the amniotic fluid of cattle in 1929.[2,6] In the 1930s, the ovarian hormones were isolated, and the “estrin” products and the synthetic estrogens, stilbestrol and ethinyl estradiol (EE), were administered to menopausal women. Edgar Allen and Edward Doisy were the first to isolate the ovarian hormone, estrogen. Allen was born in Colorado, educated at Brown University, and served in France during World War I. In 1933, he became the chairperson of the Department of Anatomy at Yale University. Doisy was born in Illinois and educated at the University of Illinois and Harvard. During World War I, he was assigned to the Rockefeller Institute in New York City and then to the Walter Reed Hospital in Washington, DC. Doisy was the first chairman of biochemistry at the St Louis University School of Medicine. He received the Nobel Prize in Medicine, along with Henrik Dam, in 1943 for his isolation and synthesis of vitamin K.

In 1919, Allen and Doisy, both discharged from the army after World War I, joined the faculty at the Washington University School of Medicine in St Louis and began working together. Although later they ended up at different institutions, they continued their collaboration. In 1923 and 1924, Allen and Doisy reported the isolation and administration of “an ovarian hormone” from pig ovaries.

In 1926, Sir Alan S. Parkes and C.W. Bellerby coined the basic word “estrin” to designate the hormone or hormones that induce estrus in animals, the time when female mammals are fertile and receptive to males. Doisy and his students Veler and Thayer in St Louis isolated a few milligrams of estrogen in crystalline form in 1929 from large amounts of urine from pregnant women. In 1932, this terminology was extended to include the principal estrogens in humans, estrone, estradiol, and estriol at the first meeting of the International Conference on the Standardization of Sex Hormones in London, although significant amounts of pure estradiol were not isolated until 1936. At this meeting, A. Girard from France introduced a new reagent to isolate crystalline estrogen from mare’s urine, which enabled chemists to overcome the inability to isolate more than a few milligrams of estrogen.[7]

In the 1920s, George W. Corner at the University of Rochester invited Willard Myron Allen, an organic chemist who was then a medical student, to join him in the study of the corpus luteum. Within 2 years, they had a pure extract; however, it was not until 1934 that crystalline progesterone was isolated. It took the corpora lutea of 50,000 pigs to yield a few milligrams. At the Second International Conference on the Standardization of Sex Hormones in London, Corner and Allen proposed the name *progestin*. Others proposed luteosterone, and, at a cocktail party, the various biochemists agreed to call the chemical "progesterone."[7]

By the 1940s, hormones were being administered to patients, but supplies were very limited and hormones were incredibly expensive. Progesterone, for example, costs $200 per gram. "To secure barely enough androsterone to cover the head of a pin, Adolph Butenandt had had to start with nearly four thousand gallons of urine; to obtain less than one hundredth of an ounce of pure testosterone crystals, Ernst Laqueur had had to process nearly a ton of bulls' testicles. It took a full ton of cholesterol, from the spinal cords or brains of cattle or from the grease of sheep's wool, to yield just 20 lb of the starting material from which progesterone could ultimately be obtained. Edward Doisy had had to process ovaries of more than 80,000 sows to get just 12,000ths of a gram of estradiol."[8]

TABLE 22.1 Menopausal Hormone Therapy

Composition of Conjugated Estrogens (Premarin)	
Sodium estrone sulfate	49.3%
Sodium equilin sulfate	22.4%
Sodium 17α-dihydroequilin sulfate	13.8%
Sodium 17α-estradiol sulfate	4.5%
Sodium Δ8,9-dehydroestrone sulfate	3.5%
Sodium equilenin sulfate	2.2%
Sodium 17β-dihydroequilin sulfate	1.7%

Composition of Conjugated Estrogens (Premarin)	
Sodium 17α-dihydroequilenin sulfate	1.2%
Sodium 17β-estradiol sulfate	0.9%
Sodium 17β-dihydroequilenin sulfate	0.5%

In the 1930s, the Ayerst Company was extracting estrogens from the urine of pregnant women. Limited by the problems of supply, low activity, and bad taste and odor, Gordon A. Grant, head of biochemistry for Ayerst, suggested in 1939 that they use urine from horses. The process produced sodium salts from the sulfate esters of the various estrogens, yielding a water-soluble conjugate. **Premarin** (**conjugated estrogens**) **was approved in Canada in 1941 and in the United States in 1942 for the treatment of symptoms associated with menopause.**[9] The tablets were and are still designated as variations of 1.25 mg, based on the equivalent amounts of Premarin and estrone (1.25 mg) that could produce the same effect in the Allen–Doisy bioassay (amount required to produce an increase in rat uterine weight). It was not until 1972 that the first quantitative analysis of Premarin was performed, based on gas chromatography. Studies indicate that there is a large number of steroids in Premarin, even androgens and progestins, but only 10 estrogens are present in sufficient quantity to have clinical effects (**Table 22.1**).

ESTROGEN FORMULATIONS AND ROUTES OF ADMINISTRATION

Oral Administration

An understanding of the relative potencies of commercially available estrogens is of great importance when prescribing estrogen, and the clinician should be familiar with the following potencies (**Table 22.2**).

The 17α-ethinyl group of EE (by resisting metabolism) enhances hepatic effects, because no matter by which route it is administered, liver function is affected.[10] The same is true for conjugated equine estrogens

(CEEs). Contrary to the case with estradiol, the liver appears to preferentially extract EE and CEEs, regardless of the route of administration. Thus, the route of administration appears to influence the metabolic responses only in the case of specific estrogens, most notably estradiol.

TABLE 22.2 Relative Estrogen Potencies

Estrogen	FSH Levels	Liver Proteins	Bone
Conjugated estrogens (CE)	1.0 mg	0.625 mg	0.625 mg
Micronized estradiol	1.0 mg	1.0 mg	1.0 mg
Estropipate (piperazine estrone sulfate)	1.0 mg	1.25 mg	1.25 mg
Ethinyl estradiol (EE)	5.0 µg	2–10 µg	5.0 µg
Estradiol valerate	—	—	1.0 mg
Esterified estrogens	—	—	0.625 mg
Transdermal estradiol	—	—	50 µg
Estetrol[a]			

FSH, follicle-stimulating hormone.

[a]Potency is ~10–20% less than of EE.

Data from Dennerstein L, Lehert P, Burger H, Dudley E. Mood and the menopausal transition. *J Nerv Ment Dis*. 1999;187(11):685-691; Smith-DiJulio K, Woods NF, Mitchell ES. Well-being during the menopausal transition and early postmenopause: a within-stage analysis. *Womens Health Issues*. 2008;18(4):310-318; Woods NF, Mitchell ES, Percival DB, Smith-DiJulio K. Is the menopausal transition stressful? Observations of perceived stress from the Seattle Midlife Women's Health Study. *Menopause*. 2009;16(1):90-97; Avis NE, McKinlay SM. A longitudinal analysis of women's attitudes toward the menopause: results from the Massachusetts Women's Health Study. *Maturitas*. 1991;13(1):65-79; Morse CA, Smith A, Dennerstein L, Green A, Hopper J, Burger H. The treatment-seeking woman at menopause. *Maturitas*. 1994;18(3):161-173; and Defey D, Storch E, Cardozo S, Díaz O, Fernández G. The menopause: women's psychology and health care. *Soc Sci Med*. 1996;42(10):1447-1456.

A major factor in the potency differences among the various estrogens (estradiol, estrone, estriol; **Figure 22.1**) is the length of time that the

estrogen binds to its receptor. The higher rate of dissociation with the weak estrogen (estriol) can be compensated for by continuous application or higher doses to allow prolonged binding and activity. Estriol has only 20% to 30% affinity for the estrogen receptor (ER) compared with estradiol; therefore, it is rapidly cleared from a cell. However, if the effective concentration is kept equivalent to that of estradiol, it can produce a similar biologic response.[11] However, at least two studies have been unable to demonstrate prevention of bone loss with the administration of 2-mg estriol daily, suggesting that target organ response may vary, even in biologically equivalent doses to estradiol.[12,13] Because estriol protects the rat against breast tumors induced by various chemical carcinogens, it has been hypothesized that a higher estriol level protects against the more potent and harmful effects of estrone and estradiol.[14] But antagonism of estradiol occurs only within a very narrow range of the ratio of estradiol to estriol, a range that is rarely encountered either physiologically or pharmacologically.[15] Commercial preparations containing estriol, estradiol, and estrone comprise sufficient amounts of estrone and estradiol to produce standard clinical effects.[16]

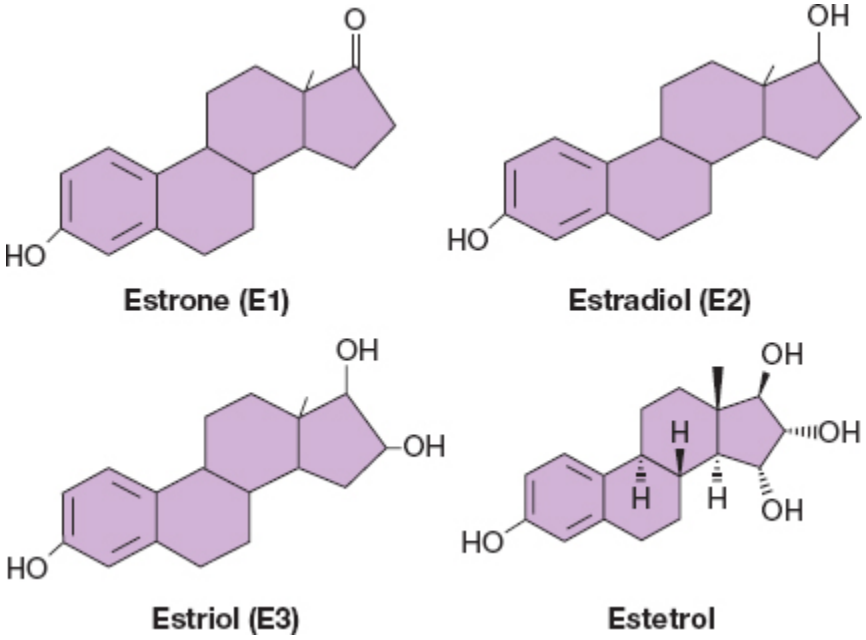


FIGURE 22.1

Esterified estrogens are synthetically prepared from plant precursors and are composed mostly of sodium estrone sulfate with a 6% to 15% component of sodium equilin sulfate. Estradiol valerate is rapidly hydrolyzed to estradiol; therefore, the pharmacology and effects are comparable at similar dosages.[17] However, a recent Swedish study noted that the peak level of thrombin is significantly higher with use of EE versus estradiol valerate, indicating that estradiol valerate would have a lower thrombotic risk. Nevertheless, estradiol valerate in hormonal contraceptive pills remains sparse in the United States.

In recent years, estetrol (E4), yet another naturally occurring estrogen, has gained attention for its therapeutic potential for women's health. E4 is unique to pregnancy, being produced exclusively in the fetal liver and can be detected in maternal blood at levels that are much lower than in the fetal circulation.[18] In potency, E4 is 10 to 20 times weaker than that of EE.[19,20] While E4 is available only as a Food and Drug Administration (FDA)-approved contraceptive formulation, its effectiveness in menopause management is actively being explored.[21]

Transdermal Estrogen Administration

Transdermal estradiol can also be administered by a patch, gel, emulsion, or spray. The patches first used for transdermal administration of estrogen contained an alcohol reservoir; estrogen was released through a semipermeable membrane attached to the skin with an adhesive. In the current generation of estrogen patches, the hormone is dissolved and distributed throughout the adhesive matrix, which has less skin reactions than traditional patches, even in tropical environments.[22] The patches are designated according to the amount of estradiol delivered per day with formulations delivering as little as 14 µg to as much as 100 µg daily and are available in various doses and various trade names. (Climara and Vivelle are commonly available in the United States.) The gel is similarly available under various trade names (Divigel, EstroGel, Estreva Gel) and in various doses and can be applied once daily on an arm, anywhere from the wrist to the shoulder, or the thigh, without rubbing or massaging and alternating sides.[23,24] The emulsion, Estrasorb, is packaged in foil pouches; usually, two packets are applied daily, one to each thigh, and rubbed in thoroughly.

Evamist is the transdermal spray, and the usual dose is one spray daily to the forearm. (If more than one dose is required daily, each spray is on a separate site.)[25] Elestrin is available in a metered dispenser. Simultaneous use of sunscreen on the site of administration should be avoided. If dosage is being monitored by blood estradiol levels, blood should be drawn from a site where transdermal estradiol has not been applied for several days. **The ideal dose of estrogen is that which allows for systemic symptom relief.**

Circulating Estradiol Levels in Users of Oral Versus Transdermal Estrogen

The concentration of estrogen in the hepatic portal system after oral administration is 4 to 5 times higher than that in the periphery.[26] Because of first-pass metabolism in the liver, oral estradiol results in a circulating estrone-to-estradiol ratio of approximately 5; with transdermal administration, the ratio is 1. The first-pass effect has important lipoprotein effects. For example, studies have demonstrated an increase in high-density lipoprotein (HDL) and decrease in low-density lipoprotein (LDL) and cholesterol with oral estrogens (discussed earlier in this chapter), an effect that is less prominent with transdermal estrogen administration.[27,28] However, English data indicate that the transdermal administration of 50-µg estradiol twice a week is as effective as 0.625-mg oral conjugated estrogens, when combined with a progestin in sequential regimens, on bone mineral density (BMD) and lipids over a duration of 3 years.[29] Standard doses of estrogen administered transdermally (50 µg) protect against fractures as do standard doses of oral formulations.[30] However, although lower doses of estrogens can provide effective suppression of VMS as well as improve BMD, data on fracture risk reduction with low-dose regimens are lacking.[31]

Studies comparing circulating estradiol levels in women receiving oral or transdermal estrogen reveal that while estradiol levels are in therapeutic range for bone protection, there exists substantial variation among individuals.[32] Furthermore, due to the chemical components of CEEs (which are not measurable in serum samples on routine assays), it is difficult to measure a therapeutic level of estrogen in CEE users. In addition, individual women metabolize estrogen differently, depending on the route of administration, liver function, body composition, body size, potential medication interactions, skin absorption (for transdermal

preparations), and the presence of binding proteins; all these can contribute to individual variations in serum estradiol levels.[33] The only way to accurately compare clinical effectiveness of oral and transdermal estrogen delivery is to determine if the two methods of administration yield comparable blood levels; however, the first-pass hepatic effect may account for differences in clinical effectiveness, and this is difficult to quantify. The first-pass effect is particularly pronounced with oral estrogen formulations and raises sex hormone–binding globulin (SHBG) levels such that total serum estradiol levels are greatly affected. A potential advantage of transdermal treatment, because it has minimal to no effect on SHBG levels, is that it does not reduce the free unbound testosterone levels (which may have implications for sexual function in a subset of users) as are observed with oral estrogen therapy (ET).[32]

Systemic Effects of Hormone Therapy

Clotting Factors

First-pass hepatic metabolism affects the synthesis of clotting proteins, markers of coagulation and fibrinolysis that can influence the risk of thrombosis and coronary heart disease (CHD) events. Oral estrogen increases factor VII and prothrombin 1 and 2 fragments, whereas transdermal estrogen decreases factor VII.[34–37] Oral estrogen also increases circulating levels of matrix metalloproteinases, MMP-2 and MMP-9, enzymes that are associated with a tendency for clotting.[38] However, what is important is to understand the different effects of oral and transdermal delivery on clotting factors and how they translate into clinical differences and cardiovascular risk.

Risk of Venous Thromboembolism

Resistance to activated protein C (APC) is an important marker for venous thrombosis; this risk is particularly exaggerated in individuals with inherited thrombogenic mutations but can happen even in the absence of these mutations. Oral estrogen increases APC resistance, whereas transdermal estrogen has no significant effect on this marker.[39,40] Based on this difference, one would predict that transdermal delivery of estrogen would be less likely than oral delivery of estrogen to be associated with venous thromboembolism (VTE).

A French case–control study (epidemiologic studies of the link between the transdermal route of administration and a relatively rare event are possible in France because of the popularity of the transdermal method) reported no increased risk of VTE in users of transdermal estrogen, as compared with a 4-fold increase in oral estrogen users.[41–43] In addition, an English nested case–control study reported that transdermal delivery of estrogen did not increase the risk for VTE, regardless of the type of estrogen used, whereas among oral estrogen formulation, CEE had a much higher rate of VTE compared to oral estradiol.[44] Estrogen users who carried a factor V Leiden mutation or a prothrombin mutation had a 25-fold higher risk of VTE than did women who did not use estrogen and did not have either mutation. The women with a prothrombotic mutation who used transdermal estrogen had a VTE risk that was similar to that of women with a prothrombotic mutation who did not use estrogen. The French E3N prospective cohort study also reported an increased risk of VTE with current users of oral therapy, a hazard ratio (HR) of 1.7 (confidence interval [CI] = 1.1–2.8), a ratio that is similar to the usual 2-fold increase repeatedly documented in the literature, and no increase with transdermal estrogen.[45] Analysis of the WHI trials noted that despite an increase in APC resistance, this did not explain the increase in ischemic stroke noted in oral HT users.[46,47] Venous thrombosis is discussed in more detail later in this chapter.

Lipids and Hepatic Enzymes

Both oral and transdermal estrogens reduce total cholesterol, LDL cholesterol, and lipoprotein(a). Compared with transdermal estrogen, oral estrogen produces significantly greater elevations in HDL cholesterol and increases triglycerides, whereas transdermal estrogen decreases triglyceride levels.[34,36,48–50] Indeed, triglyceride levels that were markedly elevated in response to oral therapy return to normal when treatment route is changed to transdermal administration.[51] In addition, oral ET is associated with an increased risk of gallstones.[52] This risk is present in current and former estrogen users and is somewhat attenuated with the addition of progestin-to-estrogen therapy.[52]

Inflammatory Markers

Women on oral estrogen have increased levels of C-reactive protein (CRP), whereas those taking transdermal estrogen do not.[34,36,48,53–56] However, oral HT, while increasing CRP, reduces the circulating levels of other inflammatory markers (E-selectin, intercellular adhesion molecule-1, vascular cell adhesion molecule-1, monocyte chemoattractant protein-1, and tumor necrosis factor-α) with inconsistent effects on interleukin-6 (IL-6).[53,57] Transdermal estrogen does not affect the levels of these inflammatory markers. It is not certain that the decrease in CRP levels with statins and the increase with oral estrogen are instrumental in clinical outcomes or reflect other effects.

A longitudinal study of 346 postmenopausal women taking oral HT reported that elevated CRP was a strong predictor of future cardiac events, but only in those with increased IL-6 levels.[55] An increase in CRP alone was not associated with an excess of events. **The difference in CRP levels between users of oral versus transdermal therapy, especially in younger postmenopausal women, is of little clinical significance.** In fact, in the Estrogen Replacement on Progression of Coronary Atherosclerosis trial, estrogen-induced increases in CRP had no effect on disease progression, as measured by serial angiograms.[56] A study from the WHI confirmed the correlation between baseline levels of CRP and an elevated risk of CHD, **but the increase in CRP induced by oral HT did not further increase the risk**.[48] While CRP may cause endothelial inflammation and subsequent atherosclerosis, it may also very well be elevated secondary to first-pass hepatic metabolism (ie, pharmacologic effect); unlike IL-6, its elevation has an overall pro-inflammatory effect.[47]

Cardiovascular Disease Risk

Both oral and transdermal administration of HT are associated with a decrease in myocardial infarction risk in observational studies.[58] However, the WHI trials and postintervention data offer additional insight and are discussed in further detail later in this chapter.

Metabolic Syndrome

The menopausal transition itself is associated with increased likelihood of metabolic dysfunction. However, in a review of several randomized controlled trials (RCTs), it was noted that overall effects on markers of the

metabolic syndrome, including insulin resistance, suggested a neutral or improved metabolic profile.[59] Despite this favorable effect, in women with the metabolic syndrome, caution is recommended given the increased risk of cardiovascular events, as noted in a nested case–control study of CHD in the WHI trials.[59,60] Transdermal estradiol has minimal effects on inflammation, coagulation, and insulin sensitivity.[60,61] In a randomized, double-blind, placebo-controlled trial, improvements in cardiac autonomic control and endothelial function indices were noted in healthy perimenopausal and early postmenopausal women following 12-month treatment with transdermal estrogen and intermittent progesterone regimen compared to placebo.[62] In addition, an analysis of the Women's Health Initiative Observational Study (WHI-OS) noted that newly diagnosed hypertension was less in women who utilized transdermal estradiol or oral estrone preparations versus CEE that was not altered by the presence of a progestational agent (HR = 0.85; 95% CI = 0.73–1.00 and HR = 0.83, 95% CI = 0.72–0.96, respectively).[63]

Effects in Smokers

Limited evidence suggests that postmenopausal women who smoke may have a better response to transdermal estrogen than to oral estrogen, including greater reductions in total peripheral resistance, vascular sympathetic tone, and norepinephrine levels and increased vascular responsivity.[64] Smokers receiving transdermal estradiol have decreased plasma viscosity and thromboxane B_2 levels.[64] These results raise the possibility, although the data are limited, that smokers may represent a group of women for whom transdermal estrogen would be an advantage.

Carbohydrate Metabolism

There is little difference between the oral and transdermal methods of delivery on carbohydrate metabolism. Both methods have a beneficial impact on central abdominal fat content, glucose levels, and insulin resistance, associated with a reduced risk of developing adult-onset diabetes mellitus.[65–70] The effect of HT on carbohydrate metabolism/diabetes risk is discussed in further detail in "Hormone Therapy" section.

Skeleton

The effects of menopausal hormones on bone metabolism, BMD, and on fracture risk are discussed in Chapter 23.

Estradiol Implants

Estradiol pellets are available in doses of 25, 50, and 75 mg for subcutaneous administration twice yearly. The 25-mg pellet provides blood levels in the range of 40 to 60 pg/mL, levels that are comparable with those obtained with standard oral doses.[71,72] However, the effect of subcutaneous regimens is cumulative, and after several years, the blood levels are 2 (b.i.d.) to 3 (t.i.d.) times higher and can persist for up to 2 years following last insertion. We believe that estradiol pellets do not confer any advantage over the standard hormone regimens. We recommend that women receiving estradiol pellets be monitored with blood levels of estradiol. In women in whom serum estradiol levels are greater than 200 pg/mL (or even >100 pg/mL), prolonging intervals between insertions should be considered.

Oral Versus Transdermal Administration

It is difficult to draw conclusions about clinical differences between oral and transdermal hormone delivery based on secondary markers. Epidemiologic studies on clinical events are needed. However, this is a challenge because of the relatively small number of women receiving transdermal estrogen. In addition, the studies must adjust for individual variability of dosing to ensure that circulating estrogen levels in the patients being studied are similar.

Given that transdermal route of delivery is suggested to lessen the risk for thrombotic events linked with exogenous estrogen use, it is often preferred by patients and, when applicable, allows monitoring of serum estradiol levels. Although comparison studies have not been performed, it is reasonable to expect similar pharmacokinetics for all transdermal methods —more stable/constant estradiol levels, less fluctuation, and theoretical benefits over oral therapy. Furthermore, because of the lack of effects of transdermal delivery on serum SHBG levels and thereby with minimal effect on free androgen levels, transdermal method for estradiol delivery may be preferable in women with impaired sexual function.

Key Points

- **Based on the evidence to date, transdermal ET seems a preferred option for women who are deemed eligible for HT use after considering individual woman's personal and family histories and ruling out absolute and relative contraindications to HT use.**
- **Sufficient evidence suggests that transdermal route of estrogen administration be preferentially considered if decision for initiating HT is made after detailed counseling and weighing of risks versus benefits of HT for the following patients:**
  - **Women deemed at risk for VTE**
  - **Women with spontaneous or estrogen-induced hypertriglyceridemia**
  - **Women who are obese with metabolic syndrome**
  - **Women who are diabetic and hypertensive**
  - **Smokers**
- **Transdermal route for ET should be preferentially considered in women with complaints of hypoactive sexual desire or decreased libido.**

Vaginal Administration of Estrogen

Management of Symptoms of Vaginal Atrophy

Very Low–Dose Method

For some women, genitourinary symptoms may dominate the symptom burden. Others who initiate hormones for managing bothersome VMS may not gain full relief from the symptoms of vaginal atrophy with systemic HT. Local vaginal administration of estrogen makes sense for these patients. Vaginal treatment is especially helpful when a rapid local response is desired. In addition, there are many women who desire the genitourinary effects of estrogen, but either must or wish to avoid systemic therapy. Overall, there is no evidence that one method or preparation is superior to the others in achieving clinical response. **Measurement of vaginal pH from the lateral vaginal wall is a simple and inexpensive way to assess adequate estrogen effects on the vagina. It has been impressive in our experience and others how an acidic pH (<4.5) obtained from the lateral, outer third of the vagina correlates well with good estrogen**

effects. Vaginal pH correlates well with vaginal maturation index, symptomatic vulvovaginal atrophy, and visual inspection of the vaginal epithelium.[73–75]

Estrogen in the form of vaginal creams is absorbed very readily from a vagina with immature, atrophic mucosa.[76] Indeed, the initial absorption is rapid, and relatively high circulating levels of estrogen are easily reached. As the vaginal mucosa matures, absorption decreases.[77] This decline takes approximately 3 to 4 months, after which lesser but still significant absorption takes place.[78] Effective treatment of vaginal atrophy with minimal absorption can be achieved with the administration of 0.3-mg conjugated estrogens, b.i.d. to t.i.d. per week.[79,80] Typically, addition of a progestogen is not indicated with local vaginal therapy; however, data regarding endometrial safety for 1 year or more are not available. **We believe that treatment with a vaginal cream longer than 12 months requires endometrial surveillance.**

The amount of estradiol delivered in low-dose tablet form, or a ring is not sufficient to treat menopausal symptoms, but effectively improves local urogenital atrophy and reduces recurrent urinary tract infections (UTIs). This has been accepted as a method to relieve atrophic vaginal symptoms in women with contraindications to estrogen treatment; however, systemic effects do occur, although not deleterious effects.[81] Although vaginal ET is effective at any age, women younger than 60 years may have improved cellular response versus women older than 60 years.[82]

Estring is a 55-mm-diameter silicone ring that contains 2-mg estradiol, with a release rate of 7.5 μg/d for 90 days.[83] European studies have demonstrated that vaginal maturation can be achieved with this ring that can be left in place for 3 months, with low level of systemic absorption.[84,85] The subjective symptoms associated with vaginal atrophy are rapidly relieved. No change in endometrial thickness was observed after 1 year of treatment.[86]

Vagifem is a vaginal formulation that is currently available in the United States as a tablet that contains 10-μg estradiol; the initial dose of one tablet daily provides relief from atrophic symptoms within 2 weeks.[87] After the first 2 weeks, the maintenance dose is twice weekly, and endometrial thickness has been reported to not change from baseline; however, the study was only 6 months in duration.[88] One 2-month study found no evidence of

endometrial stimulation; another reported one case of vaginal bleeding with endometrial proliferation.[89–91]

The systemic absorption of estrogen from vaginally administered formulations (low-dose estradiol ring or tablet) is very low, especially after the vagina achieves estrogen-induced maturation (about 3 months). Is this low level of absorption free of the risk of endometrial hyperplasia? The problem is that all studies have been too short (all ≤1 year, except one 2-year study) to determine long-term endometrial safety. Although systemic absorption occurs, the circulating estradiol levels with these low-dose methods remain in the normal postmenopausal range.[86,88,92–95] In a recent secondary analysis of RCT data, the authors compared serum estrogen levels following 12-week use of vaginal estradiol (10 μg/d for 2 weeks and then twice weekly) versus placebo; the average estradiol levels were 4.3 pg/mL in those treated with E2 versus 3.5 pg/mL in individuals receiving placebo, both levels being well within the postmenopausal range.[96] Nonetheless, because even small increases in circulating estradiol levels may cause distant target tissue responses (eg, an increase in bone density or an improvement in the lipid profile[97,98]), clinicians must retain vigilance and should not assure patients that vaginally administered estrogen is totally free of systemic activity.[99] **Although the change in blood levels is very slight and for that reason not effective for the relief of VMS, we believe that some form of endometrial surveillance is warranted with long-term treatment, such as ultrasonographic monitoring of endometrial thickness with biopsy when indicated. This ultrasonographic approach is preferable to complicating the treatment regimen with the addition of a progestational agent to vaginal estrogen just for endometrial benefit. We further suggest that each patient titrate their dose and schedule of treatment to balance an effective response with minimal dosing. For women who are breast cancer survivors and are considering this treatment, decisions should involve patients' oncologist, given the potential risk of increased systemic estrogen levels.**[100] Of note, postmenopausal women taking an aromatase inhibitor (AI) require special consideration, given their lower circulating estradiol levels. In a recent nested case–control study assessing the risk of breast cancer recurrence in women on tamoxifen or AI receiving vaginal ET, there was no increase in breast cancer recurrence; despite these reassuring

findings, caution is advised in interpreting these results, given the limited statistical power.[101]

Management of Urinary Symptoms

Several recent studies have analyzed the effect of vaginal ET on various bladder-related problems seen in postmenopausal women. A small RCT of 35 women had a statistically significant reduction in UTIs in women randomized to vaginal estrogen (cream or tablet) versus placebo.[102] A large retrospective cohort study of 5,600 women with hypoestrogenism demonstrated effectiveness of vaginal estrogen for the prevention of recurrent UTIs.[103]

Standard-Dose Method

One vaginal ring formulation (Femring, estradiol acetate) releases 50 or 100-µg estradiol acetate per day over a 3-month time span.[104,105] Estradiol acetate is a prohormone, which is rapidly hydrolyzed to estradiol, which is reflected in blood estradiol levels similar to those achieved with oral and transdermal methods. The systemic levels achieved with either dose formulation effectively suppress VMS, and a beneficial impact on bone is expected. Unlike other estrogen vaginal formulations, Femring is FDA-approved not only for the management of moderate-to-severe vulvovaginal symptoms attributable to hypoestrogenism but also for VMS-related bother. **This vaginal ring should not be considered local vaginal therapy, and users require the addition of a progestational agent for endometrial protection in the presence of a uterus.**

Role of Monitoring Blood Levels of Estradiol in Estrogen Users

Monitoring the estradiol blood level in postmenopausal women does not have a role in routine management. However, in women not responding to standard HT dosing, it may be beneficial to assess serum estradiol levels. Monitoring, however, is not as straightforward as it would seem. There are two primary difficulties. First, the clinical assays available differ considerably in their technique and quality (laboratory and antibody variations). Second, the various commercial products represent a diverse collection of estrogenic compounds, ranging from estradiol to unique

equine estrogens. Although the body interconverts various estrogens into estrone and estradiol, is this process relatively consistent within and between individuals? A highly specific assay for estradiol will detect very low levels of estradiol in women receiving 0.625-mg CEEs; nevertheless, most clinical assays will report a level of 40 to 100 pg/mL in these women.

We find measurement of blood estradiol levels very useful in selected patients, such as the patient who requests ever-increasing doses of estrogen for the treatment of symptoms, which, in the presence of very high blood levels of estradiol, can be confidently diagnosed as psychosomatic. What each clinician must do is learn what blood level of estradiol as performed by the local laboratory is associated with the standard doses of HT (0.625-mg conjugated estrogens, 1-mg estradiol, 50-µg transdermal estradiol) and consistently use the same laboratory. This range is 40 to 100 pg/mL estradiol when the estrogen is taken the evening before the office visit (with transdermal administration, blood sampling should be obtained the day before new patch placement); the range reflects individual variation, including the variability from peak to nadir values. **Remember that because follicle-stimulating hormone (FSH) is also regulated by a factor other than estrogen (ie, inhibin), FSH levels cannot be used to monitor estrogen dosage.** Menopausal HT utilizing commonly prescribed regimens will produce only a 10% to 20% decrease in FSH and luteinizing hormone (LH), and there is great individual variability in the responses.[106]

Products containing EE (commonly used in combined hormonal contraceptives) will not affect the measurement of circulating estradiol levels. EE circulates without being changed, and the antibodies in the immunoassays for estradiol will not recognize it. It is for this reason that women on oral contraceptives have very low measurements of estradiol. However, given the higher estrogenic potency of EE and hence a higher potential for adverse effects such as VTE compared to that of estradiol,[107] this aspect should be taken into consideration when choosing a hormone regimen (such as a combined hormonal contraceptive) for perimenopausal and menopausal women.

Menopausal Hormone Therapy: Sequential and Continuous Regimens

Postmenopausal HT initially consisted only of sequential regimens that were logical reflections of the cyclic estrogen and progesterone patterns in a premenopausal menstrual cycle. Clinical trials established the doses and durations for progestin administration that would effectively protect the endometrium against unchecked estrogen-driven proliferation.[108] Progestin withdrawal bleeding occurs in 80% to 90% of women on a sequential regimen.[109–111] The continuous combined method of treatment evolved to improve patient continuance that was adversely affected by bleeding and other symptoms triggered by the cyclic hormonal changes. The addition of a daily dose of a progestin to the daily administration of estrogen allowed the progestin dose to be smaller, provided effective protection against endometrial hyperplasia, and resulted in amenorrhea within 1 year of treatment in 80% to 90% of patients.[110,112–114]

In the sequential regimen, estrogen is administered daily, and progestins are administered for 2 weeks every month, using the *comparable* doses of the progestogens shown in the following list and those that are listed in **Table 22.3**[111–116]:

- 5-mg medroxyprogesterone acetate (MPA)
- 1.0-mg norethindrone acetate (NETA)
- 200-mg micronized progesterone

In the daily continuous, combined regimen, progestins are combined with estrogen in the following *comparable* doses[113,114,117]:

- 1.5 or 2.5-mg MPA
- 0.35-mg norethindrone
- 0.5 or 1.0-mg NETA
- 100-mg micronized progesterone
- 2-mg drospirenone (DRSP)
- 2-mg dienogest

Menopausal Hormone Therapy: *Estrogen Dose*

There has been a progressive decrease in estrogen doses in menopausal HT regimens. For many years, the standard doses of estrogens were 0.625-mg conjugated estrogens, 1 to 2-mg micronized estradiol, 1- to 2-mg estradiol valerate, or equivalent doses of other estrogens such as 5-μg EE. Lower doses have been proven *on average* to be as effective as these "standard" doses. Conjugated estrogens in a dose of 0.3 or 0.45 mg effectively produce a gain in BMD when combined with 1.5 mg MPA; similarly, a dose of 0.5-mg micronized estradiol produces comparable effects.[118–121] The 0.45/1.5-mg and 0.3/1.5-mg conjugated estrogens/MPA combinations effectively reduce VMS as well as improve symptoms related to vaginal atrophy and measures of sexual function in a pattern that is quantitatively and qualitatively similar to the 0.625/2.5-mg combination, and with lesser mastalgia.[122,123] These lower dose combinations are also associated with less breakthrough bleeding and higher rates of cumulative amenorrhea compared with older standard-dose regimens and retain the favorable changes in the lipid profile.[124,125] At these lower doses of conjugated estrogens, the combination with progestin produces an additive benefit; therefore, when these lower doses of estrogen are used without progestin, the effect on mitigation of VMS may not be as great as seen with the combination regimen. In a dose–response study, the most efficacious dose of oral micronized estradiol was 1 mg/d.[126] The lower dose combination of EE and NETA (2.5 μg/0.5 mg) is nearly as effective in treating hot flushes as the higher dose combination (5.0 μg/1.0 mg).[127] **Vigilance is advised in assessing response with lower dose regimens; innate differences in rate of metabolism and clearance may account for some women not attaining effective symptom control with the use of low-dose formulations.**

TABLE 22.3 Progestins Available Worldwide

		Estimated Comparable Oral Doses (mg)
Progesterone	Oral peanut oil tablet	200

		Estimated Comparable Oral Doses (mg)
21-Carbon derivatives	Medroxyprogesterone acetate	5.0
	Megestrol acetate	5.0
	Cyproterone acetate	1.0
	Dydrogesterone	10.0
	Chlormadinone acetate	5–10.0
	Medrogestone	10.0
19-Norpregnanes	Trimegestone	0.0625–0.50
	Promegestone	0.5
	Nomegestrol	5.0
	Nomegestrol acetate	3.75–5.0
	Demegestone	
	Nestorone (nonoral)	0.05–0.1
19-Nortestosterone family		
Ethinylated	Norethindrone	0.7–1.0
	Norethindrone acetate	1.0
	Levonorgestrel	0.075
	Desogestrel	0.15
	Norgestimate	0.09
	Gestodene	0.20
	Norethynodrel	

		Estimated Comparable Oral Doses (mg)
	Lynestrenol	
	Ethynodiol diacetate	
Nonethinylated	Dienogest	2.0
Derived from spironolactone and nonethinylated	Drospirenone	2.0

Menopausal Hormone Therapy: Progestational Component

Many women do not tolerate treatment with progestational hormones. Typical side effects include breast tenderness, bloating, and depression. These reactions are significant detrimental factors with continuance. Breast discomfort associated with postmenopausal HT can be attributed largely to progestins. Comparison studies have not been performed to address whether this symptom is minimized by particular progestins. Can a progestational agent be administered less frequently? We are secure in our position, supported by clinical data, that a daily estrogen plus progestin combination regimen will effectively prevent endometrial hyperplasia. A sequential regimen that incorporates progestin exposure for less than 14 days has over time an increased risk of endometrial hyperplasia.[128,129] Sequential regimens with less than 14 days of progestin monthly or *even long-term use of recommended schedules* do not match the protection offered by the daily, continuous method of estrogen–progestin treatment.

Two metabolites of progesterone, allopregnanolone and pregnanolone, are believed to be responsible for progesterone's unique sedative effect. Treatment regimens with micronized progesterone should be taken at bedtime, and these estrogen–progesterone combinations are a good choice for women with sleep difficulties. A study in a sleep laboratory has demonstrated a significant improvement in sleep quantity and quality in women using a sequential regimen of estrogen and micronized progesterone in contrast to no effect in the group using MPA.[130]

Some patients are very sensitive to MPA. One can consider a trial of norethindrone instead. In a sequential regimen, the dose of norethindrone is 0.7 mg (available in the progestin-only oral contraceptive; each pill contains 0.35 mg norethindrone). In the continuous, combined regimen, the dose of norethindrone is 0.35 mg daily. Commercial combination products are available containing estradiol and NETA. DRSP is the newest generation progestin that is available as a progestin-only contraceptive as well as in combination with 17β estradiol as a combined hormone formulation (Angeliq, containing 2-mg DRSP and 1-mg 17β-estradiol).[131]

Progesterone can also be administered vaginally. A vaginal gel allows the delivery of very low doses that can effectively protect the endometrium with low systemic levels because of a first-pass effect on the uterus.[132] The administration of 90 mg every 2 days produces secretory changes in the endometrium.[133] An application of the 4% commercial preparation (Crinone) twice weekly protects the endometrium and is associated with amenorrhea in most patients. In a sequential regimen, the 4% preparation should be applied daily for at least 14 days each month; however, long-term data on endometrial safety are lacking.[134] The application of a 100-mg vaginal tablet (Endometrin) every other day is also effective, with long-term follow-up of 3 years demonstrating no endometrial hyperplasia.[135] More recently, results of a subanalysis of the Early versus Late Intervention Trial with Estradiol (ELITE) have raised concerns regarding the effectiveness of cyclic regimen of vaginal progesterone in adequately negating endometrial effects of estrogen in menopausal women on cyclic HT; over an observation period of 80 months, those randomized to daily oral micronized 17β-E2 1 mg/d with 4% vaginal micronized progesterone gel 45 mg/d for 10 days each month were noted to have significantly increased endometrial thickness, higher rate of endometrial biopsies, and higher incidence of endometrial hyperplasia compared to those assigned to placebo.[136] Therefore, vigilance is advised if choosing a vaginal route for progesterone administration in conjunction with systemic estrogen for long-term use; in such cases, periodic endometrial surveillance utilizing ultrasound assessments and endometrial biopsy as indicated would serve well.

The transdermal estrogen–progestin combinations incorporate NETA in a daily dose of 0.140 or 0.250 mg; or levonorgestrel (LNG) in daily doses

of 0.007, 0.015, 0.030, and 0.040 mg/d; and, in a sequential regimen, NETA, 0.250 mg, or LNG, 0.010 mg.[137–139]

Infrequent Progestational Exposure: Long Sequential Regimens

Such regimens are increasingly being considered, either for the convenience of lesser frequency of withdrawal bleeding episodes associated with cyclic progesterone use or for those wishing to minimize progestin exposure duration. Experience with extended-cycle regimens, however, is very limited. The administration of MPA every 3 months was associated in one study with longer, heavier menses and unscheduled bleeding and a 1.5% incidence of hyperplasia at 1 year, whereas in another study, overall bleeding was less, but the incidence of hyperplasia was approximately 4%.[140,141] In a Dutch study that was only 12 weeks in length, simple endometrial hyperplasia was encountered at the end of the unopposed estrogen phase.[142,143] In yet another study, there was no endometrial hyperplasia encountered by 143 women who completed 2 years of treatment; however, the progestin administered every 3 months was of high dosage, 20 mg MPA daily for 14 days.[144] In Finland, the addition of progestin at 3-month intervals was associated with a striking increase in the risk of endometrial cancer when this regimen was used for many years.[145] Most impressively, the Scandinavian Long Cycle Study, a clinical trial scheduled to last 5 years, was canceled after 3 years because of a 12.5% incidence of endometrial pathology and one case of endometrial cancer.[117,146] Given the lack of long-term data on safety of extended regimens, if a patient chooses such an approach, endometrial monitoring is advised. **Any program that differs from the standard regimen should consider periodic surveillance of the endometrium** (**as discussed earlier in this chapter**). **Even the long-term use of standard sequential regimens is subject to a small increase in the risk for endometrial cancer, and endometrial surveillance should be considered in women using this method.**

We caution against long regimens in women who may be at an innately higher risk for endometrial hyperplasia and cancer, such as those with a personal history of endometrial hyperplasia, those who are obese, those who are insulin-resistant, and women who are diabetic.

The Progestin Intrauterine Device

The LNG-releasing intrauterine devices (IUDs) are increasingly being used in estrogen-taking postmenopausal women to confer endometrial protection.[147–151] The intrauterine presence of the progestin effectively protects the endometrium against hyperplasia and cancer.[152] The local site of action provides endometrial protection while minimizing systemic progestin side effects; for example, estrogen's favorable lipid effects are not attenuated with intrauterine progestin.[153] As with the oral continuous, combined regimens, irregular breakthrough bleeding may occur in the first 6 months, and after 1 year, approximately 60% to 70% of the women are amenorrheic. The LNG system has the advantage of a 5- to 7-year duration of use. These methods provide treatment options that minimize substantially the systemic effects of progestins.

Special Considerations for Progestin Use

Inclusion of a progestational agent in menopausal HT regimen is exclusively for endometrial benefit. Thus, the use of estrogen-alone hormone formulations reflects the standard of clinical care in managing menopausal symptoms in women without a uterus. However, there are some special conditions that warrant consideration of a combined estrogen–progestin regimen even in hysterectomized women.

Key Points

- In women in whom hysterectomy and bilateral salpingo-oophorectomy are undertaken for the management of endometriosis, we recommend a combination of estrogen *plus* progestogen. In general, following hysterectomy estrogen-only HT is required, if needed. However, given the role of estrogen in endometriosis growth/progression, this is one situation where combined HT is indicated following hysterectomy. Cases of adenocarcinoma have been reported in patients with pelvic endometriosis treated with unopposed estrogen.[154–159]
- Patients who have undergone procedures that have the potential to leave residual endometrium (eg, a supracervical hysterectomy) should be treated with an estrogen–progestin combination. Responsive endometrium may be sequestered in patients who have undergone endometrial ablation,[48,58] and combined estrogen–progestin treatment is also recommended for these women.

- In women undergoing hysterectomy for the management of early-stage endometrial adenocarcinoma, if HT is being considered for symptom control, a combination regimen is advised, given the potential protective action of the progestational agent.
- The combined estrogen–progestin approach makes sense for patients previously treated for endometrioid tumors of the ovary.[160]

ROLE OF ANDROGENS IN MENOPAUSE MANAGEMENT

The total amount of testosterone produced after menopause is decreased because the amount of the primary source, peripheral conversion of androstenedione, is reduced. The early postmenopausal circulating level of androstenedione decreases approximately 62% from young adult life.[161] Nevertheless, the menopausal decline in the circulating levels of testosterone is not great, from no change in many women to as much as 15% in others.[156,161–163] In an excellent longitudinal Australian study from 5 years before menopause to 7 years after menopause, the circulating levels of testosterone did not change.[164] Indeed, because of a decrease in SHBG, this Australian study calculated an increase in free androgens. The total amount of testosterone produced per day, however, is slightly decreased because the primary source, the peripheral conversion of androstenedione, is reduced. Because of this decrease, some argue for inclusion of an androgen in menopausal HT regimen.

The potential benefits of androgen treatment include improvement in psychological well-being and an increase in sexually motivated behavior. **Hypoactive sexual desire disorder is defined as a decrease in sexual activity sufficient to cause distress.** Beneficial effects of androgen treatment have been reported with the administration of relatively large doses of androgen.[165] In a well-designed, placebo-controlled study, lower doses of androgen (but still very pharmacologic, 5 mg methyltestosterone) contributed little to actual sexual behavior, although an increase in sexual fantasies and masturbation could be documented.[166] Transdermal testosterone treatment of women improved sexual function compared with a placebo group but only in the dose that raised circulating testosterone levels

to about 100 ng/dL. (The upper limit of normal for reproductive-aged women is 80 ng/dL in most laboratories.)[167] In a recent systematic review on the topic, while concluding that existing data support that testosterone therapy alleviates many of the signs and symptoms related to sexual dysfunction in menopausal women, the authors underscored a need for additional studies, given that existing evidence is limited due to the small sample sizes and the relatively few studies on the topic.

Any benefit must be balanced by the unwanted effects, in particular virilization (acne, alopecia, and hirsutism) and a negative impact on the cholesterol–lipoprotein profile. In a short-term study comparing a product with estrogen and a relatively low oral dose of testosterone (1.25-mg methyltestosterone) to estrogen alone, a negative impact on the lipid profile was apparent within 3 months of initiating treatment.[168] Over a 2-year period, the administration of estrogen (1.25 mg) combined with 2.5-mg methyltestosterone produced a significant overall adverse impact on the cholesterol–lipoprotein profile.[169] In addition, 30% of the patients experienced acne, and 36% developed facial hirsutism. A lower dose of this combination (0.625-mg esterified estrogens and 1.25-mg methyltestosterone) also significantly lowered HDL cholesterol.[170] The adverse impact on the lipid profile is less (and may even be avoided) by the parenteral administration of testosterone.[171] Of course, the clinical effects of these metabolic changes are not known.

It should be remembered that androgens do not protect the endometrium from unopposed effects of estrogen, and the addition of a progestin is still necessary. It is uncertain (and unstudied) how much aromatization, especially local aromatization in target tissues, of the administered testosterone increases the estrogen impact and whether this might increase the risk of endometrial and/or breast cancer. The addition of androgen to standard HT regimen does not reduce the amount of breakthrough bleeding women experience with a continuous combination (estrogen + progestin) regimen.[169,172] Adding testosterone to an ET program has been reported to provide no additional beneficial impact on the bone or on relief from hot flushes.[169,173] On the other hand, others have demonstrated a greater increase in bone density with an estrogen–androgen combination compared with estrogen alone, although the blood levels achieved were higher than those associated with standard menopausal HT.[171] In another

study, only a very pharmacologic dose of methyltestosterone added to the bone density achieved with estrogen alone.[174] A greater effect on bone associated with androgen treatment may be indirect, reflecting higher free estrogen levels because of a reduction in SHBG and/or androgen-induced changes in muscle mass.

There is no doubt that pharmacologic amounts of androgen can increase libido, but these same doses result in supraphysiologic levels and produce unwanted effects.[175] In addition, patients on high doses of androgens are often somewhat addicted to this therapy. Small amounts of androgen supplementation can be provided in situations in which the patient and clinician are convinced that a depressed libido cannot be explained by psychosocial circumstances. In these cases, the lipid profile should be carefully monitored. Any positive clinical response may well be a placebo effect. The products that are available in various parts of the world include oral testosterone undecanoate, sublingual micronized testosterone, intramuscular injections, subcutaneous implants, and transdermal preparations (eg, Intrinsa, applied twice a week).[176] Unfortunately, there is currently no testosterone formulation that is approved by the FDA for use in women; in clinical practice, the testosterone transdermal gel marketed for use in men (AndroGel), 5 g/d, can be used at a starting dose of about 1 g/d. Testosterone undecanoate produces very high testosterone levels with great variability and is not recommended.[177] **If testosterone use is considered, our preferred method is to use a product that will allow dose to be titrated by measuring the total testosterone blood level with the goal of maintaining concentration in the range of 20 to 80 ng/dL.**

The initial clinical trials concluding that the 300-µg transdermal dose of testosterone was effective for low libido consisted of women with either surgical (1,172 women) or natural menopause (549 women) who were also being treated with estrogen.[178,179] A 1-year, randomized, placebo-controlled clinical trial of 814 women with hypoactive sexual desire disorder and not on ET from 65 centers in the United States, Canada, Australia, the United Kingdom, and Sweden assessed the impact of transdermal testosterone that delivered 150 or 300 µg/d.[180] The higher dose of testosterone increased sexuality (including desire, arousal, orgasm, and pleasure) by 1.4 episodes per month compared with placebo. This increase appeared as early as the second month of treatment. The lower dose did not differ from placebo. In

the higher dose group, 30% reported unwanted androgenic effects (essentially an increase in facial hair). In addition, one woman in the low-dose group and three women in the high-dose group developed clitoral enlargement (the enlargement resolved in the woman receiving the low dose, but not in the high-dose women). The frequency of acne, alopecia, and voice deepening was the same in all groups. It is certainly plausible that with longer exposure to the high dose, more women would develop androgenic side effects. There were four cases of breast cancer in the treatment groups and none in the placebo group; however, one was diagnosed after only 4 months of treatment and one had a bloody nipple discharge before the trial started, making it difficult to determine if these were preexisting or de novo cancers.

In the Nurses' Health Study, the risk of invasive breast cancer associated with the use of combined estrogen and testosterone was nearly 2-fold increased.[181] This report from the Nurses' Health Study is complicated by the same problem in other breast cancer reports from this cohort: The hormone users (in this case, estrogen and testosterone) differ substantially from never users. This requires multiple statistical adjustments, a process that is further influenced by the number of cases involved. The analysis is limited by relatively small numbers; there were only 29 cases of breast cancer among the estrogen–testosterone users. Nevertheless, the results should raise caution regarding the postmenopausal use of androgens.

If testosterone affects breast tissue, does it do so directly or is it aromatized locally into estrogen? Most studies indicate that testosterone inhibits proliferation of breast cancer cell lines in vitro, as well as in vivo markers of breast epithelial proliferation in animals and women,[182,183] suggesting that aromatization is of greater concern. Testosterone preparations such as implants and transdermal applications do carry the risk of target tissue aromatization, perhaps raising *local* estrogen levels to high levels in breast tissue. Perhaps, an argument against this possibility was the failure to demonstrate any increase in breast density associated with transdermal testosterone treatment, even with the higher dose.[184] However, the mean age of the women in this study was 54.6, and an increase in breast density with estrogen–progestin therapy is largely observed in women over age 55; in younger women, it is difficult to find any differences between hormone users and nonusers.[185]

In the transdermal testosterone trial with women *not* on estrogen treatment, there was a 10.6% incidence of vaginal bleeding in the women who had not undergone hysterectomy and were receiving the higher dose, compared with 2.6% in the placebo group and 2.7% in the low-dose group.[180] Was this due to aromatization of testosterone in the endometrium? There were no cases of endometrial hyperplasia or cancer in this trial, but again, a longer duration of exposure might have unwanted consequences. This issue cannot be resolved without long-term data. In addition, the long-term effects on the cardiovascular system are unknown.

Response in the clinical trials with transdermal testosterone did not correlate with testosterone levels at baseline, and higher levels during treatment did not predict androgenic side effects. This is not surprising because measurement of free and bioavailable testosterone is subject to considerable inaccuracy and variability. For this reason, testosterone levels cannot be used to diagnose the hypoactive sexual desire disorder.[186] The transdermal clinical trials have reported that all testosterone levels remained within the premenopausal ranges. However, the mean level of free testosterone was relatively high at 6.8 pg/mL, although within the reference range. According to the data in the supplemental appendix, available only online, the mean levels were at or above the upper end of the reference age. In addition, because of individual variability, there was a wide range of testosterone levels, with a significant number of values elevated above normal. For many women, these are not physiologic levels. We do not know if it is possible to avoid unwanted consequences by careful monitoring of blood levels.

Currently, there is no testosterone formulation that is approved for exclusive use in the female population in the United States.[187] In contrast, the Australia's Therapeutic Goods Administration (TGA) approved Androfeme exclusively for women in 2019, and this drug is licensed nationwide in Australia.[188] Estratest, a combination of esterified estrogen with methyltestosterone—at higher (2.5-mg methyltestosterone) and lower (1.5 mg methyltestosterone) dose combination formulation was previously available in the United States for off-label use[189]; the product was, however, discontinued in March 2009. Compounded testosterone formulations in the form of gels, pellets, and injectable testosterone (decanoate, enanthate, cypionate) have been variably utilized but are not FDA-approved. With

gels, 5 mg (1%) is recommended.[190] Various doses have been used for injectable testosterone, with currently no adverse effects noted; however, outcomes have only been measured over a 6-month period.[191] Exercising extreme caution when considering testosterone pellet therapy is warranted, given concern for supraphysiologic doses achieved. Furthermore, in women with breast cancer, uterine cancer, CVD, or liver disease, testosterone use is generally contraindicated.[189]

There is little doubt that the pharmacologic amounts of testosterone can produce favorable effects on sexuality, but it remains doubtful that this beneficial impact can be seen while maintaining testosterone levels within the normal physiologic range. Some women receiving pharmacologic amounts of testosterone develop very high circulating levels. The fundamental problem is that the long-term consequences of pharmacologic amounts of testosterone are unknown. **If a clinician and a patient choose to use supplemental androgens, our advice is to select a treatment that can be monitored with measurements of total testosterone in serum.** The choices include the testosterone transdermal patch, a testosterone skin gel (on the market for use in men), and testosterone compounded for individual use by a pharmacist. We are left with this question: Is a modest increase in one or two episodes per month sufficient to offset the unanswered question of long-term safety? Some women would say yes, but the clinician has an obligation to avoid excessive doses and to educate the patient regarding the unanswered questions. **Prior to initiation, we recommend obtaining baseline lipid, and liver function tests and periodic surveillance** (**3 months following initiation and yearly thereafter**) **are recommended to ensure safety.** The free testosterone index can be used to monitor testosterone levels (goal of physiologic levels) with all testosterone formulations. Of note, oral methyltestosterone cannot be measured, as it is not detected in existing testosterone assays.[189] As long-term safety data are limited, it is highly recommended that a discussion for treatment discontinuation be made with patients at 6 months following initiation.[189,192]

While a role of testosterone therapy in women's health remains somewhat controversial, in the setting of reduced libido, testosterone may be beneficial for some menopausal women not responding to traditional HT.

Dehydroepiandrosterone

Adrenal androgen production decreases dramatically with aging. The mechanism is not known, but it is not due to the loss of estrogen at menopause nor can it be reversed with estrogen treatment.[193] The impressive decline (75–85%) in circulating levels of dehydroepiandrosterone (DHEA) that occurs with aging (greater in men than in women) has stimulated a search for a beneficial impact of DHEA supplementation.[194]

The only proven function of DHEA and its sulfate, DHEA-S, is to provide a pool of prohormone for conversion to androgens and ultimately estrogens. By age 70 or 80, the circulating levels in men and women are about 10% of peak levels that occur between 20 and 30 years of age. Systemic DHEA supplementation does not produce improvements in menopausal symptoms, mood, libido, cognition, or memory, but it does increase testosterone and decrease HDL cholesterol.[195] The acute administration of DHEA did produce a modest effect on sexual response in postmenopausal women, but the dose was enormous, 300 mg.[196]

Although low levels of DHEA and DHEA-S have been reported to be associated with increased risk of CVD in men, in women, conflicting results are found in cross-sectional data. In a longitudinal study of 236 women, higher levels of DHEA and DHEA-S in middle-aged women correlated with an *increased* risk of CVD.[197]

DHEA supplementation, 50 mg/d, produced levels of DHEA-S in reproductive age range in older men, did not change levels of testosterone and dihydrotestosterone, and raised estradiol and estrone levels, although still within normal range.[198] However, in women, 25 or 50 mg/d increased testosterone levels, decreased SHBG levels, and produced adverse effects on the lipid profile.[199,200] Exogenously administered DHEA is converted to potent androgens and estrogens. Potential long-term effects include hirsutism, alopecia, voice changes, breast effects, and an increased risk of CHD. Supplementation with DHEA requires dose titration using the circulating level of total testosterone and keeping the concentration below 80 ng/dL. This can be difficult because of the variability in DHEA content of the many commercial products available in the market; the FDA

measured DHEA content of 45 commercial products, and assayed values varied widely from 0% to 109.5%![201]

In contrast to systemic DHEA formulations, a prospective, randomized, placebo-controlled trial of daily intravaginal use of DHEA (trade name *Prasterone*) in a dose of 0.5% (6.5 mg) demonstrated significantly improved symptoms of vaginal atrophy, with little change in the serum levels of DHEA, estradiol, and testosterone.[202–206] Presumably, the vaginally administered DHEA is converted locally to estrogen and testosterone within the vaginal tissue, a phenomenon that is recognized as "intracrinology."[207] In clinical trials comparing DHEA to 0.3-mg CEE or 10-μg E2 daily, DHEA was found to be at least as effective as CEE and/or estradiol in improving vulvovaginal symptoms.[208] There was no effect of vaginal DHEA on the endometrium or liver; however, impact on bone is unknown.

SELECTIVE ESTROGEN RECEPTOR MODULATORS

A greater understanding of the ER mechanism (see Chapter 1) allows us to understand how mixed estrogen agonists/antagonists can have selective actions on specific target tissues. New agents are continuously being developed in efforts to isolate the desired actions (improvement in VMS and bone density) from unwanted side effects (proliferative effects on endometrial and breast tissue). Indeed, in time, we can expect to see new products with progressively better agonist/antagonist profiles, yielding increasingly user-friendly drugs.

Raloxifene

Therapeutic benefit of raloxifene is well established for the skeleton and breast tissue, and its role in menopause management is primarily for targeted benefits toward fracture and breast cancer risk reduction. Briefly, raloxifene exerts estrogenic effects on the skeleton (further discussed in Chapter 23) without having any proliferative effects on the endometrium. A major limitation of raloxifene and similar selective estrogen receptor modulators (SERMs) is the lack of efficacy against VMS; if anything, women taking raloxifene may even experience a worsening of hot flushes!

Overall, metabolic effects of raloxifene are neutral or even favorable on lipids.[209–212] The Multiple Outcomes of Raloxifene Evaluation (MORE) study of raloxifene administration to women with osteoporosis reported results from 8 years of follow-up.[213,214] Women with low *T*-scores had approximately a 50% reduction in vertebral fractures with raloxifene treatment and those with previous vertebral fractures had an approximate 35% reduction compared to placebo. However, **there has been no evidence of a reduction in hip or wrist fractures.** The major adverse effect was about a 3-fold increase in VTE. All SERMs, like estrogen, have an increased risk for VTE, normally within the first 1 to 2 years of drug initiation.[215] The size of the risk is comparable for all SERMs, and nearly all the cases occur in the first 1 or 2 years of exposure. A small number of women experience hot flushing with raloxifene. Raloxifene treatment in the MORE trial had neither a positive nor a negative effect on cognition.[216]

Women who received raloxifene in the MORE trial had about an 80% reduction in the incidence of ER-positive breast cancers. The CORE study, the Continuing Outcomes Relevant to Evista trial, was designed to measure the impact of 4 additional years of raloxifene (60 mg/d), beginning during the fourth year of the MORE trial.[217] Of the 7,705 participants initially randomized in the MORE trial, 3,510 women elected to continue raloxifene treatment (2,336 completed the CORE trial) and 1,703 continued on placebo (1,106 completed the trial). During the 4-year CORE study, raloxifene treatment was associated with a 66% (HR = 0.34; CI = 0.18–0.66) reduction of ER-positive invasive breast cancer in the treated group. There was no difference in ER-negative tumors, nor. Over the entire 8-year period, the reduction in ER-positive cancers reached 76%. In the 8-year period, there was no difference in the number of deaths in the two groups.

The Study of Tamoxifen and Raloxifene (STAR) trial enrolled 19,747 women at increased risk of breast cancer who were randomized to treatment with either raloxifene, 60 mg daily, or tamoxifen, 20 mg daily, in more than 500 centers in the United States, Canada, and Puerto Rico.[218] After an average treatment period of almost 4 years, the numbers of invasive breast cancers were identical in the two groups of women. It was estimated that these results were equivalent to about a 50% reduction (based on the previous results in the tamoxifen prevention trial),[219,220] but without a placebo arm, an accurate assessment was impossible. Thus, raloxifene

appears to achieve the same reduction as tamoxifen in invasive breast cancers with a lesser increase in venous thrombosis and perhaps no increase in cataracts and uterine cancer. Fractures, as well as strokes and heart attacks, were equally prevalent in the two groups. “Quality of life” was said to be the same for both drugs.

Tamoxifen, another well-recognized SERM, has been demonstrated to reduce the incidence of both lobular carcinoma in situ and ductal carcinoma in situ.[219,220] In the 7-year follow-up report of the tamoxifen for prevention study, the risk for breast cancer was 0.57 (CI = 0.46–0.79), a 43% reduction, and the risk for in situ disease was 0.63 (CI = 0.45–0.89), a 37% reduction.[219] Not only did raloxifene not yield a reduction in in situ cancers, the number with raloxifene in the STAR trial was greater. If raloxifene is truly preventing breast cancer, this should produce a reduction in in situ disease. Perhaps, with longer follow-up, a difference between the two treatment groups will no longer be apparent.

In a 2-year randomized trial in monkeys, raloxifene exerted no protection against coronary artery atherosclerosis despite changes in circulating lipids similar to those achieved in women.[221] The Raloxifene Use for the Heart (RUTH) study included more than 10,000 women from 26 countries, either at high risk for myocardial infarction or with known CHD.[222,223] The participants were randomized to placebo or raloxifene, 60 mg daily, and followed for up to 7 years. There was no effect of raloxifene treatment on CHD events; however, there was a small increase in stroke mortality. The results of the RUTH trial are not surprising. The known favorable impact of raloxifene on the cholesterol–lipid profile was not robust enough to prevent coronary events.

Because the Nurses’ Health Study reported a reduction in coronary events associated with ET administered to young postmenopausal women, the RUTH trial performed a post hoc analysis of the impact of raloxifene according to age of the women at entry to the study as well as subgroups such as the use of medications, including statins.[223] Overall, raloxifene did not increase or decrease coronary events in either of the treated groups. The only category demonstrating a significant difference, a 40% reduction in coronary events, consisted of women less than 60 years of age. Despite the statistically significant reduction in coronary events in women under age 60, there was no relationship in any subgroup according to years since

menopause, even in the group less than 10 years postmenopausal. The women who were less than 60 years of age were an average of 9.9 years since menopause, compared with 19.4 years for the overall study population. As with HT, decision to use raloxifene should not be influenced by its potential for facilitatory effects on the cardiovascular system, but rather for its beneficial impact on bone and breast tissue.

In our view, raloxifene is an option for the prevention of osteoporosis-related spinal fractures, especially for patients reluctant to use HT or in those wanting to combine some bone protection with a reduction in the risk of breast cancer. If using raloxifene for bone protection, periodic evaluation of BMD at the hip is recommended, and if bone loss occurs, patient and clinician should consider an alternative treatment option.

Ospemifene

Ospemifene (Osphena), the newest of these agents, has been approved by the FDA in the United States and Europe for its beneficial effects on vaginal tissue. As an oral formulation in a dose of 60 mg/d, it is effective in improving symptoms of vulvar and vaginal atrophy sites where ospemifene exerts a significant estrogenic impact.[224] In an action similar to sister SERM's, ospemifene suppressed the development of breast cancer in a mouse model, and post hoc analysis of safety data is reassuring in terms of its effects on the breast, endometrium, and bone. Case studies offer reassurance regarding safety of ospemifene in managing symptoms of vulvovaginal atrophy in women with a history of breast cancer.[225] However, similar to raloxifene, VMS can worsen.[226] More recently, improvements in urinary urge incontinence and in sexual function were observed following a 12-week treatment with ospemifene in postmenopausal women with symptoms of overactive bladder syndrome.[227]

Effect of Selective Estrogen Receptor Modulators on the Skeleton

These effects are discussed in Chapter 23.

Tissue-Selective Estrogen Complex

The combination of an estrogen combined with an SERM is called a TSEC (tissue-selective estrogen complex). The idea is to gain the benefits of estrogen (improved VMS, improved BMD, and reduced fracture risk) while mitigating potential for adverse effects of estrogen on certain end organs (such as the endometrium and the breast). A series of RCTs (Selective Estrogens, Menopause, And Response to Therapy [SMART]) have paired conjugated estrogen with an SERM, bazedoxifene (BZA), with the goal of achieving symptom and bone benefit without the need for adding progestational agent to HT regimen in women who have a uterus, while allowing synergy of both agents on certain end organs such as the bone.[228] BZA belongs to the estrogen agonist–antagonist family of drugs. It has favorable effects on the bone and lipids but does not affect the endometrium or the breast.[229,230] Treatment with BZA alone for 2 years had no effect on mammographic breast density.[231] Furthermore, in the SMART-5 trial (using BZA paired with CEE), there was no increased incidence of breast density or tenderness when compared to CEE/MPA; existing data thus are reassuring regarding breast safety of combination of BZA and CEE.[232]

BZA combined with conjugated estrogens effectively suppresses hot flushes, improves vaginal atrophy, prevents bone loss, and does not stimulate the endometrium or cause breast tenderness.[229,232–236] The combination of 20 mg BZA with CEE prevents endometrial hyperplasia and has an extremely high rate of amenorrhea (at least 80%).[237,238] Given BZA's antiestrogenic effects specific to the endometrium (even in the presence of CEE), the TSEC approach may be the future of HT, given that it maximizes the benefits of HT and also minimizes harm. It also allows for the avoidance of progestational agents. **The first TSEC to be approved by the FDA in the United States is Duavee**. This combination of BZA and estrogen may even be beneficial in special patient populations, such as multiple sclerosis (MS), where VMS may exacerbate MS symptoms. Preclinical data suggest a potential of BZA in facilitating myelin repair.[239] A small sample RCT compared tolerability and effectiveness of Duavee versus placebo in 24 perimenopausal and postmenopausal women (mean age 51 ± 3.6 years) with MS. Reassuringly, there was no difference in MS-related relapses between Duavee versus placebo groups; symptom improvement was greater and sustained in the combination BZA+CEE

compared to placebo group, although this difference was not of statistical significance, most likely due to small sample size and short duration of intervention. At first diagnosis of MS, the preponderance of women is premenopausal; in recent decades, a shift in disease epidemiology has been observed with an increasing prevalence of MS in aging populations.[240,241] Menopause transition and postmenopausal years may be particularly challenging, given the dual whammy of menopausal symptoms adding on to the burden of MS. The earlier-mentioned feasibility trial highlighted safety as well as a need for larger RCTs[242] of HT in perimenopausal and menopausal women with MS.

TIBOLONE

Tibolone is marketed for menopausal HT in many countries throughout the world but is not approved in the United States. Research on this product was initiated in the 1960s. Although tibolone was specifically developed as a drug to treat osteoporosis, the clinical performance of tibolone led rapidly to its approval for the treatment of menopausal symptoms as well as prevention of osteoporosis. Because of its unique metabolism to estrogen, progesterone, and androgens, tibolone can exert different hormonal activities at different sites. It has beneficial effects on bone density, improves VMS, and does not have estrogenic effects on the endometrium.[243] Despite its many beneficial effects, however, there are concerns regarding its safety. Adverse effects of tibolone on breast tissue and increased stroke risk are described with its use, and overall, it is perceived to be less effective than estrogen-based HT.[244] Given these concerns, we do not recommend it as a first-line management approach to menopause.

The Chemistry of Tibolone

Tibolone is structurally related to the 19-nortestosterone progestins that are used clinically in oral contraceptives; however, its activity depends on its metabolism. Tibolone (7-α,17-α-17-hydroxy-7-methyl-19-norpregn-5(10)-en-20-yn-3-one) is metabolized among human and nonhuman primates into three biologically active metabolites (**Figure 22.2**); the 3α-hydroxy (3α-

OH) metabolite and the 3β-hydroxy (3β-OH) metabolite have estrogen agonist properties, whereas the Δ-4 ketoisomer has progestogenic and androgenic effects.[245,246] Although tibolone itself binds to the ER, in vivo the activity of 3-hydroxymetabolite's estrogenic activity is 100 times greater, with a greater affinity for the ER-α than for ER-β.[246] The loss of the hydroxyl group at position 3 of the A ring eliminates estrogenic activity in the Δ-4 isomer. The Δ-4 isomer exerts its androgenic effects primarily in the liver and brain.

The conversion of tibolone into metabolites (**Figure 22.2**) occurs chiefly in the liver and intestine. The metabolism of the parent compound is rapid and very near total, yielding mainly the 3α-OH and 3β-OH metabolites in the circulation; the level of the 3α-OH metabolite is 3-fold higher compared with the 3β-OH metabolite.[247,248] Tibolone and the Δ-4 isomer can be detected only at peak levels 2 hours after ingestion, and, even then, the levels are very low, at the limit of detection. The half-life of the metabolites that predominate in the circulation (3α-OH and 3β-OH metabolites) is approximately 7 to 8 hours, and a steady state is attained by day 5.[249] Eating does not affect the metabolism, and tibolone can be taken at any time of the day.[247] The pharmacokinetics of tibolone are not affected by impaired renal function. There is a very weak effect of the metabolites on cytochrome P450 enzymes, and no interference is to be expected with coadministered drugs.[248] After the initial metabolism of tibolone, the products are rapidly sulfated, and more than 75% of the metabolites circulate as the sulfates to be activated by tissue sulfatases.[248]

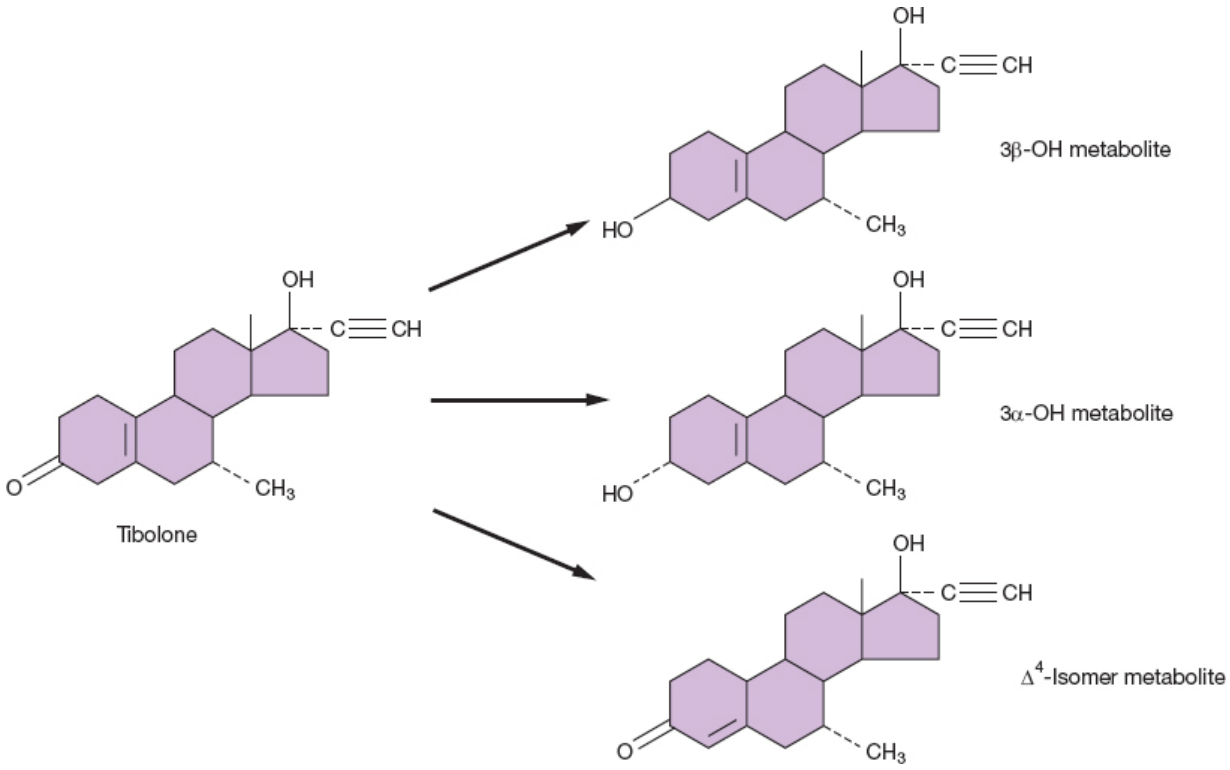


FIGURE 22.2

The metabolism of tibolone is not limited to the liver and intestine. Important effects are explained by specific local tissue metabolism. For example, the Δ-4 isomer is primarily produced within the endometrium, binds to the progesterone receptor (PR), and protects the endometrium from the agonist effects of the two estrogenic metabolites.[248–253]

Tibolone is available in two daily doses, 1.25 and 2.5 mg. There is considerable variability (~30–40%) within and between subjects, but the 1.25- and 2.5-mg doses produce the same bioequivalence as measured by maximum levels and areas under the curve for the 3α-OH and 3β-OH metabolites.[247] However, there are differences in clinical responses, which influence the choice of dose.

Effect of Tibolone on Menopausal Symptoms

Menopausal symptoms provide the main motivation for women to use postmenopausal HT. Tibolone must perform well in this category for it to be an attractive option for clinicians and patients. Clinical studies have

established that tibolone exerts an estrogenic beneficial impact on hot flushing and vaginal dryness. Appropriate studies have documented that tibolone in a daily dose of 2.5 mg is as effective as standard postmenopausal hormone regimens in treating hot flushing.[254–260] The 1.25-mg dose takes longer to be effective, and this dose also has a higher incidence of persistent VMS.[261] Fortunately, tibolone treatment provides an estrogenic effect on the vagina. Tibolone, 2.5 mg daily, relieves vaginal dryness and dyspareunia, and in most studies, tibolone is as effective as estrogen treatment.[256–260,262–265] In addition, tibolone effectively treats the side effect of hot flushing associated with gonadotropin-releasing hormone (GnRH) agonist therapy in premenopausal women.[266]

A decided advantage for tibolone over standard HT can be found in studies examining sexuality. In prospective, randomized trials comparing tibolone with estrogen or estrogen–progestin therapy, tibolone has been associated with a better sexual response.[257,260,267–270] An increase in libido has been reported in studies comparing tibolone with placebo,[265,271] and the response has been greater than that with ET, comparable to that associated with androgen treatment.[272] The overall effect has included an increase in sexual interest and sexual performance, specifically fantasies, arousal, and orgasm.

There are two possible mechanisms for tibolone's effect on sexuality: a direct androgenic effect of the Δ-4 isomer and/or an increase in the circulating level of free testosterone. Tibolone is associated with a profound change in the circulating levels of SHBG, about a 50% decrease.[265,273] This is undoubtedly due to the Δ-4 isomer and an androgenic effect on the liver. Tibolone treatment, therefore, produces a decrease in the concentration of total testosterone (bound and unbound) but a substantial increase in the amount of free, unbound testosterone. This hormonal profile is a striking contrast to that associated with ET, which increases SHBG and decreases both total and free testosterone levels. The androgen side effects of acne and hirsutism, however, have not been reported with tibolone treatment.

When women who had been on tibolone for 10 years were compared with a matched group, the treated women were less clumsy, were less anxious in response to mild stress, and demonstrated better memory for facts, although there was no difference in memory for events and worse performance on sustained attention and planning.[274] Overall, tibolone exerts

a positive effect on mood that is modest in impact.[273,275] However, this is an area in which it is not easy to achieve consistent effects, a problem often due to the differences in measurement tools and definitions. The study of cognition is difficult because of the need to match treated and control groups for intelligence, age, occupation, education, and mental state (eg, depression). Because of this difficulty, the literature reporting the effects of HT on cognition provides an inconsistent picture. This is further complicated by the sensitivity and appropriateness of the assessment tools that are used. This is an area that requires standardization and new approaches for research, not only for tibolone but for all pharmacologic treatments that affect the central nervous system.

Effect of Tibolone on the Cardiovascular System

Consistent with reports of tibolone's effects on HDL cholesterol in postmenopausal women, tibolone-treated monkeys have much lower HDL cholesterol compared with control monkeys.[276] Although tibolone treatment resulted in lower circulating HDL cholesterol, coronary artery atherosclerosis extent in monkeys was not significantly different from the control group. Similar results were observed in the carotid arteries.[277] That observation prompted the question of whether the HDL cholesterol reductions noted among the animals treated with tibolone were associated with physiologically meaningful reductions in HDL cholesterol function. HDL cholesterol has a critical role in reverse cholesterol transport, the mechanism by which cell cholesterol (ie, artery wall cholesterol) can be returned through the plasma to the liver for excretion.[278] Further, it has been found that cholesterol efflux capacity predicts the severity and extent of coronary artery disease in human patients.[279] Postmenopausal monkeys treated with tibolone had *no* reduction in cholesterol efflux.[280] This disassociation between reductions in circulating concentrations of HDL cholesterol and the lack of change in HDL cholesterol function suggests the likelihood that this may account in large part for the finding that coronary artery atherosclerosis was not increased or decreased in the monkey model.

Short-term clinical studies uniformly document that tibolone treatment, 2.5 mg/d, reduces HDL cholesterol levels in women by about 20%; however, there is also a reduction in total cholesterol (about 10%) and

triglycerides (about 20%) and a slight decrease or no change in LDL cholesterol levels.[268,276,281–286] In women, therefore, tibolone does not increase LDL cholesterol, and the reduction in HDL cholesterol is less than that recorded in monkeys. In addition, tibolone decreases LDL cholesterol oxidation and produces a shift away from the more atherogenic small dense LDL cholesterol, which would be beneficial.[287] The potential harmful effects associated with reductions in HDL cholesterol are further balanced by tibolone-associated reductions in endothelin and lipoprotein(a), anti-ischemic effects detected in women with angina and an improvement in insulin sensitivity.[286,288–291] In longer term studies, HDL cholesterol levels did not come back to baseline at the end of 2 years of treatment, but did return to baseline at the end of 3 years.[286,292–294] Other studies have found that the decrease in HDL cholesterol is statistically insignificant.[295,296]

The recognition that reductions in HDL cholesterol are potentially harmful is based on the important roles for HDL cholesterol in the mediation of cholesterol movement from lipid-laden cells and inhibition of LDL cholesterol oxidation. However, the experimental results in the monkey model indicate that reductions in HDL cholesterol concentrations are not directly paralleled by reductions in important HDL cholesterol functions. At least one reason for this lack of direct correlation is the complex nature of HDL cholesterol lipoproteins, a heterogeneous collection of particles that differ in their activities.[297] The overall change in HDL cholesterol levels will not reflect specific changes in particles that can affect specific biologic activities. Like results in the monkey model, a randomized trial in women demonstrated that significant reductions in HDL cholesterol levels (average 27%) caused by tibolone treatment, 2.5 mg/d, were due to a decrease in one subclass of HDL cholesterol particles, and measures of HDL cholesterol antiatherogenic functions (reverse cholesterol transport and inhibition of LDL cholesterol oxidation) were not impaired.[291] The study was limited by the short, 12-week duration of treatment; however, the findings are consistent with those obtained in the 2-year monkey experiment. These human results were confirmed and strengthened by a study of 68 postmenopausal women randomized to daily treatment for 3 months with either 2.5-mg tibolone or placebo.[298] Changes in HDL cholesterol were associated with an increase in hepatic lipase activity, an

androgenic effect, again without impairing the ability of plasma to maintain cholesterol efflux.

Results in the monkey model are consistent with an overall neutral impact on the cardiovascular system.[277] A long-term (average of 7.5 years) follow-up of women treated with tibolone found no increase in carotid artery intimal–media thickness (cIMT) nor the number of atherosclerotic plaques, results that are consistent with the monkey model.[299] This neutral impact is further supported by failing to find any effect of tibolone on experimentally induced brachial artery dilation or on vascular resistance measured in the carotid and middle cerebral arteries.[295,300] On the other hand, a method studying venous dilation in the hand found an improvement in endothelium-dependent responses after tibolone treatment.[301] Myocardial infarction and heart failure have been reported to be associated with overactivity of the sympathetic component of the cardiac autonomic nervous system, and tibolone treatment decreases plasma levels of free fatty acids, an effect that results in an improved ratio of cardiac sympathetic tone to parasympathetic tone, and a theoretical lowering of myocardial infarction and heart failure risk.[302] Another favorable effect connected to tibolone and its metabolites is a direct impact on endothelial cells that results in a beneficial decrease in endothelial–leukocyte adhesion molecules, another human finding similar to that in the monkey trial.[303]

The OPAL (Osteoporosis Prevention and Arterial effects of tibolone) study was a 3-year, randomized, double-blind trial in six US centers and five European centers, treating 866 postmenopausal women with either daily 2.5-mg tibolone, 0.625/2.5 mg daily of conjugated estrogens/MPA, or placebo.[304] The arterial end point of the study was cIMT measured by ultrasonography every 6 months. Both the tibolone-treated group and the estrogen/progestin-treated group demonstrated an increase in intima–media thickness at a rate significantly greater than the placebo group, leading to the conclusion that both tibolone and estrogen/progestin treatment increased atherosclerosis compared with the placebo group.

In the OPAL trial, European women differed from American women in multiple ways: higher lipids, higher blood pressure levels, and more smokers. Hysterectomized women were excluded in the United States, but not in Europe (28% of the study population). The overall mean results indicated a difference comparing both treatment groups to placebo.

However, the European women had improvement in atherosclerosis in the placebo group, making it easy to calculate a significant difference compared to the treated groups. In American women, there were no differences comparing the three treatment groups; all demonstrated progression of thickness. Thus, the overall conclusion was inordinately influenced by the results in the European women. The investigators could not explain these differences. Unfortunately, the OPAL trial did not achieve its goal of providing robust data on cardiovascular effects, due to the older age of the women and the notably different results in American and European women. There continues to be good reason to believe that tibolone has a neutral effect on the cardiovascular system. In addition, tibolone does not adversely affect the blood pressure in women with established hypertension.[284]

A case–control study assessed the risk of VTE in a very large population of postmenopausal women (23,505 cases and 231,562 controls) derived from the UK General Practice Research Database.[305] No increase in risk was observed with the current use of either tibolone or transdermal estrogen compared with a significant increase associated with the current use of oral estrogen.

Effect of Tibolone on Diabetes

The administration of tibolone, 2.5 mg/d, to older women with type 2 diabetes mellitus produced no significant changes in the lipid profile.[306] Tibolone treatment is associated with an increase in insulin sensitivity in women with insulin resistance, although some have reported no effect in normal women.[283,291,307,308] Therefore, tibolone is an attractive option for postmenopausal women with diabetes mellitus.

Effect of Tibolone on the Uterus

Tibolone does not stimulate endometrial proliferation. This is because the predominant if not exclusive tibolone metabolite produced within the endometrium is the Δ-4 isomer, which binds to the PR and protects the endometrium from the agonist effects of the two estrogenic metabolites.[250–253] This protective effect has been documented in long-term (up to 8 years) human studies.[252,253,256,263,264,309–311] Isolated cases of endometrial proliferation have been reported, for example, 4 of 150 women treated with 2.5 mg daily

for 2 years.[312] In a 5-year follow-up, 47 of 434 women experienced bleeding, and of these, 11 had endometrial polyps or fibroids, but there were two with simple hyperplasia and two with endometrial carcinoma in situ.[313] This underscores the standard clinical principle to investigate persistent vaginal bleeding in any postmenopausal woman. In the major US clinical trial, three cases of endometrial cancer were observed, but, in each case, preexisting carcinoma was later detected when the initial biopsy samples were more extensively examined.[286] Nevertheless, a second large 2-year trial was conducted, the THEBES study, and no endometrial hyperplasia or cancer occurred in the tibolone-treated groups.[314]

The reported breakthrough bleeding rates with tibolone treatment have been comparable to treatment with combined, continuous estrogen–progestin therapy, but well-designed comparison clinical trials indicate that the rate is less with tibolone.[257–260,265,282,309,315,316] In addition, amenorrhea is achieved more rapidly; 90% of tibolone-treated women are amenorrheic by 6 months.[258,313,317] Bleeding is less in older women and can be greater with the 2.5-mg dose compared with the 1.25-mg dose, but the difference is too small to be detected in some studies.[261,286,318] Importantly, a lack of correlation has been observed between bleeding and endometrial thickness measured by ultrasonography.[318,319] **This again emphasizes the need to biopsy tibolone-treated women with persistent bleeding**.

Careful evaluations of women with fibroids who have been treated with tibolone have revealed no evidence of myoma growth, with up to 3 years of follow-up.[320–322] Furthermore, add-back treatment with tibolone effectively prevents flushing and bone loss and does not impair the fibroid response to therapy with GnRH analogues.[323]

Effect of Tibolone on the Breast

The breast tissue, normal and abnormal, contains all the enzymes necessary for the formation of estrogens (sulfatase, aromatase, and 17β-hydroxysteroid dehydrogenase) and the conversion of estrogens into their sulfates (sulfotransferase) (**Figure 22.3**). Estrone sulfate concentrations are high in the breast (higher than in plasma) and even higher in cancer tissue. This state is achieved in postmenopausal women with very low systemic levels of estrogen, indicating that a local mechanism is operative.

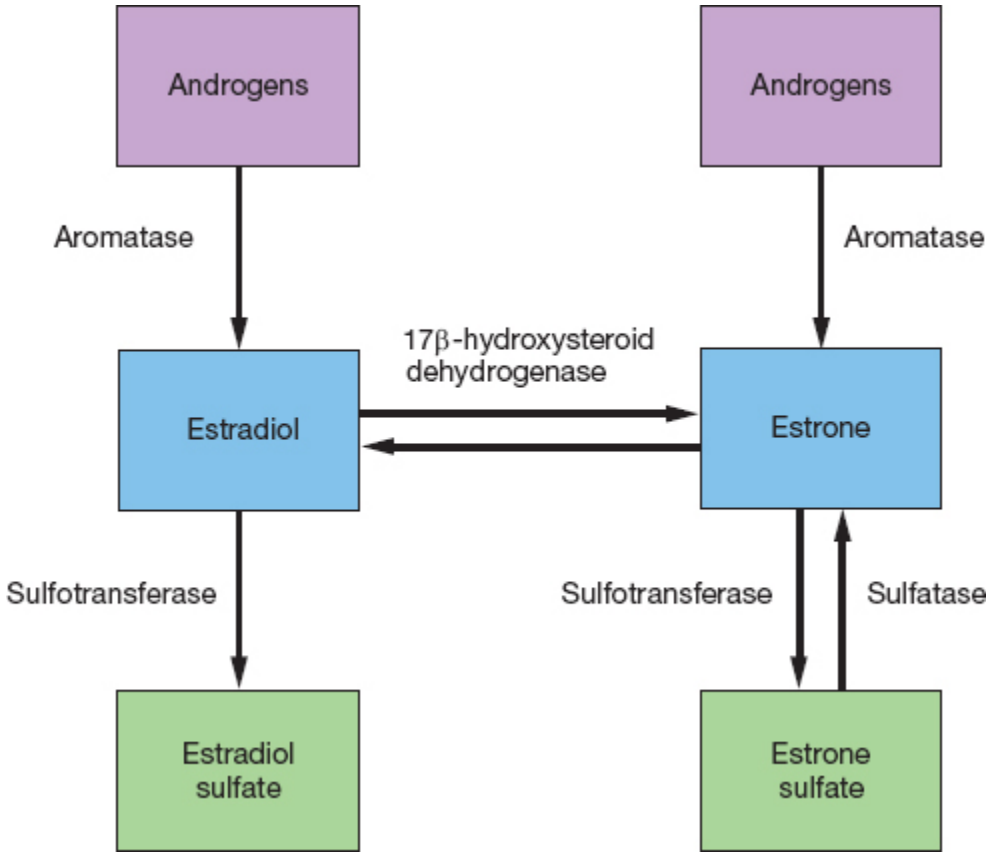


FIGURE 22.3

The major pathway of estrogen synthesis in human breast tumor cells is by conversion of estrone sulfate to estrone by estrone sulfatase, a pathway that is more important than the aromatase pathway.[324] Aromatase is an enzyme complex that produces the irreversible conversion of androgens to estrogens. The location of aromatase activity is predominantly in the stromal tissue of the breast. Comparing normal to tumor tissue, the levels of estrone sulfate and estradiol were higher in the tumor tissue.[325] Sulfatase activity is 130 to 200 times greater than aromatase activity in all breast tissues examined, and the sulfatase and aromatase activity was higher in the tumor tissue than in normal tissue. Thus, estrogen concentrations in the breast are elevated in women with breast cancer, and formation of estradiol from sulfated estrogen is the primary pathway. Most importantly, this increase in estrogen activity is independent of the ER status of the tissue.

Tibolone and its metabolites inhibit estrone sulfatase and 17β-hydroxysteroid dehydrogenase in normal stromal cells and in hormone-

dependent breast cancer cells (MCF-7 and T47D).[326–329] This inhibits conversion of estrone sulfate to estradiol. In addition, tibolone and its 3-hydroxymetabolites increase the conversion of estrone back to estrone sulfate by increasing the activity of sulfotransferase.[330] Tibolone and all three metabolites inhibit the conversion of estrone to estradiol by 17β-hydroxysteroid dehydrogenase.[327] Although the combined effects resemble progestin activity, tibolone is more potent. Tibolone increases aromatase activity in stromal cells but only at high concentrations that are beyond in vivo levels.[328] These tibolone-induced enzyme changes would lower the active estrogen concentrations in breast tissue.

In the rat and mouse breast cancer models (cancer induced by 7,12-dimethylbena[a]anthracene, DMBA), tibolone exerts protective effects to the same degree as tamoxifen.[331] However, tibolone is not antiestrogenic and does not inhibit aromatase. Therefore, the mechanism is explained by the enzyme effects summarized previously, inhibition of sulfatase and 17β-hydroxysteroid dehydrogenase and stimulation of sulfotransferase to increase the production of inactive sulfates.[328] In addition, tibolone increases cellular differentiation and stimulates apoptosis, at least with normal breast cells in vitro.[332] An increase in apoptosis is an action of the parent tibolone and its Δ-4 isomer. Thus, tibolone acts like progestins and weak androgens in breast cell line studies examining proliferation, differentiation, and apoptosis.

Tibolone and its metabolites do not display the same activity directed toward the sulfatase enzyme in all tissues. Strong inhibition of sulfatase is a major feature in breast cells, but tibolone and its metabolites inhibit sulfatase only moderately in the endometrium (still contributing to an antiestrogenic effect) and provide no inhibition of sulfatase in the bone (allowing a greater estrogenic impact).[333]

Postmenopausal HT increases breast density on mammography in about 10% to 20% of estrogen users and about 20% to 35% of estrogen–progestin users, an effect that occurs within the first months of treatment. In contrast, tibolone does not increase breast density and causes far less mastalgia than that seen with estrogen treatment.[258,270,286,316,334–338] In addition, in women at high risk of breast cancer who underwent a bilateral salpingo-oophorectomy, treatment with either tibolone or traditional HT was still associated with a decrease in breast density. However, a greater decrease

was noted with tibolone.[339] It is logical to conclude that these favorable responses are a consequence of the tibolone effects on the breast tissue enzymes involved in local estrogen production.

The Livial Intervention following Breast cancer: Efficacy, Recurrence, And Tolerability Endpoints (LIBERATE) trial was a multinational, placebo-controlled, randomized study of women with VMS who had had breast cancer surgically treated within the previous 5 years.[340] The study was designed to demonstrate that 2.5-mg daily dose of tibolone was superior to placebo, but when the drug monitoring safety board notified the sponsor that there appeared to be an excess of breast cancers in the treated group, the trial was canceled on July 31, 2007, 5 months before its scheduled end. The median duration of participation and treatment was about 3 years, with a wide range from a few weeks to almost 5 years. The participants used a variety of adjuvant treatments for breast cancer, mostly tamoxifen, 66.8%, while 6.5% used AIs. Final numbers for analysis were 1,556 women in the treated group and 1,542 in the placebo group. The women aged under 40 to 79 years, with a mean age of 52.7 years. An estimated 57.8% had positive lymph nodes, and 70% had a tumor stage of IIA or higher. ER status was known in 2,808 women in whom the tumors were ER-positive in 77.8%. In the intent-to-treat analysis, the HR for recurrent breast cancer in the tibolone-treated women was 1.40 (CI = 1.14–1.70). The absolute risk for tibolone was 51 cancers per 1,000 women per year and 36 in the placebo group. The increase occurred only in women with ER-positive tumors. There was no difference in mortality rates between the two groups during the 5-year study period. There were no differences in cardiovascular events or gynecologic cancers, while VMS, quality-of-life measures, and bone density all improved with tibolone treatment.

How do the LIBERATE results that indicate an estrogenic action of tibolone in breast cancer survivors jibe with the literature indicating that tibolone exerts a nonestrogenic effect on breast tissue? Indeed, it was realistic to expect tibolone to have a salutary effect on the breast. It is well documented that the breast responds to tibolone with less stimulation compared with estrogen, judged by changes in mammographic breast density and the characteristics of tissue obtained by fine-needle aspiration. In the LIFT clinical trial (discussed in Chapter 23) that had vertebral fractures as the primary end point and breast cancer as a secondary end

point, the risk of breast cancer after 3 years was significantly 68% *reduced* with tibolone treatment, although the dose was lower, 1.25 mg daily.[341]

It is important to note that the previous literature documenting beneficial actions of tibolone on the breast reflected the impact of tibolone on normal breast tissue; it is plausible that tibolone's activity to lower local bioactive estrogen levels in target tissues might be lost in cancer cells. The contrary results in the LIFT trial could reflect its older population of women at high risk for fractures, a population that also differed by having lower body weights, no history of tamoxifen treatment, and lower risk factors for breast cancer.

Although the LIBERATE trial may apply to all breast cancer survivors, speaking strictly in a scientific sense, the results were derived mainly from tamoxifen users with 10-fold fewer users of AIs. The possibility that estrogen or tibolone would interfere with the beneficial effects of tamoxifen or AIs has always been one of the objections to treating breast cancer survivors with estrogenic hormones. In a subgroup analysis of the LIBERATE trial, the group of women who had used AIs had a greater risk of recurrent breast cancer compared with tamoxifen; however, the CI was wide because of relatively small numbers. Possibly, the estrogenic effect of tibolone would be more pronounced on an occult breast cancer in estrogen-depleted tissue compared with tissue where tamoxifen was bound to the ER and prevented estrogenic stimulation. We do not know if the LIBERATE data are meaningful for future treatment regimens. Nevertheless, **until there are new data, the use of tibolone in women with a history of breast cancer remains relatively contraindicated.**

Effect of Tibolone on the Bone

These effects are discussed in Chapter 23.

Key Points: Tibolone

- **Tibolone is an appropriate choice for HT, suitable for many postmenopausal women.**

- **The standard dose of tibolone for many years was 2.5 mg daily, but the clinical trials support the use of the lower dose, 1.25 mg daily, with no major loss of efficacy.**
- **Because of its unique and varied metabolism, tibolone has different actions in different tissues, which provide an overall favorable risk–benefit profile.**
- **Tibolone treats menopausal symptoms, including hot flushes and vaginal dryness, as effectively as ET and, most importantly, improves sexual response.**
- **Endometrial safety and prevention of bone loss (discussed under the section on osteoporosis) are comparable to that achieved with continuous, combined estrogen–progestin regimens and with a lower rate of breakthrough bleeding.**

The sum of the various biologic effects of tibolone and its metabolites on the cardiovascular system should neither increase nor decrease the risk of coronary artery disease. Thus far, there has been no indication for an increased risk of VTE, but this is a potential side effect that requires further epidemiologic studies. Tibolone does not stimulate the proliferation of breast cells and affects enzyme activity in the breast to lower breast tissue concentrations of active estrogen. Tibolone does not increase breast density on mammography and does not increase the frequency of mastalgia. The reported increased risks of breast cancer and endometrial cancer in observational studies very likely represent "preferential prescribing" of tibolone in Europe.[342,343] **Women prescribed tibolone in Europe more often had chronic breast disease, a personal history of breast cancer, previous dysfunctional uterine bleeding, hypertension, and previous uterine operations. Most importantly, more women prescribed tibolone had a history of previous treatment with unopposed estrogen. Thus, clinicians were more likely to prescribe tibolone to women they believed were at higher risks for these two cancers, and this would yield higher rates in treated groups compared with control groups.**

NONHORMONAL TREATMENT OPTIONS FOR VASOMOTOR SYMPTOMS

The first-line approach for the management of VMS (hot flushes and night sweats) in otherwise healthy but symptomatic population of perimenopausal and recently menopausal women is HT. However, there exist a substantial number of women who either cannot, should not, or will not accept HT. Pharmacologic nonhormonal options for managing VMS are listed in **Table 22.4**.

There are many different medications and compounds that have been tried for the treatment of hot flushes, yet only a few successfully limit symptoms and the potential for harmful or bothersome side effects. Clonidine, bromocriptine, and naloxone given orally are only partially effective for the relief of hot flushes, yet require high doses with a high rate of side effects, such as drowsiness and dry mouth.[344,345] Bellergal treatment (a combination of belladonna alkaloids, ergotamine tartrate, and phenobarbital) is slightly better than a placebo and a potent sedative in the short term; however, one study documented a similar response with Bellergal and placebo after 8 weeks.[346,347] Veralipride, a dopamine antagonist that is active in the hypothalamus, is relatively effective in inhibiting flushing at a dose of 100 mg daily but is associated with major side effects, including mastodynia and galactorrhea.[348–350] 800 IU vitamin E, daily is barely more effective than placebo.[351] Dong quai, ginseng, black cohosh, isoflavones (including soy protein), yoga, and acupuncture all have little clinical difference compared with placebo treatment.[352–363] Clonidine (given as a patch or orally at 0.1 mg/d) is only partially effective for the relief of hot flushes and has a high rate of side effects, such as drowsiness and dry mouth.[344,345] MPA (10–20 mg daily) and megestrol acetate (20 mg daily) are also effective (as effective as estrogen), but concerns regarding exogenous steroids, especially in patients who have had breast cancer, would apply to progestins as well.[364–366]

TABLE 22.4 Drugs for Hot Flushing—Randomized Clinical Trial Results

Drug	Dose (mg/d)	Reduction in Flushing (%)
Citalopram (Celexa) placebo	20	50, same as placebo
Fluoxetine (Prozac)	20	50, same as placebo

Drug	Dose (mg/d)	Reduction in Flushing (%)
Sertraline (Zoloft)	50,100	40, same as placebo
Paroxetine (Paxil)	12.5	62
	25	65
	7.5	40
Paroxetine (Brisdelle)	7.5	40
Venlafaxine (Effexor)	37.5	37
	75	61
	150	61
Desvenlafaxine succinate (Pristiq)	100	64
Gabapentin (Neurontin)	900	50
Pregabalin (Lyrica)	150	65
Fezolinetant	45	51–61

In recent decades, selective serotonin reuptake inhibitors (SSRIs) and selective norepinephrine reuptake inhibitors (SNRIs) have gained a reputation for significant efficacy in treating hot flushing. The drugs that have been studied include citalopram (Celexa), fluoxetine (Prozac), sertraline (Zoloft), paroxetine (Paxil, Brisdelle), and SNRIs, venlafaxine (Effexor) and desvenlafaxine succinate (Pristiq). In addition, antiseizure medications, gabapentin (Neurontin) and pregabalin (Lyrica), have been demonstrated to reduce VMS (see **Table 17.10**).

Low-dose paroxetine is the first of non-HT medication that was FDA-approved for the treatment of hot flushes. In an RCT comparing low-dose paroxetine (7.5 mg daily) to placebo for the treatment of hot flushes, treatment with paroxetine had a statistically significant reduction in VMS compared to placebo.[367] However, it is less effective than HT in relieving

VMS and should be reserved for use in those women who have a contraindication to HT.

Venlafaxine was studied in breast cancer survivors; although the optimal dose was 75 mg, an appreciable response with 37.5 mg indicated that it would be worthwhile to begin treatment with the lower dose.[368–370] The response was very rapid, within days, and therefore, the dose can be increased in 1 to 2 weeks. The main side effects were mouth dryness, anorexia, nausea, and constipation. The efficacy of venlafaxine was demonstrated to be the same in women taking or not taking tamoxifen. Desvenlafaxine succinate is a metabolite of venlafaxine and equally effective as the parent compound.[371,372] **The effects of citalopram, fluoxetine, and sertraline are no more effective than placebo, about a 50% reduction in short-term trials.**[373–377] A 2015 systematic review demonstrated that fluoxetine and sertraline are less effective than other SSRI or SNRI, which can reduce hot flushes by approximately 65% within the first week. Due to variable individual response, if symptoms do not improve within the first 2 weeks, switch to an alternative medication is warranted.[378] Similarly, prospective RCT of postmenopausal Mexican women compared only sertraline and citalopram and found that citalopram reduced VMS and urogenital symptoms more than sertraline and also improved mental health factors, such as mood, irritability, and exhaustion.[379]

Gabapentin (Neurontin) is a γ-aminobutyric acid analog that has been used for seizures since 1994. It is also effective for migraine headaches, tremors, and panic disorder. In a gabapentin clinical trial, 67% of the treated women experienced more than a 50% reduction in flushes at week 12, compared with 38% in the placebo group.[380] The most common side effects were somnolence (20%) and dizziness (13%). Peripheral edema occurs occasionally because of an induced decrease in serum protein. The potency of this agent appears to be more modest than the SSRIs in a dose of 900 mg/d.[381,382] Side effects are common at higher doses, and further studies are needed to compare gabapentin to HT.[383,384]

Pregabalin (Lyrica), a more potent form of gabapentin, is an anticonvulsant drug that has been used in doses of 150 to 300 mg daily to treat anxiety and neuropathic pain, for example, diabetic neurogenic pain, pain after shingles, and fibromyalgia. Side effects include dizziness,

drowsiness, visual disturbances, tremor, weight gain, and a decrease in libido. In a phase III randomized trial, a dose of 75 mg b.i.d. (the recommended dose because of more side effects with higher doses), hot flushing was reduced by 65% after 6 weeks of treatment, an impact that was only 15% greater than placebo.[385] Although the data are limited to this short-term, small clinical trial, the effect of pregabalin appears to be comparable to gabapentin.

It is worth trying to titer the dose down to its lowest effective level because of a bothersome incidence of decreased libido. In addition, clinical experience indicates that it is best to slowly titrate upward to the recommended dose and, likewise, to wean the patient slowly when discontinuing treatment. SSRIs are effective for flushing secondary to both tamoxifen and hypoestrogenemia, and the efficacy is similar in women with and without breast cancer.[386] **An added advantage of the SSRIs is the fact that the clinical studies have also reported improvements in depression, anxiety, and sleep. Gabapentin is useful in those with difficulty sleeping, while clonidine may be more beneficial in women who also have hypertension.**

Caution is advised when considering SSRIs in women with a history of breast cancer being treated with tamoxifen. Tamoxifen is converted to an active metabolite by enzymes that are inhibited by certain SSRIs. Paroxetine coadministration decreases plasma concentrations of the active tamoxifen metabolite.[387,388] A lesser effect is associated with fluoxetine and sertraline. In a retrospective cohort study, only paroxetine use during tamoxifen therapy was associated with an increased risk of death due to breast cancer.[389] **Paroxetine, fluoxetine, and sertraline are, therefore, best avoided in women with a history of breast cancer who are being treated with tamoxifen.**

Until recently, SSRIs were the logical choice for symptomatic women for whom HT is contraindicated or not accepted by patients, although the reduction in hot flushing is considerably less than what can be achieved with estrogen treatment. The therapeutic landscape in the world of menopause was recently transformed with the addition of fezolinetant, a neurokinin 3B receptor antagonist that became the second nonhormonal drug (after Brisdelle) to gain FDA approval (May 12, 2023) for the management of moderate-to-severe VMS.[390–392] This class of drugs

acts by suppressing the pathogenesis of hot flash at its source— that is, at the level of the thermoregulatory center. The KNDy neurons (kisspeptin, neurokinin, and dynorphin) are a unique population of cells that project onto and influence the activity of the hypothalamic thermoregulatory center. Neurokinin, acting via its receptors (3BR and 1BR), is a stimulant for the KNDy neurons, resetting the hypothalamic thermoregulatory center toward heat conservation; the net result of neurokinin signaling is a transient rise in the core body temperature that underlies the vasomotor phenomenon of hot flash (**Figure 22.4**). By blocking hypothalamic neurokinin 3BR's, fezolinetant modulates and restores the normal sensitivity of the hypothalamic thermoregulatory neurons, thus effectively reducing both the severity and frequency of VMS.

BIOIDENTICAL HORMONES

Publication of the WHI hormone trials was followed by a period of much confusion and concern regarding safety of prescription HT. In the wake of both prescriber and patient distrust of HT, an upsurge of interest in bioidentical hormones occurred. Bioidentical hormones have since garnered much interest from the lay public, as well as generated much political, financial, and legal conflict. Bruce Patsner, research professor in the Health Law and Policy Institute at the University of Houston Law Center, has written what is, in our view, a masterful analysis of the problem, with suggestions for its resolution.[393]

The History of the Conflict

The operations of a pharmacy are regulated in the individual states by state boards of pharmacy, in a system similar to the regulation of medical practice. The first federal law regulating drugs, the Federal Food, Drug, and Cosmetic Act, was passed in 1938, at a time when most drugs were compounded according to a doctor's prescription. The American Pharmacists Association defines pharmacy compounding as the preparation of a prescription drug that is "individualized" to the needs of the patient. This changed after World War II with the development and growth of the

pharmaceutical industry. The Kefauver–Harris Amendment in 1964 extended the role of the FDA to include safety and efficacy of manufactured drugs.

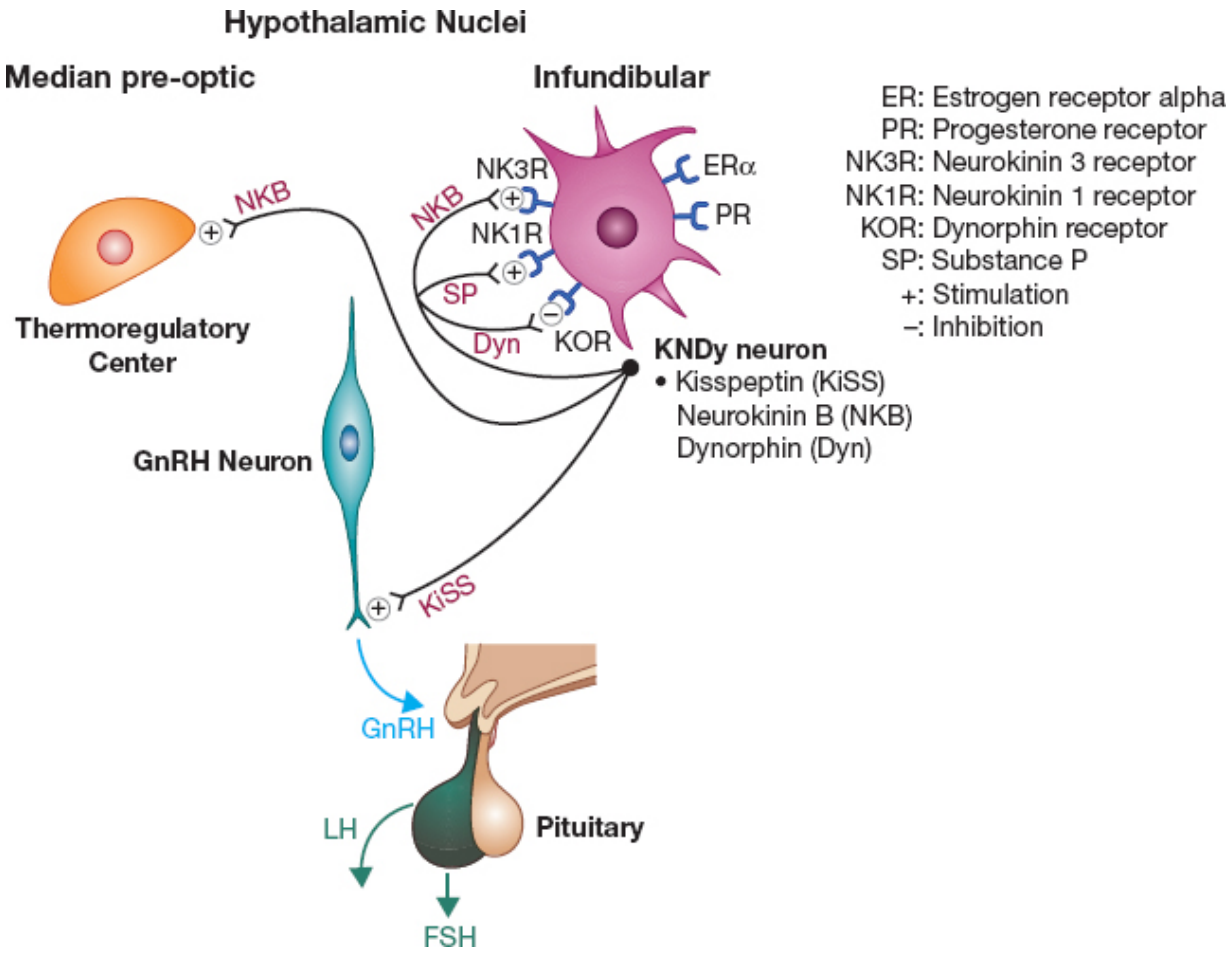


FIGURE 22.4 Hypothalamic neurokinin signaling as a mechanism for menopausal hot flush.

In the 1990s, the FDA began to regard the drugs coming from compounding pharmacies as falling under the "new drug" regulations, and therefore, the FDA had jurisdiction over the marketing and promotion of those drugs. The pharmacy world was immediately challenged; there was no way that an individual pharmacy could carry out the kind of clinical studies required for the approval of new drugs. Thus, the pharmacists immediately realized that all compounded drugs would be illegal. At the same time, the FDA was a bit ambivalent, acknowledging that there were

examples where the individual needs of a patient required the compounding of a drug, for example, the creation of a liquid preparation when none was available. This was before compounding took to the internet for marketing and promotion.

In 1992, the FDA issued its Compliance Policy Guide on Compounding, reserving a right for "selective enforcement," as a compromise between believing it was correct in assuming that compounded drugs represented new drugs and admitting that some patients required compounding. The pharmacy profession immediately rejected the idea that the FDA had any regulatory jurisdiction over pharmacies. The 1997 Food and Drug Modernization Act attempted to clarify the situation. An amendment was added to the existing laws stating that compounded drugs were not "new drugs," but at the same time, the 1997 act prohibited the marketing of compounded drugs.

The pharmacy profession sued the FDA, arguing that a restriction on advertising and promotion of compounded drugs was unconstitutional, a restriction of free speech. The District Court ruled against the FDA in 1999. The FDA appealed and lost again in the Ninth Circuit Court of Appeals, which further invalidated the entire 1997 act. In 2002 the U.S. Supreme Court upheld the Circuit Court decision.

The FDA issued a new Compliance Policy Guide in 2002, stating that selective enforcement would hinge on three major factors: (1) a potential adverse effect of a drug, (2) whether drugs were compounded from non–FDA-approved components, and (3) whether compounded drugs were similar to drugs already removed from the market for safety reasons. At this point, the FDA affirmed that it did not want to infringe on the traditional practice of compounding, the preparation of a drug according to a doctor's prescription to fit an individual patient's requirements.

Wyeth Pharmaceuticals filed a Citizen Petition with the FDA in October 2005 requesting that the FDA take action against several compounding pharmacies that were primarily internet based. The Petition's major allegation was that these pharmacies were essentially manufacturing new drugs and should be subject to new drug regulations. On January 9, 2008, the FDA announced it would take action against seven pharmacies providing prescription bioidentical hormones and issued warning letters that

potentially could be followed by seizures of drugs and injunctions against production.

The FDA would like to regard compounded drugs as “new drugs,” but the legal precedent has now been set by the courts: Compounded drugs are not “new drugs.” This was reaffirmed in a 2006 decision in the U.S. District Court for Texas. The FDA would further like to regard the giant compounding pharmacies, especially those operating over the internet, as manufacturers, like pharmaceutical companies, but again, the court decisions have prevented the FDA from requiring compounding pharmacies to meet “new drug” standards. The “new drug” argument does not work.

“Bioidentical” and “natural” are often used in concert. Strictly defined, to meet the definition of bioidentical, the hormones must reflect the endogenous milieu (ie, the right balance of estrone, estradiol, and estriol, the three endogenous estrogens) and natural progesterone (the progestational agent synthesized by the ovarian corpus luteum after ovulation) and right levels and ratio of circulating androgens (testosterone, androstenedione, and DHEA). The formulations that are available as bioidentical are created in compounding pharmacies and contain several of the aforementioned hormones, but neither the regimens nor the formulations are standardized. Furthermore, batch-to-batch variability in dosage is inherent.[100] The term *bioidentical* holds marketing value, erroneously implying greater safety and better efficacy. The situation is further complicated because consumers assume that the marketed formulation offers better efficacy and safety. This, however, is not the case as these compounded hormones are not subject to the same regulations as approved HT nor are there studies that have demonstrated long-term safety or better efficacy in comparison to the approved “natural” formulations.[394] The problem is that compounding pharmacies are not required to compare the formulation with the performance of an approved product, nor is there any way for a patient to be assured that the dosage is correct (that the drug contains what it is supposed to contain). Thus, there are no RCTs demonstrating safety and efficacy, let alone superiority to the approved formulations.[394]

Lay proponents of bioidentical compounded hormones often propose testing of salivary hormone levels to guide dosing of compounded formulations. Assessments of this approach by researchers, as well as

organizations such as the American College of Obstetricians and Gynecologists and the Endocrine Society, have concluded that the variations in salivary sex steroid levels from individual to individual and from specimen to specimen preclude clinical interpretation.[100,395–397] For the majority of patients, laboratory testing is not necessary in hormone decision-making. Furthermore, given the lack of scientific data demonstrating safety, the use of bioidentical hormones over approved HT regimens is not recommended.[398]

A Better Approach

The American Pharmacists Association and the National Association of Boards of Pharmacies define compounding as the steps required in order to provide a drug in response to a clinician's prescription according to an individual patient's needs and the preparation of drugs in anticipation of a demand. Therefore, there are three people involved: the patient, the clinician, and the pharmacist. This is in contrast to the production of large amounts of a drug for a national market of unknown users. **The American Pharmacists Association says that if an FDA-approved product is commercially available that meets a patient's needs, it should be the drug provided**.

The key to the position of the pharmacists is the contention that there are circumstances, decided by the patient, that make the use of commercial products not a good choice. This seems reasonable, but it is also reasonable that this decision requires the involvement of the clinician because ultimately a prescription is still required. The traditional view of compounding, therefore, is one of personal relationships with patient, clinician, and pharmacists. This becomes a totally different story when a large internet-based pharmacy responds to thousands of prescriptions with no knowledge of the patients. What happened to the "individualization" aspect of compounding? Is it practicing medicine by the pharmacy to have a registered clinician employed by the pharmacy to interpret hormone levels and adjust doses?

Clinicians are appropriately frustrated by the claims made that bioidentical compounded drugs have greater efficacy and safety. Bruce Patsner argues that it should be accepted that bioidentical drugs from the

big compounding pharmacies do not meet the definition of compounding supported by the pharmacist's own organization, the American Pharmacists Association: a personal relationship of patient, clinician, and pharmacist addressing an individual's needs.[399] The FDA can argue that the big operations are not legitimate compounding, but rather big commercial operations directed to unknown consumers.

Patsner also argues that the most vulnerable point is the false safety and efficacy claims. The contention should not be that the safety and efficacy claims are inaccurate, because the pharmacies can always compose their words to avoid legal assaults. The point of emphasis should go back to the pharmacist's published credo: If a commercial, approved product is available to meet the patient's needs, a compounded product is not indicated. Replacing a commercial product with a "natural," untested, unregulated product is not the same thing as prescribing a compounded product when no commercial product will meet the individual's needs.

Pastner summarizes his argument by saying that the large compounding pharmacies are not true compounders because they advertise and promote their products as replacements for commercially available, approved, and tested drugs and that the attempt at "individualization" uses an unsubstantiated method that marginalizes clinicians.[399]

The bioidentical hormones and the various commercial female hormone products are produced by pharmaceutical companies using similar methods that start from the same raw material, usually soy or yams. Some of the commercial products available consist of estradiol, testosterone, and progesterone, the exact same steroid drugs provided by compounding pharmacies. A major difference between the commercial products and products from compounding pharmacies is the important fact that commercial products are federally regulated and tested for purity and potency; compounding pharmacies have not been regulated in this manner.

The compounded estrogen formulations that contain combinations of estrone, estriol, and estradiol contain sufficient estradiol to produce the same biologic effects associated with commercial preparations. There are no clinical studies documenting that these combinations confer better results or safety. Whether the presence of estriol reduces the risk of breast cancer has not been tested in appropriate clinical studies. Case–control data indicate that estriol used without a progestational agent increases the risk of

endometrial cancer; thus, its biologic behavior is similar to that of other estrogens.[400]

Custom-compounded formulations have not been proven to be safer or better and, therefore, should not be regarded as having similar risks and benefits as commercial products. Claims for custom-compounded products have not been scientifically tested. Tailor-making an HT regimen according to salivary testing is an appealing idea that has not been addressed scientifically, and given the variability in salivary hormone levels, it is unlikely that clinical studies would yield useful information. Recommendations promoting customized compounded formulations individualized to salivary sex steroid hormone profiles thus should be viewed with cynicism as the salivary hormone levels vary widely between individuals and from measurement to measurement within the same individual. Books and pharmacies promoting their own products should similarly be viewed with caution. Patients who wish to use products similar to endogenous hormones should be made aware of the content of available commercial formulations and reassured that marketed and approved 17β estradiol and micronized progesterone formulations are indeed reliable bioidentical representatives. Books and pharmacies promoting their own products should be viewed with caution; do not confuse marketing with science.

ALTERNATIVE THERAPIES

The business of selling alternative therapies is now a worldwide phenomenon. The promotion of many of these treatments relies on a network of alternative providers, authors, and compounding pharmacies. Why are herbs and botanicals not regulated? In the United States, the Dietary Supplement Health and Education Act of 1994 deregulated the industry by classifying dietary supplements as neither foods nor drugs. Thus, manufacturers of dietary supplements are not required to demonstrate that they are safe or effective. In addition to a lack of regulation, there are many other problems associated with herbs and botanicals. The products vary in the amount and purity of active ingredients; indeed, products on the

shelf are often adulterated and contaminated with drugs or metals.[401] And very importantly, there is enormous variation in the plants themselves because of genetic, harvest year, and processing differences and in individual metabolism of the products.

Alternative Therapies for Vasomotor Symptoms: Phytoestrogens

"Phytoestrogens" is a descriptive term applied to nonsteroidal compounds that have estrogenic activity or are metabolized into compounds with estrogen activity. Phytoestrogens are classified into three groups: isoflavones, lignans, and coumestans.[402,403] They are present in about 300 plants, especially legumes, and bind to the ER. Soybeans, a rich source of phytoestrogens, contain isoflavones, the most common form of phytoestrogens. The isoflavones in soybeans are mainly genistein and daidzein, and a little glycitin.

Examples of phytoestrogens include the following:

- **Isoflavones (genistein, daidzein, glycitin): soybeans, lentils, chickpeas (garbanzo beans), and red clover**
- **Lignans: flaxseed, cereals, vegetables, and fruits**
- **Coumestans: sunflower seeds and bean sprouts**

Isoflavones exist in plants bound as glycoside conjugates attached at the three position, called *glycones*. The carbohydrate component requires gut bacteria to remove the sugar moiety to produce active compounds, the aglycones. Individual variability in gastrointestinal microflora, as well as absorption, influences the bioavailability of isoflavones. Biochanin and formononetin are methylated precursors that are metabolized to genistein and daidzein. Red clover and lentils contain significant amounts of these precursors. The isoflavones are in the active, deconjugated forms in fermented soy foods like miso and tempeh. The concentration of isoflavones in tofu is highly variable.

The phytoestrogens are characterized by mixed estrogenic and antiestrogenic actions, depending on the target tissue and local estrogen concentration. Variations in activity may also be due to the fact that the soy

phytoestrogens have a greater affinity for the ER-β compared with ER-α, although the affinity for the β-receptor is still only 35% that of estradiol.[404] Despite a low affinity for the α-receptor, circulating levels many times that of steroidal estrogens produce the potential for biologic activity.

You can eat soybeans every day and never see a bean. Soybeans are defatted to produce soy flour. Soy flour is then prepared to remove the carbohydrates. Ninety-five percent of soy flour is toasted and used as animal feed. Alcohol washing is used to get a taste-free product, but alcohol extraction removes the phytoestrogens.[405] SUPRO, known as "isolated soy protein," from Protein Technologies International, the major supplier for commercial products and research, is extracted by aqueous washing and retains the isoflavones.

The reason why most of the soybean crop is devoted to animal feed is because what is left after removing lipids is totally bland. The solution is to mix soybeans with other foods, for example, beans and soups. Unfortunately, they require standing in water for about 12 hours and simmering for 2 to 3 hours to be cooked. The average Japanese intake of isoflavones is about 50 mg/d.[406] The rest of Asia has an average consumption of about 25 to 45 mg/d, and Western consumption is less than 5 mg/d.[407,408]

Equol is the active metabolite in all phytoestrogens. Interestingly, not all individuals have the ability to convert phytoestrogens into their active metabolite.[344] Given conflicting results, regarding efficacy, routine use is not recommended, especially with data from a Cochrane review demonstrate no conclusive evidence.[344,409] Furthermore, phytoestrogens are **generally** contraindicated in women with hormone-dependent **cancers**, thromboembolic disease, or **CVD**, as the amount of estrogen from consumption of these products is not known.[344]

Other Alternative Therapies for Flushing

Red Clover

Promensil is an extract of red clover (*Trifolium pratense*) containing formononetin, biochanin, daidzein, and genistein. Formononetin and biochanin are metabolized to daidzein and genistein, respectively. Red clover is a legume used to enrich nitrogen levels in soils. Promensil is produced by Novogen in Australia and marketed by Solvay in the United

States. A 500-mg tablet contains 200 to 230 mg of dried extract, which contains 40 mg of isoflavones. Two randomized, placebo-controlled studies of the effect of Promensil on hot flushes were reported in 1999.[410,411] Neither demonstrated a significant difference compared with the placebo group. In one of the reports, 4 times the recommended dose (four tablets daily) also had no effect.[411] On the other hand, an appropriately designed Dutch study, two tablets daily, detected a significant reduction of flushing in a 12-week period of time.[412] A large placebo-controlled trial randomized 252 women with severe hot flushing to either Promensil (two tablets daily) or another red clover extract Rimostil (two tablets daily for an intake of 57-mg isoflavones).[413] The quantitative reduction in flushing (about 41% in 12 weeks) was identical in the Promensil, Rimostil, and placebo groups, although Promensil had a very slightly faster response. In another randomized clinical trial, the effect of red clover (a daily intake of 128-mg isoflavones) on VMS was no better than placebo treatment.[414] The best evidence indicates that the impact of red clover on VMS is the same as placebo treatment.

Why do these randomized, blinded, and placebo-controlled trials lack agreement? One reasonable explanation is that isoflavones have a mild impact on hot flushing, detectable only in women with frequent and severe flushing. A major clinical response should not be expected. Another possibility is the role of equol (see later discussion).

Dong Quai, Ginseng, and Vitamin E

Dong quai, a Chinese herb, is created from the root of the plant, *Angelica sinensis.*[352] One randomized, placebo-controlled trial examined the effect of dong quai on hot flushing, where no improvement in VMS or vulvovaginal symptoms was observed.[352] No estrogenic effects could be detected on flushing, endometrium, or vagina; furthermore, it could have potential adverse effects including light sensitivity and increased bleeding risk in those taking warfarin.[352] The effects of ginseng and vitamin E supplementation on VMS have been shown to be comparable to placebo.[351,353]

Evening Primrose

Evening primrose is often recommended for mastalgia, premenstrual syndrome (PMS), and menopausal symptoms. Evening primrose oil is extracted from the seed of the evening primrose; it provides linoleic and γ-linoleic acids (precursors of prostaglandin E). Appropriately blinded and controlled studies have failed to find any differences comparing primrose oil with placebo.[415–417]

Black Cohosh

Black cohosh (*Cimicifuga racemosa*), also called *black snakeroot and bugbane*, has been widely promoted to treat hot flashes. Most of the early reports supporting the efficacy of black cohosh were case series or studies without placebo-controlled groups, or the studies did not directly and quantitatively measure hot flushing. Black cohosh has been suggested to contain formononetin, a methylated precursor that is metabolized to the two primary phytoestrogens, genistein and daidzein. More sophisticated analysis, however, using liquid chromatography methods, has failed to detect the presence of formononetin in various black cohosh preparations, nor in black cohosh roots and rhizomes.[418]

An older clinical trial was noteworthy and alone in finding a similar impact on hot flushing with black cohosh and placebo treatment.[354] Well-designed trials are confirming that early study is providing us with a uniform story. The Herbal Alternatives for Menopause (HALT) study is centered in Seattle, Washington. This double-blind trial randomized 351 women to placebo or one of the four treatment groups: (1) black cohosh 160 mg daily (note the higher dose); (2) a multibotanical treatment containing 50-mg black cohosh, alfalfa, chaste tree, dong quai, false unicorn, licorice, oats, pomegranate, and Siberian ginseng, four capsules daily; (3) the multibotanical plus counseling to increase dietary soy intake; and (4) conjugated estrogens 0.625 mg with or without 2.5-mg MPA.[419] After 1 year, no differences were observed in hot flushing comparing any of the three herbal treatment groups to placebo.[419] The herbal remedies also had no effect on sleep quality as reported after 3 months.[420]

A randomized trial in Chicago compared black cohosh, 128 mg, and red clover, 120 mg, to standard HT and placebo treatment.[414] Over a period of 1 year, only HT reduced VMS greater than placebo. In this same clinical trial, neither black cohosh nor red clover had an impact on the measures of

cognition.[421] A Mayo Clinic study reported the results of a double-blind, randomized, crossover clinical trial to assess the efficacy of black cohosh for the treatment of menopausal hot flushes.[358] The dose was 20 mg b.i.d., the dose of the most commonly marketed black cohosh product in the United States. The similarity of the studied product with Remifemin was confirmed by high-performance liquid chromatography and proton nuclear magnetic resonance analysis. One hundred and thirty-two patients were treated for two 4-week crossover periods. Black cohosh reduced hot flushing scores by 20% in the fourth treatment week compared with 27% in the placebo group, and frequency was reduced 17% on black cohosh and 26% on placebo. A randomized trial in Australia found no difference between placebo and a combination of black cohosh with Chinese herbs.[422]

Black cohosh is not estrogenic, and black cohosh has no effect on menopausal symptoms.

An expert committee of the US Pharmacopoeia concluded that black cohosh may be associated with hepatotoxicity; however, a European review of cases with hepatotoxicity emphasized the difficulty in establishing a cause–effect relationship.[423,424] Hepatotoxicity remains a concern, awaiting the accumulation of definitive data.

Ginkgo Biloba

Ginkgo biloba is an extract prepared from the leaves of the *Ginkgo biloba* tree. It contains flavonoids and unique terpene lactones. *G. biloba* is a multimillion-dollar herb sold in the United States for the preservation of memory. In vitro studies suggested that ginkgo had antioxidant (from the flavonoids) and antiamyloid (from the lactones) effects. Indeed, the biologic studies provided a rationale for the use of ginkgo to prevent dementia.

A randomized, double-blind, placebo-controlled trial comparing *G. biloba* with placebo for the prevention of dementia enrolled 3,069 older individuals (over age 75) in five academic centers in the United States.[425,426] The participants were randomized to b.i.d. doses of 120-mg ginkgo or placebo (45% female in the ginkgo group and 47% female in the placebo group). The ginkgo formulation and dosage were that used in many of the brands sold in the United States. The dementia rate steadily increased in both groups over a 7-year period of follow-up, accumulating 277 (17.9%)

cases in the treatment group and 246 (16.1%) cases in the placebo group. The rate of dementia did not differ between the two groups, nor did the rate of Alzheimer disease. In addition, treatment with *G. biloba* did not produce less cognitive decline in adults with normal cognition or those with mild cognitive impairment. Other randomized trials have failed to demonstrate any beneficial effects on Alzheimer, learning, memory, attention, verbal fluency, or concentration.[427,428] Caution is warranted, however, when considering treatment in those with CVD, as it may be proarrhythmic; further studies in those with cardiac disease are needed.[429]

The American trial robustly demonstrated that *G. biloba* in the tested and commonly used dose did not delay the onset of dementia or cognitive decline.[425,426] The concept of "delay" is important. A treatment that could delay the onset of dementia by 5 years would reduce the number of dementia cases by 50%. In fact, this clinical trial found a statistically significant increase in the risk for developing dementia with ginkgo treatment in the 25% of participants who had CVD prior to enrollment. However, the authors appropriately urged caution in interpreting this subgroup analysis. **A Cochrane review in 2007 of 35 clinical trials with 4,247 participants concluded that there was no convincing evidence that ginkgo treatment benefited individuals who already had dementia or cognitive impairment.**[430]

More recently, a 2021 Romanian multicenter noninterventional study analyzed *G. biloba* from a different angle by recruiting patients with mild cognitive impairment to trial a standardized extract called *EGb761*. More than half of their study population were women, and they noted improvement in the Mini-Mental State Examination after 24 months. They noted that in patients with other mental health disorders, there was less of an improvement. Although results are encouraging, important to note that this was not a placebo-controlled study.[431]

St. John Wort

St. John wort has been reported to be comparable to tricyclic antidepressants in treating mild-to-moderate depression, based on eight appropriate trials.[432] This is the conclusion of two meta-analyses.[433,434] All studies were short term, lasting about 4 to 6 weeks, and with small

numbers. The treatment consisted of a 300-mg plant extract in tablet form, administered t.i.d. However, two large, American 8-week trials found no difference between treatment and placebo.[435,436]

A small, randomized, placebo-controlled Iranian study published in 2021 observed improvement in VMS and depressive symptoms after 2 months of treatment with *Hypericum perforatum* (St. John wort).[437] Despite the potential for benefit for some, St. John wort should be treated with an abundance of caution due to a risk for serious adverse effects. The FDA issued an alert in February 2000 that St. John wort may interact with drugs known to be metabolized by the cytochrome P450 pathway: theophylline, digoxin, immune suppressants, and oral contraceptives.[438,439] St. John wort activates an orphan receptor that induces the expression of metabolic enzymes.[440] In clinically depressed individuals being treated with prescription antidepressants, manic reactions can result (central serotonergic syndrome).

Phytoestrogens and Cardiovascular Disease

The cardiovascular story with phytoestrogens received a large boost in 1995, when a meta-analysis concluded that an intake of an average of 47-g soy protein per day lowered total cholesterol and LDL cholesterol.[441] This was supported by studies in the monkey indicating that isoflavone increased HDL cholesterol, enhanced vasodilation, and decreased atherosclerosis.[442]

Only intact soy protein has a beneficial effect on lipids. Separation of the protein component from dietary soy protein loses the effect, as noted early in the processing of soy. This effect depends on the inhibition of cholesterol absorption by the nonisoflavone protein.[443,444] The mechanism involves upregulation of the LDL cholesterol receptor and catabolism of LDL cholesterol, leading to an increase in bile excretion. The soy peptide binds bile acids and prevents resorption. Alcohol extraction removes the isoflavones from soy protein and causes a loss of the beneficial effect on atherosclerosis in monkeys.[445] Thus, both the isoflavone portion and the protein component are required for a full cardiovascular effect. Non–alcohol-washed soy protein extract has been extensively studied in monkeys. This preparation lowers total cholesterol and LDL cholesterol, raises HDL cholesterol,[446,447] produces coronary artery vasodilation,[448]

inhibits reduction in coronary flow after collagen induced platelet aggregation and serotonin release,[449] and inhibits atherosclerosis but not as robustly as estrogen.[442,447]

In women, soy protein reduces total and LDL cholesterol and does not affect triglycerides or HDL cholesterol. The ethanol-extracted soy protein also has no effect.[450–453] The minimal dose is about 60-mg isoflavones daily, which is present in 25 g soy protein per day.[454] LDL cholesterol must be above 130 mg/dL to have an effect. Studies of healthy men and women could detect no effect of phytoestrogens (25- to 80-mg isoflavones per day) on lipids or brachial vasodilation.[455–457] In a 12-week study of women with type 2 diabetes mellitus, dietary supplementation of 30-g soy protein (132-mg isoflavones) daily improved insulin resistance and glucose control in addition to lowering total and LDL cholesterol levels.[458] Soy intake also prevents LDL cholesterol oxidation in men and women with hyperlipidemia, even when circulating LDL cholesterol levels are unaffected.[459] Promensil (red clover extract), in a 10-week study, had no effect on lipids (it only contains isoflavones, no protein) but did improve arterial compliance.[460] A randomized, placebo-controlled trial of phytoestrogen examined the effects on progression of cIMT over a 2-year period in healthy early (n = 315, ages 40–55 years) and late (n = 231, ages 60–69) Russian postmenopausal women who were without evidence of CVD at baseline. The rate of cIMT progression was significantly lesser in the older postmenopausal population treated with phytoestrogens compared to placebo, suggesting antiatherosclerosis effects of phytoestrogens, finding that stand in contrast to those of ELITE wherein cardiovascular benefit from oral estradiol was observed only in the younger population of early postmenopausal women[461]; ELITE is further discussed later in this chapter. The FDA, in October 1999, authorized the use in food labeling of health claims related to the association between soy protein and reduced risk of CHD, “based on the totality of publicly available scientific evidence, soy protein included in a diet low in saturated fat and cholesterol may reduce the risk of CHD by lowering blood cholesterol levels.”[462]

Remember that both protein and isoflavones are needed for a cardiovascular effect. Isoflavones by themselves have no effect on lipids.[460,462–464] Proteins without isoflavones have no effect on vasodilation and atherosclerosis.[445] The FDA has stated that there is insufficient evidence

to allow them to exclude alcohol-washed products from the health claim, but it makes sense that a combined protein–isoflavone product is best. Even in older women with moderate hypercholesterolemia, a high intake of soy phytoestrogens (purified isoflavones without protein) had no effect on the lipid profile.[465] Also remember that there is no effect on the lipids in individuals who already have a normal profile. Even in individuals with high cholesterol levels, the beneficial impact of soy protein intake is modest and likely to have little clinical effect. A 2021 randomized, double-blind, placebo-controlled study analyzed the effect of soy isoflavones **daidzein and genistein** on lipids, high sensitive CRP, and uric acid levels in a cohort of Chinese women (*n* = 165, ages 30–70 years) with abnormal glucose regulation. At 12 and 24 weeks of intervention, no differences were seen between the intervention and placebo groups on any of the markers of interest.[466]

Another randomized crossover trial from the United States examined the effects of 8-week treatment with a specific peptide Lunasin that is present in soybeans, on cardiometabolic risk indices including fasting lipids, glucose, and anthropometric measures (body mass index [BMI] and waist circumference) in a small aging population (19 females and 12 males, mean age 61 ± 9.9 years). Based on the results of in vitro and animal studies, Lunasin is suggested to possess antioxidant, anticarcinogenic, and hypocholesterolemic properties; hence, cardiometabolic benefit was hypothesized from Lunasin intervention. There were nonsignificant reductions in cardiometabolic risk factors after 8 weeks of treatment with the use of Lunasin.[467]

It will require appropriate clinical trials to determine how phytoestrogens compare in the cardiovascular system with estrogens and to determine the efficacy, safety, and correct dosage. (Studies thus far recommend a daily intake of 60-g soy protein.) In addition, the intake of sufficient soy to produce a clinical response is not easy; intake is handicapped by gastrointestinal symptoms, a major alteration in diet or the use of an unpalatable supplement, and great variability in plant contents and products (due to processing). A dietary intake to match the isoflavone dose used in the studies on the lipid profile, for example, would require about 1 lb daily of tofu! In addition, individuals demonstrate great variability in absorption and metabolism. A user-friendly preparation must be developed

that minimizes individual variability in response. **Despite the abovementioned observations, a preventive role for soy intake against CVD remains to be proven.**

Phytoestrogens and Cognition

Phytoestrogens upregulate cognition markers and improve memory in rats equally when compared with estrogen.[468,469] Soy supplementation has been suggested to improve measurements of memory and attention in postmenopausal women.[470,471] On the other hand, the majority of randomized trials detected no effects of soy protein, red clover, or black cohosh on tests of memory, executive function, language, visual perception, cognition, or measures of quality of life.[421,457,472,473] On the contrary, there is one human study involving men that showed the opposite effect. In a U.S. National Institutes of Health (NIH) study that began in 1965, men reported on their tofu consumption.[474] Cognition was tested in 1991 to 1993 between the ages 71 and 93. Higher midlife tofu consumption (two or more servings per week) was associated with poor cognitive test performance, enlargement of ventricles, and low brain weight. **At the present time, there is no role of soy products for cognitive benefit.**

An Australian randomized, placebo-controlled, crossover trial undertaken in 125 postmenopausal women (mean age 65 ± 7 years) published in 2021 reported on the effects of resveratrol versus placebo on cognitive function (primary outcome) and middle cerebral artery blood flow and cardiometabolic indices (secondary outcomes).[475] Participants were randomized to 75 mg *trans*-resveratrol, a phytoestrogen, or placebo twice daily for 12 months and then crossover to the alternative treatment for another 12 months. A significant 33% improvement in cognitive performance was noted with resveratrol treatment compared to placebo. Furthermore, improvement in verbal memory was observed with resveratrol intervention in women aged 65 years or above compared to those younger than 65 years. In addition, improvements in cerebral blood flow and metabolic indices were also noted following treatment with resveratrol. Overall, the results of this Australian trial suggest that regular supplementation with low-dose resveratrol may offer cognitive and metabolic benefit in postmenopausal women.

Phytoestrogens and the Breast

In the parts of the world where soy intake is high, there is a lower incidence of breast, endometrial, and prostate cancers.[476] For example, a case–control study concluded that there was a 54% reduced risk of endometrial cancer, and another case–control study indicated a reduction in the risk of breast cancer in women with a high consumption of soy and other legumes.[477,478] Daidzein and genistein urinary excretion is lower in Australian women who develop breast cancer.[479] High soy and tofu consumption and high urinary excretion of isoflavones have been reported to be associated with a lower risk of breast cancer in Singapore, China, and Australia. There is even a lowered risk of breast cancer in American women consuming a diet rich in isoflavones.[478,480–484] These studies have supported the belief that high phytoestrogen intake protects against breast cancer. It is by no means certain, however, that there is a direct effect of soy intake.[485] Indeed, a 6-month study of the impact of administered soy protein on breast secretions in premenopausal and postmenopausal women revealed increased breast secretions with the appearance of hyperplastic epithelial cells.[486] Epithelial hyperplasia based on cytology in breast secretions was demonstrated in 7 (29.2%) of 24 subjects. Swedish and English cohort studies could not detect a relationship between dietary phytoestrogens and the risk of breast cancer.[487,488]

Genistein increases epidermal growth factor in immature rat mammary tissue, and it has been hypothesized that earlier exposure to genistein promotes early cell differentiation, leading to breast glands that are more resistant to the development of cancer.[489] On the other hand, using the chemically induced rat breast cancer model, no evidence of isoflavone inhibition on tumor development has been detected.[490] In the monkey, treated for 6 months, no proliferation was reported in either endometrium or mammary tissue.[491,492] A recent meta-analysis of the seven cohort and 17 case–control studies examined dose–response relationships between isoflavones and breast cancer risk and demonstrated a 29% decrease in odds for breast cancer when comparing the highest to the lowest isoflavone intake (summary odds ratio [OR] = 0.71, 95% CI = 0.72–0.81). A dose threshold for isoflavones was noted such that no benefit was evident at isoflavone doses less than 10 mg/d. In the dose–response meta-analysis of

the cohort studies, an inverse association between isoflavone intake and breast cancer was noted such that a 10 mg/d increase in isoflavone intake was related to nearly a 7% reduction in breast cancer risk (OR = 0.93, 95% CI = 0.90–0.96). The authors of this recent meta-analysis concluded that the present evidence demonstrates that dietary isoflavone is helpful in reducing breast cancer risk.[493]

One hypothesis speculates that phytoestrogens protect the breast by decreasing exposure to the more potent endogenous estrogens. High-dose treatment (100 mg of daidzein plus 100 mg genistein) does lower estradiol and DHEA-S levels in premenopausal women and increases cycle length.[494] However, these are extremely high doses. One study reported that treatment with Asian soy foods (~32-mg isoflavones per day) was associated with a 9.3% significant decrease in luteal serum estradiol levels, but there were no other changes, including follicular phase estradiol, progesterone levels, and SHBG levels, or cycle length.[495] Interestingly, the reduction in luteal estradiol was observed only in Asian participants in whom urinary excretion of isoflavones was higher than non-Asians.[495] These same investigators reported that a high intake of the soy protein alone (with the isoflavones removed) reduced estradiol and progesterone levels throughout the cycle.[496] Other studies have found no effects on estradiol, FSH, LH, or SHBG in premenopausal women[497] and, most importantly, no effects on circulating hormones in postmenopausal women.[498,499] The lack of an effect on gonadotropin and steroid levels is important, depriving the clinician of a method to assess dosage.

Catechol estrogens (2-hydroxyestrone and 4-hydroxyestrogens) have long been proposed as a metabolite pathway that could be protective or at least antiestrogenic. Hydroxylation in the 2 or 4 position produces inactive metabolites. In one study, eight premenopausal women treated with a soy milk supplement increased their urinary excretion of 2-hydroxyestrone by an average of 47%.[500] Another study could detect no change in 2-hydroxyestrogens.[497] A study limited to Asian American women also was unable to identify an impact of soy intake on overall estrogen metabolite excretion; however, an increase in catechol estrogens was observed with greater soy intake, balanced by a decrease in 16-hydroxylation.[501]

In response to soy, no significant increase in nipple aspirate levels of genistein and daidzein could be detected.[502] However, an indication of

estrogenic stimulation occurred, as measured by pS2 (a protein upregulated by estrogen) levels, but there was no evidence of an effect on epithelial cell proliferation, ER and PR, apoptosis, or mitosis. Thus, no antiestrogenic effect could be detected, and at best, there was a very weak estrogen effect. In another study, 48 women with normal breasts received a 60-g soy supplement for 14 days, and in these women, lobular epithelial proliferation and PR expression increased, an indication of estrogen stimulation.[503] Some argue that the key to a beneficial impact on the breast may be early exposure, and a sudden increase late in life of dietary phytoestrogens may be harmful. On the other hand, a Chinese cohort study of 5,042 breast cancer survivors documented a reduced risk of recurrence and death associated with increasing levels of soy intake, evident among women with either ER-positive or ER-negative disease and among either tamoxifen users or nonusers.[504] In an American cohort of 1,954 breast cancer survivors, a 60% greater decrease in breast cancer recurrence was observed in postmenopausal women using tamoxifen comparing the highest level of soy intake with the lowest.[505] **Most of the evidence indicates that a high intake of phytoestrogens is associated with a reduced risk of breast cancer, including recurrence in breast cancer survivors. It is not known whether this effect is a marker for beneficial metabolic responses to phytoestrogens or whether there is a direct impact on breast tissue. The evidence also indicates that phytoestrogen consumption does not adversely interfere with tamoxifen's mechanism of action.**

TABLE 22.5 Summary of Phytoestrogen Clinical Effects

Flushes	Insignificant effect
Coronary heart disease	Weak impact
Bone	No effect
Cognition—Maybe protective	Unknown
Breast	May be protective
Endometrium	No effect

Vagina	No effect

There is agreement that phytoestrogens have no effects on the uterus or vagina.[352,410,411,463,498,499,506–510] **A beneficial effect on vaginal dryness and dyspareunia cannot be expected; however, the lack of a proliferative stimulus on the endometrium is a wanted consequence of phytoestrogen supplementation** (**Table 22.5**).

Currently, the recommended intake expected to have some effect on CHD is 50 to 60 mg isoflavones per day, an amount that is in 25 g of soy protein aqueous extract. A beneficial impact on CHD in women with abnormal lipid profiles is to be expected, a consequence of a decrease in total and LDL cholesterol and an increase in vascular reaction, but the actual clinical effect is unknown. Excess intake can cause gastrointestinal upset and flatulence, inhibition of enzymes necessary for the digestion of proteins, possibly obstruction of mineral uptake, and weight gain.

The Role of Equol

Equol is a bacterial metabolite and the only hormonally active metabolite of the soy phytoestrogen, daidzein. It is one of the estrogenic compounds in pregnant mare's urine, hence its name. At least in vitro, equol stimulates gene transcription with both ERs and with a greater potency than any other isoflavone.[511] Equol formation is totally dependent on intestinal microflora; therefore, strictly speaking, it is not a phytoestrogen. To be accurate, equol is a nonsteroidal estrogen, a member of the isoflavone family, and exclusively a metabolic product of intestinal bacteria.

The most important observation regarding equol is that 30% to 50% of adults do not produce equol, even when challenged with high doses of soy.[512] This is in contrast to nonhuman primates and other animals; all that have been studied produce high levels of equol. Thus, there are two human populations: equol producers and equol nonproducers. The key question is whether equol producers receive greater clinical effects from phytoestrogens than nonequol producers. As noted, thus far, the clinical effects of isoflavones on the bone have not been impressive. In a 2-year randomized trial of postmenopausal women, isoflavone-rich soy milk

increased spinal bone mass in the 45% of the subjects who were equol producers, with essentially no effect in equol nonproducers.[513] More profound beneficial effects on the lipid profile have been reported in equol-producing women.[512] Therefore, the population destined to receive a benefit from soy intake may be limited to equol producers. Studies need to be repeated, measuring the responses in individuals who are identified as equol producers or equol nonproducers. If the population destined to receive a benefit from soy intake is limited to equol producers, a convenient, inexpensive method must be developed to identify equol production. In addition, it may be possible to convert nonproducers to producers. However, at least one study did not show a difference in cognitive performance between equol producers versus nonproducer, but this same study did show a greater improvement in VMS with equol producers.[514]

An emerging approach is to administer equol itself. Daidzein yields two forms of equol, the *R*-equol inactive isomer and *S*-equol, the active isomer that binds to ER-β. *S*-Equol has been synthesized, and its administration is effective for the treatment of menopausal symptoms.[515] Another alternative is the *S*-equol supplement made by incubating equol-producing bacteria with soy isoflavones.[516,517] *S*-equol also blocks the activity of dihydrotestosterone, and thus, it has potential to treat androgenic effects, such as acne, hirsutism, male pattern baldness, and prostate cancer.[518] At this time, due to the absence of high-quality evidence, testing to differentiate between equal producers versus nonproducers cannot be recommended.

Estriol

Interest in estriol can be traced to Lemon's report in 1975 that estriol limited the growth of breast tumors in the chemical-induced rat tumor model. However, it is usually overlooked that estradiol worked equally well in that model. Estriol treatment of postmenopausal women has no overall effect on lipids and no effect in the prevention of myocardial infarction.[519,520] Estriol, without concomitant progestin treatment, does increase the risk of endometrial cancer with the long-term oral use of 1 to 2 mg/d.[400] At least two studies have been unable to demonstrate prevention of bone loss with the administration of 2-mg estriol daily.[12,13] Moreover, one

case–control study found no reduction in hip fractures with estriol compared with a lower risk with estradiol.[520] *There is no evidence indicating any beneficial effects unique to estriol.*

Transdermal Progesterone

Transdermal (or percutaneous) compounded progesterone cream has been erroneously promoted to have multiple benefits. In order to achieve widespread effects, absorption must yield adequate blood levels. Two English randomized, blinded, placebo-controlled studies used b.i.d. to 4 times the recommended dose and reported blood levels of about 1 ng/mL, supported by very low urinary pregnanediol levels.[521,522] An American study achieved progesterone blood levels of 2 to 3 ng/mL with application twice daily.[523] A 1-year Italian study did not measure blood levels but could detect no effects on bone density, lipid profiles, or depression scores.[524]

These studies indicate very little systemic absorption of progesterone from the cream product (the levels do not reach normal luteal phase concentrations), and there is great variability.

An English randomized clinical trial using transdermal doses of 5, 20, 40, and 60-mg progesterone cream could detect no differences in measures of psychological symptoms, somatic symptoms, and VMS compared with placebo.[525] An Australian study of 16, 32, or 64-mg transdermal progesterone cream administered daily could detect no significant absorption and, most importantly, no endometrial response and no effect on flushes, lipids, bone, moods, or sexuality.[526,527] Incidentally, this study found salivary progesterone levels to be so variable that they had no meaning. Progesterone cream can produce high salivary levels, without a significant change in serum or urinary levels (the mechanism is unknown).[528,529] Red cell levels reflect serum levels and do not indicate preferential transport or sequestration.[529] Wild yam creams are marketed as progesterone precursors or “balancing” formulas. Yam contains diosgenin, a plant steroid that can be converted to progesterone in a chemical laboratory but not in the human body. Predictably, a wild yam cream has no effects on a wide range of measurements in postmenopausal women.[508] Some do contain progesterone, added by the manufacturer. Creams with less than 0.016% progesterone can

be sold over the counter. There is no evidence to indicate that these preparations produce systemic effects.

Better absorption is provided by progesterone gels, an alcoholic solution with hydroxypropyl methylcellulose and water.[509] With a 100-mg dose of a progesterone gel, serum progesterone levels are well into the luteal phase range, but clinical use awaits studies documenting the impact on the endometrium.[530]

Clinicians and patients should be aware that transdermal progesterone cream will not reduce hot flashes more than a placebo response, but most importantly, this treatment will not protect the endometrium against the risk of endometrial cancer associated with ET.

Lastly, for women with VMS, additional nonpharmacologic options include environmental and lifestyle changes. Remaining in a cool environment and weight loss have been shown to decrease the number of hot flushes. Complementary and alternative medicine can also be attempted; however, treatments with dong quai, ginseng, black cohosh, isoflavones (including soy protein), yoga, and acupuncture with placebo treatment.[352–362]

Key points: Vasomotor Symptom Management

- HT remains the most effective of available therapeutic options for managing VMS.
- In patients in whom HT is contraindicated, nonhormonal pharmaceuticals can be effective against VMS.
- Patients and providers should be reassured regarding availability of effective standardized and approved bioidentical HT formulations.
- Utilization by patients of nonstandardized, unapproved compounded formulations that are being advertised direct to consumers is to be discouraged due to concerns regarding safety, uncertain dosing or content, as well as effectiveness of such products.
- Benefit of alternative therapies is at best minimal, if any.

MANAGING BLEEDING DURING MENOPAUSAL HORMONE THERAPY

With sequential therapy, approximately 80% to 90% of women experience monthly withdrawal bleeding. With continuous, combined estrogen–progestin therapy, one can expect 40% to 60% of patients to experience breakthrough bleeding during the first 6 months of treatment; however, this percentage decreases to 10% to 20% after 1 year.[110,111,531] Although this percentage of amenorrhea with continuous, combined therapy is a gratifying accomplishment, the number of women who experience breakthrough bleeding is considerable, and it is a difficult management problem. Indeed, the single most aggravating and worrisome problem with daily, continuous therapy is this breakthrough bleeding.

Why call it breakthrough bleeding? The bleeding experienced by women on continuous, combined therapy is similar to that seen with oral contraceptives. It originates from an endometrium dominated by progestational influence; hence, the endometrium is usually atrophic, and yields little, if anything, to the exploring biopsy instrument. Breakthrough bleeding is due to a progestational effect on vascular strength and integrity, producing a fragility that is prone to breakdown and bleeding. It is helpful to explain to patients that this bleeding represents tissue breakdown as the endometrium adjusts to its new hormonal stimulation. From our experience with oral contraceptives, we have learned to be comfortable with this type of bleeding. We have learned that for most patients, the incidence of breakthrough bleeding with oral contraceptives is greatest in the first few months of treatment and usually disappears in the majority of women. Indeed, this is the same pattern exhibited by postmenopausal women on continuous, combined therapy, and therefore, the most effective management strategy is patient education and support.

It is common for women on a sequential regimen to begin bleeding during progestin administration. The timing of withdrawal bleeding in women on a sequential estrogen–progestin program was suggested as a screening method for biopsy decision-making. In women taking a variety of progestins for 12 days each month, bleeding on or before day 10 after the addition of the progestin was associated with proliferative endometrium. Bleeding beginning on day 11 or later was associated with secretory

endometrium, presumably indicating less need for biopsy.[532] But does this correlate with the risk of hyperplasia and cancer? According to a study of 413 postmenopausal women, the day of bleeding did not predict endometrial safety.[533] Late regular withdrawal bleeding on a sequential program does not give 100% assurance that there is no hyperplasia and perhaps endometrial cancer. This uncertainty with the sequential program is another reason to turn to the daily, combined method where irregular bleeding and sonographic measurement of increased endometrial thickness provide good indications for endometrial biopsy.

Evaluation of abnormal uterine bleeding in the setting of hormone use is identical to the paradigm discussed earlier in this chapter. The thickness of the postmenopausal endometrium as measured by transvaginal ultrasound (TVUS) in postmenopausal women correlates with the presence or absence of pathology. However, the severity of pathologic change does not correlate with the measured thickness.[534] Endometrial thickness (the two layers of the anterior and posterior walls in the longitudinal axis) 4 mm or less is highly[535] reassuring (negative predictive value >99%), supported by the American College of Obstetricians and Gynecologists, and allows conservative management.[536–540]

It is estimated that 50% to 75% of patients experiencing abnormal uterine bleeding on HT and evaluated by TVUS will eventually require a biopsy.[534,538] It seems logical that endometrial thickness by TVUS in patients on a sequential regimen can be affected by day in the treatment cycle, and for that reason, ultrasonography assessment should be obtained toward the end of the progestin phase or at the beginning of the cycle.[541,542] An Italian study concluded that endometrial thickness measured soon after withdrawal bleeding in women on a sequential regimen was comparable to thickness in women on a continuous, combined program of estrogen–progestin treatment.[543] When a thick endometrium is associated with atrophic endometrium on biopsy, polyps or submucous myomas should be suspected. A thorough curettage can miss such pathology, and either an SHBG or hysteroscopy should be considered the next step as discussed earlier.[544] Doppler velocimetry does not improve the accuracy of discriminating between normal and abnormal endometrium.[545] **A clinician should not be satisfied with “normal” findings on ultrasonography if a patient has persistent bleeding. The pursuit of abnormal bleeding**

despite “normal” findings should reduce missed cases of pathology to nearly zero.[546] **In this circumstance, hysteroscopy is recommended.**

There is no effective method supported by clinical studies, or a large experience, of drug alteration or substitution to manage breakthrough bleeding. The breakthrough bleeding rate is only slightly better with a higher dose of progestin (5.0 mg MPA) than with a lower dose (2.5 mg).[110,531] Therefore, there is not a strong reason to use the higher dose, thus minimizing side effects. The best approach is to gain time, because most patients will cease bleeding. This means good educational preparation of the patient beforehand and frequent contact to allay anxiety and encourage persistence. Estrogen–progestin combinations that contain a 19-nortestosterone progestin (eg, NETA) demonstrate the same pattern of bleeding, but fewer patients bleed in the first 6 months and the amenorrhea rate by 1 year is higher than with other regimens.[547–549]

There is a subgroup of patients (10–20% at the end of 1 year) who continue to experience breakthrough bleeding. The closer a patient is to having been bleeding (either to their premenopausal state or to having been on a sequential method with withdrawal bleeding), the more likely that patient will experience breakthrough bleeding. Some clinicians, therefore, prefer to start patients near the menopause on the sequential method and convert to the continuous method some years later. Some patients may choose progestin IUD as a preferred HT strategy. The local release of progestin is effective in suppressing endometrial response and preventing unscheduled bleeding in the long term. The LNG-IUD in menopausal women can be left in place for up to 10 years, a decided advantage.[148,550] **A combined estrogen–progestin program, however, will not totally prevent endometrial cancer.**[551] **Vigilance on the part of the clinician, however, will detect endometrial cancer at an early stage, a stage that can be treated with excellent results**.

For the smaller subset of hormone-using menopausal women who are bothered by persistent unscheduled bleeding that remains unresponsive to earlier-mentioned strategies, consideration for definitive surgery (such as vaginal hysterectomy) may not be unreasonable.

HEALTH IMPLICATIONS OF MENOPAUSAL HORMONE THERAPY

Cardiovascular Effects[552]

A Favorable Impact on Lipids and Lipoproteins

The most important lipid effects of postmenopausal estrogen treatment are the reduction in LDL cholesterol and the increase in HDL cholesterol. Estrogen increases triglyceride levels and LDL cholesterol catabolism as well as lipoprotein receptor numbers and activity, resulting in decreasing LDL cholesterol levels.[553–555] Estrogen induces a change in LDL cholesterol toward a smaller more dense particle, but it is in a form with a more rapid turnover in the circulation, allowing less time for oxidation and acquisition of cholesterol.[556,557] The increase in HDL cholesterol levels, particularly due to the HDL_2 subfraction, is to an important degree the consequence of the inhibition of hepatic lipase activity, which converts HDL_2 to HDL_3 (**Figure 22.5**). Postmenopausal ET with or without added progestin also produces a reduction in the circulating levels of lipoprotein(a).[558,559]

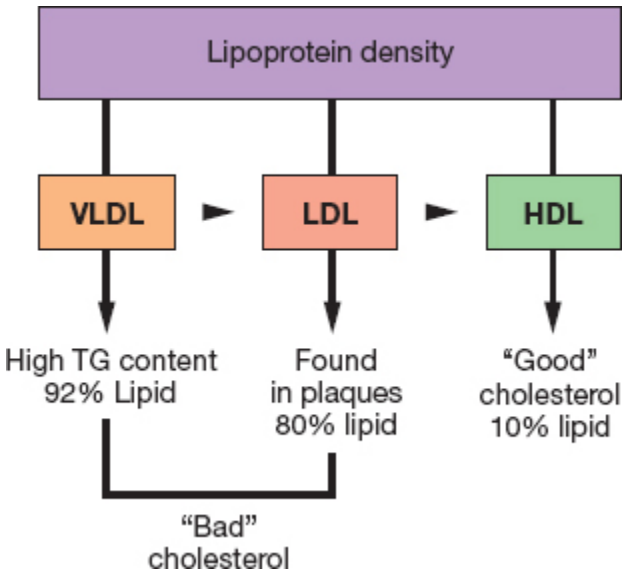


FIGURE 22.5

The changes in circulating apoprotein levels mirror those of the lipoproteins: Apolipoprotein B (the principal surface protein of LDL cholesterol) levels diminish in response to estrogen, and apolipoprotein A-I (the principal apolipoprotein of HDL cholesterol) increases. The positive effects of estrogens on cholesterol may be mitigated by the concomitant use of progestins.[111,113,560–565] In an interesting approach to understanding the differential in cardiovascular risks noted in the two WHI hormone trials (CEE+MPA and CEE alone), ametabolomic analysis was undertaken at baseline and 1-year samples in 503 and 431 participants in the WHI CEE and CEE+MPA trial, and relevance of differentially altered metabolites by type of HT (CEE alone vs CEE+MPA) was evaluated for an association with incident CHD in 944 participants (472 CHD cases) of the WHI-OS; these associations were further confirmed in an independent replication cohort of 980 participants (men and women) in the PREDIMED trial (Prevención con Dieta Mediterránea) deemed at high risk for CHD. A differential effect of HT regimen on the metabolome was apparent. Twelve metabolites had discordant effects by HT and were associated with incident CHD in the WHI-OS. All 12 metabolites were altered in the CHD protective direction by CEE exposure, whereas a single metabolite (lysine) was significantly altered in the direction of increased CHD risk by CEE+MPA exposure. Associations of a subset of four metabolites (C58:11 triacylglycerol, C54:9 triacylglycerol, C36:1 phosphatidylcholine, and sucrose) were replicated in the PREDIMED population.[566]

The concomitant administration of estrogen and an HMG-CoA reductase inhibitor (such as pravastatin) produced a more favorable change in the lipid profile in women with hypercholesterolemia than either treatment alone.[567]

Direct Antiatherosclerotic Effects

Studies in nonhuman primates (such as monkeys) have suggested that estrogen may have antiatherosclerotic effects that are independent of the cholesterol–lipoprotein profile. Oral administration of a combination of estrogen and a high dose of progestin to monkeys fed a high-cholesterol diet decreased the extent of coronary atherosclerosis despite a reduction in HDL cholesterol levels.[568–570] In somewhat similar experiments, estrogen treatment markedly prevented arterial lesion development in rabbits, and

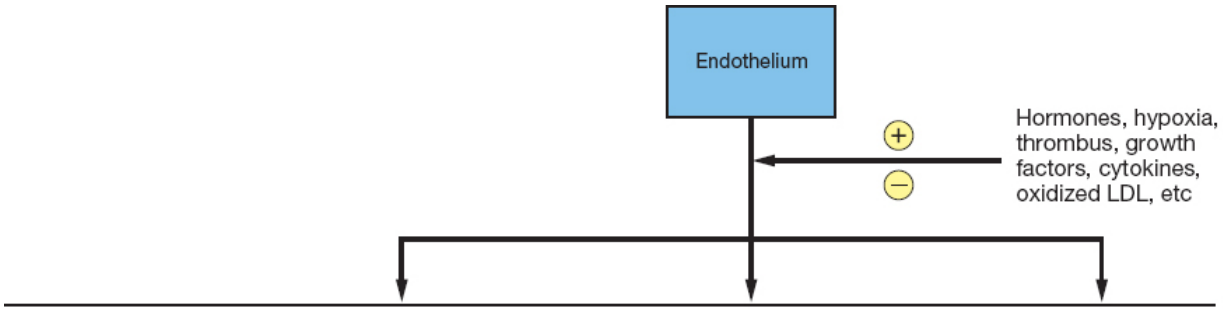
this effect was not reduced by adding progestin to the treatment regimen.[571–574]

The monkey studies were extended to a postmenopausal model (ovariectomized monkeys). Compared with no hormone treatment, treatment with either estrogen alone or estrogen with progesterone in a sequential manner significantly reduced atherosclerosis, once again independently of the circulating lipid and lipoprotein profile.[575,576] A direct inhibition of LDL cholesterol accumulation and an increase in LDL cholesterol metabolism in arterial vessels could be demonstrated in these monkeys being fed a highly atherogenic diet.[577] The daily administration of MPA in this monkey model did not prevent the beneficial effect of CEE on coronary artery atherosclerosis.[442]

Estradiol fatty acid esters are present in low concentrations in the circulation, transported in lipoproteins. These esters are potent estrogens and protect against the oxidation of LDL cholesterol; the antioxidant efficacy of estradiol may require esterification and incorporation into LDL cholesterol.[578] Estradiol fatty acid ester concentrations are increased by oral estrogen, but not by transdermal administration.[579]

Endothelium-Dependent Vasodilation and Antiplatelet Aggregation (see Figure 22.6)

Endothelium modulates the degree of contraction and function of the surrounding smooth muscle, primarily by the release of endothelium-derived relaxing and contracting factors. In hypertension and other CVDs, the release of relaxing factors (such as nitric oxide) is blunted, and the release of contracting factors (the most important being endothelin-1) is augmented. The endothelins are a family of peptides that act in a paracrine manner on smooth muscle cells. Endothelin-1 appears to be exclusively synthesized by endothelial cells. Endothelin-induced vasoconstriction is a consequence of a direct action on vascular smooth muscle cells, an action that is reversed by nitric oxide. Impaired release of nitric oxide, therefore, enhances endothelin action. Hypertension and atherosclerosis are believed to be influenced by the balance among these factors. Women have lower circulating levels of endothelin, which decrease in response to oral and transdermal estrogen treatment.[580,581]



	Endothelin-1	Nitric oxide	Prostacyclin
Flow	Vasoconstriction	Vasodilation	Vasodilation
Platelet activity	Increases adhesion and aggregation	Inhibits adhesion	Inhibits aggregation
Vessel changes	Stimulates smooth muscle proliferation and migration	Inhibits smooth muscle proliferation and migration	Inhibits smooth muscle proliferation and migration

FIGURE 22.6

Nitric oxide (and estrogen) also inhibits the adhesion and aggregation of platelets in a synergistic manner with prostacyclin (also a potent vasodilator derived from the endothelium).[582,583] Increased blood flow due to vasodilation and decreased peripheral resistance can be observed to occur rapidly following the administration of estrogen. This response can be produced by both transdermal and oral administration.[584–586] The synthesis and secretion of nitric oxide (the potent endothelial vasodilating product) can be directly stimulated by estrogen in in vitro experimental preparations of coronary arteries.[587] In both normotensive postmenopausal women and women with hypertension, hypercholesterolemia, diabetes mellitus, or coronary artery disease, the intra-arterial infusion of physiologic amounts of estradiol into the forearm potentiates endothelium-dependent vasodilation, and there is a dose–response effect.[588,589] Similarly, brachial artery dilation has been reported with 0.3 and 0.625 mg conjugated estrogens.[590] Comparing brachial artery responses in HT users versus nonusers (estrogens with/without progestin), improved endothelium-dependent vasodilation was observed with standard doses.[591] Furthermore, the addition of NETA or MPA did not reduce the beneficial effect of estrogen on peripheral artery blood flow.[592,593] However, not all studies agree. A Danish assessment of brachial artery responses demonstrated no difference between

postmenopausal women on long-term combined estrogen–progestin therapy compared with those receiving no treatment.[594]

The synthesis of nitric oxide is involved in the regulation of vascular (and gastrointestinal) tone and neuronal activity. A family of isozymes (nitric oxide synthases) catalyzes the oxidation of L-arginine to nitric oxide and citrulline. The action of nitric oxide synthase in the endothelium is calcium dependent.[595] In animal experiments, the endothelial basal release of nitric oxide is greater in females, a gender difference that is mediated by estrogen.[587,596] In women treated with postmenopausal estrogen and either cyproterone acetate or MPA, circulating nitric oxide (as reflected in nitrite–nitrate levels) is increased, a consequence of estrogen-induced nitric oxide production in the endothelium.[597,598] In contrast, long-term treatment with estradiol and NETA was not associated with changes in nitric oxide, endothelin-1, prostacyclin, or thromboxane A_2, suggesting that different progestins have differential effects.[599]

Acetylcholine induces vasoconstriction in coronary arteries; however, the direct administration of estradiol in physiologic doses into the coronary arteries of postmenopausal women with and without CHD converts acetylcholine-induced vasoconstriction into vasodilation with increased flow.[600] This favorable vasomotor response to acetylcholine can also be demonstrated in acute experiments with transdermal administration of estradiol (achieving blood levels of 67–89 pg/mL).[601] This is an endothelium-dependent response, mediated to a significant degree by an increase in nitric oxide.[602] In the monkey, the vasodilatory response to acetylcholine required a blood level of estradiol higher than 60 pg/mL.[603]

Endothelium-Independent Vasodilation

Estrogen causes relaxation in coronary arteries that are denuded of endothelium.[604] This response is not prevented by the presence of inhibitors of nitric oxide synthase or prostaglandin synthase, thus suggesting that some degree of vasodilation in response to estrogen is achieved through a mechanism that is independent of the vascular endothelium, perhaps acting via calcium-mediated events.[605] The vasodilation produced by sodium nitroprusside is endothelium-independent. In otherwise healthy postmenopausal women and in those with risk factors for atherosclerosis

(hypertension, hypercholesterolemia, diabetes mellitus, coronary artery disease), administration of physiologic doses of estradiol increased forearm vasodilation induced by sodium nitroprusside.[588] However, others have reported no effect of estrogen administration on endothelium-independent vasodilation.[586]

Actions on the Heart and Large Blood Vessels

Estrogen treatment in some studies was associated with increased left ventricular diastolic filling and stroke volume,[586,606–608] an effect that probably reflects a direct inotropic action of estrogen.[609] In a 3-month study, MPA (5 mg daily for 10 days each month) did not attenuate the increase in left ventricular output (systolic flow velocity) observed with estrogen treatment.[610] On the other hand, others have detected attenuation of estrogen's beneficial effects on compliance (stiffness) associated with combined estrogen–progestin treatment.[609,611] And others have not been able to demonstrate an effect of short-term oral estrogen or long-term transdermal estrogen treatment on cardiac structure and function.[612,613] The reasons for these observations as well as the differences remain unclear.

Actions on Glucose Metabolism

An age-related decline in the basal metabolic rate is accentuated at menopause, associated with an increase in body fat, especially central (android) body fat.[614,615] Insulin resistance and circulating insulin levels increase in women after menopause, and impaired glucose tolerance predicts an increased risk of CHD.[616,617] Estrogen (with or without progestin) prevents the tendency to increase central body fat with aging.[618–621] The WHI randomized clinical trial documented improvements in fasting glucose and insulin levels in the estrogen/progestin-treated group.[622] Hyperinsulinemia also has a direct atherogenic effect on blood vessels, perhaps secondary to insulin propeptides. In addition to its vasoconstrictive properties, endothelin-1 exerts a mitogenic effect and, therefore, contributes to the atherosclerotic process. Insulin directly stimulates the secretion of endothelin-1 in endothelial cells, and the circulating levels of endothelin-1 are correlated with insulin levels.[623]

Postmenopausal women being treated with oral estrogen have lower fasting insulin levels and a lesser insulin response to glucose.[562,622–627] In a 1-

year randomized trial comparing unopposed conjugated estrogens to the usual sequential and continuous regimens of conjugated estrogens and MPA, no differences in the treatment groups were observed in the favorable decreases in fasting insulin levels.[562] Nonoral administration of estrogen has little effect on insulin metabolism, unless a dose is administered that is equivalent to 1.25 mg conjugated estrogens.[625,628] Because a lower oral dose produces a beneficial impact, this suggests that the hepatic first-pass effect is important in this response, at least in normal women; reports with transdermal HT have indicated improvements in insulin resistance and hyperinsulinemia, but no effect in women with normal insulin sensitivity.[629,630] In double-blind, crossover, placebo-controlled studies of postmenopausal women with type 2, non–insulin-dependent diabetes mellitus, estrogen treatment improved all glucose metabolic parameters (including insulin resistance), the lipoprotein profile, and measurements of androgenicity.[631,632]

The evidence strongly indicates that postmenopausal ET improves glucose metabolism. Epidemiologic studies impressively document that this beneficial metabolic effect associated with estrogen lowers the incidence of adult-onset, type 2 diabetes mellitus. Three large cohort studies, the Nurses' Health Study, the Finnish Kuopio Osteoporosis Risk Factor and Prevention Study, and the French E3N study, reported decreases in new-onset diabetes associated with ET.[633–635] In the French cohort, no effect of progestins was observed, and the reduction in the incidence of diabetes (32%) was greater with oral administration of estrogen compared with the transdermal method.[635] Clinical trial results are in agreement. In the Heart and Estrogen–Progestin Replacement Study (HERS) trial, the hormone-treated group developed diabetes at a rate that was 35% lower compared with the placebo group.[627] Similar findings were observed in the WHI hormone trials wherein a 21% reduction in incident diabetes was observed in the combined CEE and MPA trial, whereas a 12% reduction with the estrogen-alone trial.[68,636]

Inhibition of Lipoprotein Oxidation

The oxidation of LDL cholesterol particles is a step (perhaps the initial step) in the formation of atherosclerosis, and smoking is associated with a high level of lipoprotein oxidation. In animal experiments, the

administration of large amounts of antioxidants inhibits the formation of atherosclerosis and causes the regression of existing lesions. Estrogen is an antioxidant. Estradiol directly inhibits LDL cholesterol oxidation in response to copper and decreases the overall formation of lipid oxides.[637,638] Importantly, this antioxidant action of estradiol is associated with physiologic blood levels.[639] In addition, estrogen may regenerate circulating antioxidants (tocopherols and β-carotene) and preserve these antioxidants within LDL cholesterol particles. This antioxidant action of estrogen preserves endothelial-dependent vasodilator function by preventing the deleterious effect that oxidized LDL cholesterol has on endothelial production of vasoactive agents.[640] In an assessment of peroxide formation by platelets, women treated with both estrogen and MPA in a sequential regimen had greater antioxidant activity compared with the days on estrogen alone.[641] In a 1-year study, the presence of LNG did not attenuate the antioxidant activity of estradiol.[642]

A Favorable Impact on Fibrinolysis

Menopause is followed by increases in factor VII, fibrinogen, and plasminogen activator inhibitor-1 (PAI-1).[643,644] These changes produce a relatively hypercoagulable state and are associated with an increased risk of cardiovascular events. Postmenopausal women treated with estrogen have lower fibrinogen and plasminogen levels. Reduced levels of fibrinogen, factor VII, and PAI-1 have been observed in premenopausal women compared with postmenopausal women, and oral estrogen alone or combined with a progestin prevents the usual increase in these clotting factors associated with menopause.[645–649] This would be consistent with increased fibrinolytic activity, a possible cardioprotective mechanism probably mediated, at least partially, by nitric oxide and prostacyclin. Platelet aggregation is also reduced by postmenopausal estrogen treatment, and this response is slightly attenuated by MPA.[582] In a randomized 1-year trial, the addition of MPA, either sequentially or continuously, produced a more favorable change in coagulation factors compared with unopposed estrogen.[650]

The transdermal and oral routes of administration of estrogen (combined with MPA) have puzzling differences in the reported effects on most hemostatic risk factors, such as factor VII, fibrinogen, PAI-1, and

antithrombin III. In at least one study, antithrombin III levels were reduced by oral estrogen, but not by transdermal administration; however, the values remained within the normal range.[651] In regard to PAI-1, studies with transdermal estrogen have provided conflicting data, varying from favorable changes in PAI-1 levels to no effect.[35,652,653] However, in a crossover study designed to compare 100 μg transdermal estradiol with 0.625 mg oral conjugated estrogens (both combined with 2.5 mg MPA daily), only the oral estrogen had a favorable reduction in PAI-1 levels.[653] Appropriate doses of HT have been reported to not have an adverse impact on clotting factors[646,654,655]; however, the clotting story is difficult to unravel. While no RCTs have analyzed the difference in VTE risk between oral and transdermal estrogen, observational studies have demonstrated a difference in risk based on routes of administration. A recent meta-analysis showed that oral estrogen administration resulted in an increased risk of VTE, which was not seen with transdermal estrogen administration.[656,657] In addition, oral estrogen use in conjunction with progesterone has been associated with a greater risk of VTE than oral estrogen use alone.[658] Several factors, which are not controlled for in observational trials, also make it difficult to draw a conclusion from the aforementioned data. The frequency (cyclic vs continuous) and derivative of progesterone used were not controlled for in observational trials. Inherent differences in estrogen's route of administration also likely affected the observed results—estrogens' effects on hepatic first-pass metabolism (namely, oral estrogen's ability to alter the synthesis and clearance of hemostatic proteins), oral estrogens' ability to activate the coagulation cascade, and estrogens' effects on thrombin generation. Thus, a randomized controlled study comparing the effects of oral versus transdermal estrogen, with or without the addition of progesterone derivative, is needed before a definitive statement regarding the superiority of one form of administration or another can be made.

How can there be favorable changes indicating an increase in fibrinolysis and at the same time an increased risk of venous thrombosis, and why in older women, especially those with clinically apparent CHD, does estrogen seem to have a prothrombotic effect? Decreases in antithrombin III and protein S associated with estrogen treatment, a hypercoagulable change, may have a greater impact on the venous system.[659] There may also be subtle variations of inherited susceptibilities

that tilt the balance toward thrombosis; for example, concentrations of factors that favor arterial thrombosis have been reported (tissue factor pathway coagulation inhibitor and thrombin-activatable fibrinolysis inhibitor) in women treated with estrogens.[660] Another possibility is that the fibrinolysis is a response to coagulation activity and, therefore, not necessarily a beneficial response.

Estrogen has adverse effects on already-established atherosclerosis. MMP enzymes are secreted by inflammatory cells and smooth muscle cells. These enzymes digest the proteins in the fibrous cap of an atherosclerotic plaque, making the plaque unstable and predisposed to rupture. Estrogen induces MMP enzymes and decreases their specific inhibitors (tissue inhibitors of metalloproteinase or TIMP); this is a mechanism involved in the prothrombotic effects of estrogen in the presence of established atherosclerosis. This effect of estrogen may be dose-related and might be avoided with transdermal administration.[661]

Inhibition of Intimal Thickening

Hypertension and atherosclerosis are associated with increased proliferation of vascular smooth muscle cells. This growth of smooth muscle cells is also characterized by migration into the intima. Arterial intimal thickening is an early indicator of atherosclerosis. The proliferation and migration of human aortic smooth muscle cells in response to growth factors are inhibited by estradiol, and, importantly, this inhibition is not prevented by the presence of progestins.[662,663] Nitric oxide, which is regulated by estrogen, also inhibits smooth muscle proliferation and migration.[664] Imaging studies have documented a reduction in intimal thickening in postmenopausal women who are estrogen users compared with nonusers, and this beneficial effect is not compromised by the addition of a progestational agent to the treatment regimen.[611,665–667] Thus, postmenopausal HT can bring about a reduction in atherosclerosis, and this effect is comparable with that produced by a lipid-lowering drug.[665,668]

Protection of Endothelial Cells

Endothelial cells can respond to injury by initiating the clotting process. Animal studies indicate that estrogen accelerates healing and recovery of the endothelium in response to injury.[669] This is correlated with inhibition of

intimal thickening and recovery of important functions, such as nitric oxide production. In vitro studies of human endothelial cells demonstrate that estrogen can inhibit cytokine-induced apoptosis.[670] In the rat, MPA blocked the estrogen-induced healing response after carotid artery injuries.[671]

Inhibition of Macrophage Foam Cell Formation

A feature of atherosclerotic plaque formation is monocytic infiltration into the arterial wall and the formation of macrophage foam cells. In a non–antioxidant activity, estrogen inhibits macrophage foam cell accumulation in atherosclerotic lesions.[672]

Reduction of Angiotensin-Converting Enzyme and Renin Levels

Although oral estrogen, but not transdermal estrogen, increases angiotensinogen levels, angiotensin-converting enzyme (ACE) and renin levels are decreased (with or without progestin) by both routes of administration.[673,674] The angiotensin II receptor (AT_1 receptor) is involved in vasoconstriction, aldosterone release, sodium and water retention, and growth and proliferation of myocardial and vascular cells. Estrogen induces downregulation of the AT_1 receptor, and hypercholesterolemia is associated with AT_1 upregulation and function.[675,676]

Reduction of Adhesion Molecules

Adhesion molecules recruit leukocytes to the endothelium and play a role in attaching platelets to the endothelium. Studies with multiple markers report that oral ET increases CRP, the only marker synthesized in the liver; however, it reduces the circulating levels of other markers (E-selectin, P-selectin, intercellular adhesion molecule-1, vascular cell adhesion molecule-1, monocyte chemoattractant protein-1, and tumor necrosis factor-α) with inconsistent effects on IL-6.[53,54,677,678] An increase in CRP levels may be due to estrogen's well-known effect to stimulate the hepatic synthesis of proteins, especially because of the first-pass phenomenon with oral administration. For this reason, transdermal estrogen treatment reduces adhesion markers but does not change CRP levels.[679–681]

Reduction of Homocysteine

Increased circulating levels of homocysteine are correlated with increased risks of atherosclerosis and thrombosis. Homocysteine levels increase after menopause and are associated with hypertension and a degree of atherosclerosis.[682] Homocysteine levels are significantly lowered by estrogen or estrogen–progestin treatment, administered either orally or transdermally.[683,684]

Reduction in Cellular Senescence

Cell senescence refers to a state of cell cycle arrest and occurs in response to various stressors.[685] Expression of the senescence-associated secretory phenotype, cell cycle arrest factors, senescence-associated β-galactosidase, morphogenesis, and chromatin remodeling are some of the biologic features of senescent cells. Persistent cellular senescence is associated with pathologies including aging.[685,686] Several markers of cell senescence were analyzed in a secondary analysis in Kronos Early Estrogen Prevention Study (KEEPS), a RCT of oral CEE versus transdermal estradiol versus placebo (discussed later in this chapter under Menopausal Hormone Use and Cardiovascular Disease: Primary Prevention Randomized Clinical Trials Addressing the Timing Hypothesis); a reduction in several senescence markers (eg, macrophage inflammatory protein-1α) was observed in both oral CEE and transdermal estradiol, with a greater reduction seen with oral therapy. The authors attribute their observations to differences in circulating estrogen metabolites due to differences in the estrogen formulations and in their mode of delivery and suggested that their findings allow for generation of new hypotheses with regard to the effects of menopause on the biology of aging.[687]

Menopausal Hormone Use and Cardiovascular Disease: Evidence From Observational Studies

A review of case–control studies in the literature finds overwhelming support for about a 50% reduced risk of CHD in estrogen users.[688–705] In three studies of women undergoing angiography, a comparison of coronary artery occlusion in users and nonusers of estrogen indicated a significant protective effect of postmenopausal estrogen.[697–699] Women using HT at the time of a myocardial infarction or with congestive heart failure have been

reported to have an improved rate of survival.[706,707] Little attention has been given to peripheral artery disease, but one case–control study did report a decrease in risk in users of HT.[708]

In a large number of cohort studies, most uniformly reported a reduction in CHD in estrogen users; only three produced conflicting data.[709–724] In the Nurses' Health Study with 20 years of follow-up, the age-adjusted relative risk (RR) of coronary disease in current users of HT was 39% reduced (RR = 0.61; CI = 0.52–0.71).[725] The benefit was observed with both the 0.625- and the 0.3-mg doses of conjugated estrogens. The beneficial impact was observed to diminish beginning 3 years after discontinuation. It was suggested that higher doses might be harmful because there was an apparent increase in the risk of coronary disease among women taking more than 0.625 mg conjugated estrogens per day. Current postmenopausal hormone users in the Nurses' Health Study have had a 37% reduced risk of mortality due largely to protection against CHD, an effect that was still present after adjusting for dietary factors, alcohol intake, vitamin or aspirin use, and exercise.[720]

Electron beam tomography (also called ultrafast computed tomography [CT]) can assess for the presence of coronary artery disease by quantifying the amount of calcium in the coronary arteries, a measure that is known to correlate with the degree of disease and the risk of coronary events. Studies using this technique have demonstrated a lower prevalence of coronary artery calcium (CAC) in women younger than age 60, a prevalence comparable to men (of any age) in women older than 60, and less calcium (and, therefore, less coronary artery disease) in women using postmenopausal HT compared with nonusers.[726,727] In women with an average age of 59 who had used HT for an average of 9 years, coronary artery calcification was significantly reduced, with a greater effect observed with increasing duration of use.[728] This salutary effect of estrogen was confirmed in a substudy of the WHI estrogen-only arm.[729]

These observational studies have been criticized by arguing that estrogen treatment is a marker for variables (eg, better diet and better health care) that place postmenopausal estrogen users in a low-risk group for CVD (the "healthy user" effect). Moreover, indeed, women who choose to use HT have been reported to have a better cardiovascular risk profile than nonusers.[730] This question was addressed by the Lipid Research Clinics

Study, the Leisure World Study, and the Nurses' Health Study.[713,731,732] These epidemiologists concluded that their evidence strongly indicated that in women receiving estrogen treatment who have the same risk factors for CVD as those not receiving treatment, the same beneficial effect of estrogen was present. This is especially the case in the Nurses' Health Study, in which the participants are of a relatively homogeneous socioeconomic group. A cohort follow-up study in Southeastern New England documented similar levels of total cholesterol, HDL cholesterol, BMI, and blood pressure in estrogen users and nonusers, indicating that selection of significantly more healthy women for estrogen use could not fully explain the beneficial effect of estrogen on the risk of CVD.[733] In a comparison of health variables among users and nonusers in South Australia, there was no evidence to support the presence of a "healthy user" effect.[734] In Chile, users and nonusers of HT had identical risk factors for CVD.[735]

In contrast to the uniform results from observational studies of the association between postmenopausal HT and CHD, epidemiologic data over the last 30 years regarding estrogen use and stroke have not been consistent. The many studies have indicated either a small increase or no effect of postmenopausal HT on the risk of stroke or a reduction in risk associated with estrogen or estrogen–progestin use.[711,713,719,725,736–745] A prospective cohort study in Denmark recorded an increase in ischemic strokes, but *only* among women with hypertension, and a large cohort study from Sweden found no link between stroke and HT.[746,747]

Within this confusing mixture of results on stroke, there was one consistent observation. The cohort studies (with a sufficient number of cases) that have assessed the impact of hormone use on the risk of death from stroke have all indicated a beneficial impact. For example, the NHANES recruited a very large cohort of women in 1971 to 1975 for epidemiologic analysis. The follow-up longitudinal study of this cohort yielded a US national sample of 1,910 White postmenopausal women. Postmenopausal hormone use in this cohort provided a 31% reduction in stroke incidence and a strongly significant 63% reduction in stroke mortality.[740] These RRs were present even after adjusting for age, hypertension, diabetes, body weight, smoking, socioeconomic status, and previous CVD. This study specifically addressed the criticism that one should expect less disease in estrogen users because they are healthier.

After adjusting for physical activity as a marker of general health status, the risk estimates remained identical.

Hypertension is both a risk factor for cardiovascular mortality and a common problem in older people. Studies have either shown no effect or a small, but statistically significant, decrease in blood pressure due to estrogen treatment.[748–753] This has been the case in both women who are normotensive and hypertensive.[754–759] The addition of a progestin did not affect this response.[111,760] Discontinuing HT in women with hypertension does not result in a decrease in blood pressure (an expected response if the treatment were raising blood pressure), and in some patients, discontinuation is followed by an increase in blood pressure.[761] The acute administration of estrogen to women with hypertension is followed by decreases in blood pressure, pulse rate, and circulating levels of norepinephrine.[762] **The very rare cases of increased blood pressure due to oral ET truly represent idiosyncratic reactions. Blood pressure should be assessed every 6 months in women with hypertension being treated with postmenopausal hormones, and if the blood pressure is labile, blood pressure should be measured every 3 months.**

Observational studies have also reported that hormone users have a decreased risk of developing venous leg ulcers or pressure ulcers.[763,764]

Menopausal Hormone Use and Cardiovascular Disease: Evidence From Clinical Trials

The Women's Health Initiative

The WHI was organized by the NIH in 1992 to study the health of postmenopausal women and was scheduled to be completed in 2007.[765] From 1993 to 1998, the WHI enrolled 161,809 women aged 50 to 79 years in 40 clinical centers. The major components of the WHI were (1) two randomized trials of postmenopausal HT scheduled to conclude in 2005, (2) a dietary modification trial that randomized 48,000 women to either a sustained low-fat or a self-determined diet, (3) a calcium/vitamin D supplementation trial, and (4) an observational study. One of the randomized trials of postmenopausal HT, the combined estrogen–progestin arm (daily 0.625-mg conjugated estrogens and 2.5-mg MPA), randomized 16,608 women to either treatment or placebo. The other hormone trial, an

estrogen-only arm (daily 0.625 mg conjugated estrogens), randomized 10,739 hysterectomized women to treatment or placebo.

On May 31, 2002, the Data and Safety Monitoring Board (DSMB) made its periodic review of the data accumulated by the WHI. The DSMB made two recommendations that were announced on July 9, 2002: (1) to discontinue the trial arm administering daily estrogen–progestin and (2) to continue the trial arm with daily unopposed estrogen in hysterectomized women. The combined estrogen–progestin arm was discontinued after about 5 years of follow-up because of a statistically significant increase in invasive breast cancer and an increase in cardiovascular events.[766] The statistical parameters for benefit or harm were established in 1997, early in the study. When the increase in breast cancer exceeded the predetermined boundary, the DSMB was obligated to recommend discontinuation of this arm of the trial.

On March 2, 2004, the National Heart, Lung, and Blood Institute of the NIH canceled the estrogen-only arm of the WHI. This arm of the WHI included 10,739 hysterectomized, postmenopausal women who had completed an average of 6.8 years of follow-up. The WHI DSMB made their last periodic review of the study data in December 2003. The DSMB was not unanimous in its decision; some members wanted to stop the study, and others wanted the study to continue after sending a letter to the participants describing the findings. Even though none of the findings had crossed the predefined boundaries, the NIH made the decision to stop the study on February 2, 2004. The decision was based on the following results[767]:

- An increased risk of stroke similar to that reported in the canceled estrogen–progestin arm of the WHI
- No increase or decrease in CHD
- A trend toward an increased risk of probable dementia and/or mild cognitive impairment
- A reduction in hip fractures
- No increase in breast cancer

With the exception of breast cancer and CHD, the results in the estrogen-only arm were essentially identical to those in the estrogen–progestin arm of the study. However, keep in mind that the populations in the two clinical, randomized trial arms of the WHI were not identical.[768] Considering risk factors for CVD, the women in the estrogen-only arm were more obese, were less active, and had more preexisting CVD. The estrogen-only arm also differed in regard to risk factors for breast cancer: more early births and bilateral oophorectomy and more and longer duration of previous HT. **Therefore, these were two different trials with two different populations and treatments, making direct comparisons inappropriate.**

The published results of the WHI trial agree with more than 30 years of case–control and cohort data with the exception (**as first presented by the WHI**) **of the cardiovascular results.** The updated results on the risk of CHD from the canceled estrogen–progestin arm of the WHI reflected central adjudication of the cardiac diagnoses in contrast to the initial report that relied on local diagnoses.[769] The final report covered an average of 5.6 years of follow-up, compared with 5.2 years in the initial report. Based on these data, there would be an increase of six cases of CHD per 10,000 women per year in the treated group.

Central adjudication disagreed with 10% of the diagnoses for myocardial infarction and 3% for death due to CHD. This small degree of disagreement changed the strength of the conclusions comparing the initial report[766] with the updated report. Indeed, the overall results by definition did not achieve statistical significance in the follow-up report, and only the first-year results were statistically significant in the year-by-year analysis, a conclusion based on a difference of only 19 cases. In all of the WHI reports, the intent-to-treat analyses were adjusted for multiple outcomes, by the Bonferroni adjustment. All adjusted results were not statistically significant. It is difficult to understand the clinical meaning of this manipulation, but most believe that this indicates a slightly lower mathematical conclusion than presented in the nonadjusted data. This, of course, would further weaken the power of the reported results.

Consider also the possibility of diagnostic bias. In all, 40.5% of the estrogen–progestin group in the WHI (nearly 5,000/8,500 in the treated group), in contrast to 6.8% of the placebo group, were unblinded because of

vaginal bleeding. What was the impact on the clinicians' final management and diagnosis when told that the patient is in the WHI study and experiencing vaginal bleeding? This problem affects the data not only in regard to CVD but also for breast cancer. Unblinding was not a problem in the estrogen-only arm of the WHI and no increase in CHD was recorded—was this because of an absence of diagnostic bias in the estrogen-only arm?

The characteristics of the participants in the two WHI hormone trials are noted in **Table 22.6**.

TABLE 22.6 WHI Hormone Trials

	Estrogen–Progestin Arm	Estrogen-Only Arm
Average age	63.3 y	63.6 y
Drop-out rate	42%	53.8%
Drop-in rate (began hormone use)	6.2%	5.7%

WHI, Women's Health Initiative.

The women in the estrogen–progestin arm were an average of slightly more than 12 years distant from menopause.[767] **Most had been without HT for more than a decade. In the estrogen-only arm, the published results do not specify the number of years distant from menopause, but this duration may have been even greater, influenced by the age of subjects at the time of bilateral salpingo-oophorectomy.** Women with significant menopausal symptoms were excluded from the study to avoid an exceedingly high drop-out rate in the placebo group. Women who had been on HT (about 25% of the participants in the estrogen–progestin arm and 35% in the estrogen-only arm) and then underwent a 3-month "washout" period and experienced menopausal symptoms were discouraged from participation. (~12.5% of the participants in the estrogen–progestin arm reported VMS on entry but were willing to be assigned to placebo, and, therefore, their symptoms were unlikely to have had a major disturbing effect.) This exclusion means that only a small number of women in the WHI were close to their age of menopause. (About

16.5% of the participants in the estrogen–progestin arm were <5 years since their menopause.) For example, there was only a total of 574 women aged 50 to 54 years in the estrogen–progestin arm.[770]

Over the time of the studies, the participants discontinued their medication at a consistently increasing rate so that at termination, about half were no longer adhering to treatment. The WHI investigators argued that the high drop-out rate could lead to an underestimation of adverse effects; however, this would not be the case if longer duration of treatment exerts a beneficial effect. For example, a case–control study in the United Kingdom found a significant reduction in the risk of myocardial infarction only with the use of HT for more than 5 years.[771] Indeed, a trend for an emerging protection against CHD was observed in both arms of the WHI with increasing duration of treatment. Analysis of subsamples in the WHI revealed that the treated group had greater reductions in total cholesterol, LDL cholesterol, glucose, and insulin levels and greater increases in HDL cholesterol and triglyceride levels. It is tempting to link these findings with the test for trend that revealed a favorable, decreasing RR of CHD over time, which was statistically significant. However, this analysis was hampered by decreasing numbers over time, and the conclusion was not a strong one.

In subgroup analyses, only the women in the estrogen–progestin arm who were 20 years or more distant from menopause had a statistically significant increased risk of CHD. Subtracting this group from the rest of the participants, CHD now was observed in an identical prevalence comparing the treated and placebo groups. It is not appropriate to conclude, based on the WHI, that HT increases the risk of coronary clinical events in all postmenopausal women; this conclusion can only be applied to a specific older group of women. Indeed, as early as 2004, the data from the estrogen-only arm suggested that younger women experienced a reduced risk of CHD with estrogen treatment.[767]

A reanalysis of the CHD data in the canceled estrogen–progestin arm of the WHI, published 7 years after the initial report, contributed nothing new, confirming that a statistically significant increase in coronary heart events occurred only in those women who were 10 years or more distant from onset of menopause.[772] An excellent review from 2022 has placed in

perspective the lessons learned from and since the WHI hormone trials and offers reassurance toward safety of HT for chronologically younger population of otherwise healthy perimenopausal and early menopausal women.[773]

One response to the publications from the WHI has been a scientific and clinical effort to assess and use lower doses of estrogen. Half of the standard dose of CEEs has been demonstrated to effectively treat menopausal symptoms and to prevent bone loss. It is reasonable to ask whether symptoms and bone are especially sensitive to the effects of estrogen and whether lower doses of estrogen will beneficially impact other target tissues. The cardiovascular system is of obvious concern because it was already apparent that lower doses of estrogen do have a lesser effect on circulating lipids and lipoproteins.

Clarkson and his colleagues studied the effects of a lower dose estrogen trial in a monkey model of coronary atherosclerosis.[774] The animals were fed an atherogenic diet for 10 months, calculated to induce atherosclerosis comparable to that observed in early postmenopausal women. After oophorectomy, the animals were randomized to treatment for 2 years with a placebo or a dose of CEEs equivalent to 0.3 mg/d in women. This dose had no effect on circulating lipid levels; nevertheless, the treated animals had an average of 52% reduction in coronary atherosclerosis. This degree of protection was similar to studies in this model using a dose of conjugated estrogens equivalent to 0.625 mg/d.

The reliability and value of results obtained in Clarkson et al’s monkey model have stood the test of time. Repeatedly, the results from this model proved to be predictive of hormonal effects in women. Therefore, this experiment using a lower dose of estrogen is important, providing information regarding the effect of a lower dose on coronary atherosclerosis. Consistent with some reports in women, the lower dose of estrogen had no effect on levels of LDL cholesterol, HDL cholesterol, or triglycerides. However, the treatment markedly reduced the extent of coronary artery atherosclerosis, a further indication that estrogen-induced inhibition of atherosclerosis occurs to a large extent independently of changes in lipids and lipoproteins. In the dose–response clinical trial that led to FDA approval of lower doses of CEEs, the 0.3-mg dose still

produced statistically significant beneficial changes in lipids and lipoproteins, and this dose prevented bone loss.[119,125]

The Women's Health Initiative and Stroke

The WHI reported an overall increase in the estrogen–progestin arm of ischemic stroke, but no increase in fatal strokes.[766,775] The increase in nonfatal ischemic stroke in the estrogen-only arm of the WHI was of similar magnitude.[747,776] A randomized, double-blind, placebo-controlled secondary prevention trial (the WEST trial) of daily 1 mg estradiol therapy was conducted in postmenopausal women after a recent (within 90 days) ischemic stroke or transient ischemic attack (25% of the women).[777] After an average of 2.8 years of follow-up (range 16–50 months), there were no significant overall differences comparing the treatment and placebo groups in any of the assessed outcomes, including nonfatal stroke, fatal stroke, coronary death, nonfatal myocardial infarction, or transient ischemic attack. The WEST trial retrospectively analyzed the time course of cerebrovascular events and found a significantly increased risk of stroke only at 6 months based on 21 strokes in the estradiol group and 9 strokes in the placebo group.

A major limitation of the WEST study was the reduced compliance with treatment because of the problems associated with unopposed estrogen treatment. Over a 3-year period, 116 women in the estradiol group discontinued treatment (34%) compared with 79 in the placebo group (24%). **Nevertheless, the clinical meaning is straightforward: Patients should not be given estrogen treatment after a vascular event in the expectation that recurrent vascular events would be prevented by the initiation of estrogen treatment. However, this recommendation is specifically targeted to women with existing vascular disease.**

The Nurses' Health Study reported an update of its data on the use of HT and stroke, focusing on the timing of initiation of treatment and the effect of estrogen doses.[778] In the analyses adjusted for age, BMI, cholesterol levels, diabetes, hypertension, smoking, and family history of early CHD, the following RRs were observed for ischemic stroke (there was no significant increase in hemorrhagic stroke):

Current use of estrogen alone: RR = 1.43 (CI = 1.17–1.74)

Current use of estrogen–progestin: RR = 1.53 (CI = 1.21–1.95)

Comparing the initiation of HT near menopause with initiation 10 years or more after menopause, there was no major difference.

The Nurses' Health Study also reported an increasing risk of stroke with an increasing dose of estrogen (**Table 22.7**).

It is not easy to derive a take-home message from the Nurses' Health Study report. The authors stated that their findings are "virtually identical to those of the WHI trials." However, in the last report from the WHI, when women with prior CVD or those older than 60 years were excluded, the risk of stroke with hormone use in women less than 10 years since their menopause was not significantly increased.[779] Therefore, there is disagreement.

TABLE 22.7 Estrogen Dose and Stroke Risk

0.3-mg estrogen	**25 cases**	**RR = 0.93 (CI = 0.62–1.40)**
0.625 mg	268 cases	RR = 1.54 (CI = 1.31–1.81)
1.25 mg	60 cases	RR = 1.62 (CI = 1.23–2.14)

CI, confidence interval; RR, relative risk.

In women with risk factors for stroke, it is prudent to use low doses of estrogen and to vigorously address the risk factors, such as effective treatment of hypertension. Would the transdermal route of hormone administration be safer? This is an important question that cannot be categorically answered because of the lack of high-quality prospective data. However, as has been discussed earlier in this chapter, it is quite plausible that transdermal HT confers a lower risk of thrombosis compared to oral formulations. Therefore, it seems wise to preferentially recommend transdermal route of HT for older postmenopausal hormone users.

Secondary Prevention Randomized Clinical Trials

The Heart and Estrogen–Progestin Replacement Study

HERS was a randomized, double-blind, placebo-controlled clinical trial designed to determine whether daily treatment with 0.625-mg conjugated estrogens and 2.5-mg MPA would reduce CHD events in women with preexisting coronary disease.[780–782] In this trial, 2,763 women (average age 66.7 years) were enrolled in 20 US clinical centers and randomized to treatment and placebo beginning in February 1993 and ending in July 1998. Overall, there were 172 myocardial infarctions and coronary deaths in the hormone group and 176 in the placebo group—no difference.

At baseline, the use of statins and aspirin was essentially equally prevalent in the treated and placebo groups (about 40% of the subjects used statins and 80% used aspirin). However, more women in the placebo group began treatment with statins so that by the end of the follow-up period, the 69% versus 65% difference comparing placebo with treatment was statistically significant. The authors addressed this potential confounder by adjusting for the difference in statin use (as well as other confounders) and concluded that the adjusted analyses were essentially identical to the original analyses. However, no mention is made of the fact that the percentage use of statin use is impressively high. What if any beneficial effect of estrogen is lost because of the impact of statin therapy? Indeed, in a primary prevention trial, inhibition of atherosclerosis with estrogen treatment was observed only in women *not* receiving statins.[783] The HERS investigators compared CHD events in the hormone group with the placebo group in women not using statins or aspirin and found no difference, but this very important possible explanation for the lack of a beneficial effect of estrogen in HERS cannot be answered by the analysis of the HERS data because statin and aspirin treatments were not randomized and the number of events in women not on statins or aspirin was very small.

Of the 2,763 postmenopausal women in the HERS trial, 2,321 (93%) agreed to be involved in additional follow-up evaluation, HERS II. The original study[780] lasted 4.1 years, and the average extended follow-up equaled 2.7 years, for a mean total of 6.8 years. At the beginning of the follow-up period, the average age of the participants was 71 (67 at baseline and 74 at closure). The investigators could detect no significant differences in the rates of coronary events or secondary cardiovascular events

comparing the treated group with the placebo group. There was no statistical trend for a beneficial effect of HT with longer duration of treatment. Because of the absence of a difference, the follow-up period, scheduled to last 4 years, was terminated early.

The additional follow-up period was unblinded; patients and physicians could choose to continue, discontinue, or initiate HT or other therapy. Hormone use in the original treated group in HERS declined from 81% after 1 year to 45% during the sixth year (and 11% were using preparations other than the original 0.625-mg conjugated estrogens and 2.5-mg MPA). During the sixth year, 8% of the placebo group were now receiving HT. Raloxifene or tamoxifen had even been initiated, 3% in the hormone group and 4% in the placebo group. The investigators recognized this problem conceding that their power to detect an increasing benefit was eroded by the changing treatments; however, their analysis indicated an ability to detect at least an 18% reduction in cardiac risk.

The original HERS report indicated a 2- to 3-fold increase in deep vein thrombosis and pulmonary embolism in the hormone-treated group. In the follow-up period, there was no longer a statistically significant increase in deep vein thrombosis. There was no reduction in pulmonary embolism, but the number of events was too small to provide accurate assessment. The event rates for venous thrombosis were 5.9 per 1,000 women per year of treatment and 2.8 in the placebo group. Overall, there was a 48% increase in risk for biliary tract surgery in the treated group, 6 more cases per 1,000 women per year compared with placebo.

Intention-to-treat analysis compares all individuals in the treated group to all in the placebo group, regardless of individual compliance or completion of the study. Proponents argue that this is the best method of analysis for clinical trials because it reflects the full impact of randomization. Opponents contend that this method is intuitively wrong; how can the long-term benefit of a treatment be assessed if subjects receiving treatment for only a short period of time are included? HERS II performed an “as-treated” analysis, focusing on women with 80% or more compliance, and found relative hazards (RHs) (like RR) similar to those in the intent-to-treat analysis. However, the RH in the as-treated analysis for primary CHD events in HERS II was reduced, although not statistically significant (RH = 0.81; CI = 0.52–1.32). Events were fewer in the as-treated

analyses because only 37% of the events qualified. Adjustment for statin use was performed only in the intent-to-treat analysis ("only a trivial effect on the findings"). The HERS clinical trial results that reflect intent-to-treat analyses are compromised by a difficulty in detecting a long-term effect, and the results that reflect the as-treated analysis are compromised by few events because of compliance and drop-out problems. Therefore, unanswered questions remain: whether reported increases in cardiovascular events early after the initiation of HT reflect a true risk of HT or the effect of reduced events in the placebo groups because of new-onset treatment with statins and aspirin, or an effect limited to women with significant preexisting coronary artery disease.

Other Secondary Prevention Trials

The results of a multicenter trial (the Estrogen Replacement and Atherosclerosis [ERA] trial) examined the effect of postmenopausal HT on the progression of coronary atherosclerosis as assessed by angiography.[784] A total of 309 women were randomly assigned to receive either unopposed estrogen, 0.625-mg conjugated estrogens per day; a daily combination of estrogen and progestin, 0.625-mg conjugated estrogens and 2.5-mg MPA; or placebo. Over 3.5 years of treatment, angiography did not detect any differences in disease progression between any of the groups. The women in this study had documented heart disease on entry and were a relatively older group of women (mean age 65.8 years). Half had a previous myocardial infarction. There were no reported increases in cardiac events in any of the three treatment groups.

The ERA trial joins the HERS trial in demonstrating no secondary preventive effect of postmenopausal HT on older women with significant CHD. However, in **comparing the two trials, there is an important observation. The ERA trial contained an estrogen-only arm, and the absence of a difference between the estrogen-only arm and the estrogen–progestin arm argues against a negative effect due to the daily administration of MPA.**

Another secondary prevention, 3-year trial (Women's Estrogen–progestin Lipid-Lowering Hormone Atherosclerosis Regression Trial, WELL-HART) assessed whether unopposed estradiol or a sequential regimen of estradiol and MPA could slow the progression of

atherosclerosis.[785] The double-blind, placebo-controlled trial involved 226 postmenopausal women with an average age of 63.5 years (range 48–75), who already had at least one demonstrated coronary artery lesion. The results were based on follow-up angiograms in 59 women in the placebo group, 54 in the estradiol group, and 53 in the estradiol/MPA group. A reduction of LDL cholesterol to less than 130 mg/dL was achieved by dietary intervention, but coronary angiography to measure the change from baseline in the percent stenosis failed to demonstrate a difference among the groups receiving placebo; unopposed, daily 1 mg estradiol; or daily 1 mg estradiol and 12 days each month of 5 mg MPA. **There were also no differences in cardiovascular events during treatment. The results indicated that MPA administered in a sequential regimen is not associated with an adverse cardiovascular effect.**

At least three other secondary prevention trials in women with CHD failed to demonstrate a beneficial impact of HT.[786–788] These various trials tested oral conjugated estrogens, oral estradiol valerate, and transdermal estradiol combined with either MPA or norethindrone. **The results of the secondary prevention trials in older women with established heart disease are uniformly consistent in finding no beneficial effects of HT, and the data indicate that different estrogens and different progestins behave similarly.**

The Timing Hypothesis

The timing hypothesis argues that estrogen can reduce the risk of CHD when administered to relatively young postmenopausal women before atherosclerosis has developed to the stage of unstable plaques (plaques with necrosis and inflammation).

The WHI investigators conducted a secondary analysis of the two canceled clinical hormone trial arms.[779] The results in the estrogen-only arm, in the combined estrogen–progestin arm, and with the participants combined were separated into age groups at randomization (50–59, 60–69, and 70–79) and according to years since menopause (<10, 10–19, and ≥20). **An increased risk for CHD was present only in the oldest women in the trials. There were no increases for CHD, stroke, or total mortality in women aged 50 to 59 years. In fact, only the increase in CHD events in**

women 20+ years since menopause reached statistical significance. There was no apparent increase in CVD risk in treated women close to their menopause. Indeed, a statistically significant reduced risk was present for total mortality in women aged 50 to 59 years.

The data in this 2007 WHI report were not new. A careful reading of the initial adjudicated reports reveals that the risk of CHD was present only in the oldest women in the trials.[769,789] In subgroup analyses, the only significant increase in stroke occurred in the estrogen-only arm in women aged 60 to 69 years. However, as noted previously, when women with prior CVD or those older than 60 years were excluded, the risk of stroke in women less than 10 years since their menopause was not significantly increased. In a meta-analysis of RCTs examining CHD outcomes when HT was used in younger versus older women, lower CHD was noted in the younger group.[790] To further assess the effects of ET on coronary health, CAC was measured in women aged 50 to 59 years by CT. Calcium atheromas are indicative of the chronic inflammatory process associated with atherosclerosis and are the best known predictors of clinical heart disease. As such, calcium atheroma scores were used to assess CVD. Women in the ET group had a statistically significant lower calcium atheroma score than those in the placebo group ($P = 0.02$). Moreover, in participants with greater than 80% adherence (to ET or placebo), there was a 61% lower risk of severe coronary calcium in the ET group ($P = 0.002$).[790]

Will postmenopausal HT begun at or near the time of the menopause, and maintained for a relatively long duration of time, provide protection against coronary artery disease (primary prevention)? The design of the canceled arms of the WHI did not allow an answer to this question. As noted previously, women with significant menopausal symptoms were excluded from the study to avoid an exceedingly high drop-out rate in the placebo group. The WHI addressed this problem by pointing out that the ratios of cardiovascular events in the treated and placebo arms were the same when assessed by decades of age, 50s, 60s, and 70s. However, this was not the critical analysis. It is very likely that a small number of the participants were close to their age of menopause. Only 574 in both the treated and placebo groups were age 50 to 54 in the estrogen–progestin arm, and it is likely that even some of these women were relatively distant from their menopause. Even with the appropriate analysis according to years

from menopause, the results are limited by very small numbers of women in their early postmenopausal years. Furthermore, the high drop-out rates in these clinical trials erode the statistical power for assessing year-by-year new statin or aspirin treatment.

There is a small primary prevention trial of 199 healthy postmenopausal women randomized to a daily dose of 1 mg estradiol or placebo and followed for 2 years measuring with ultrasonography the change in cIMT.[783] The women receiving estradiol had a small decrease in intimal–media thickness in contrast to a marked increase in the placebo group. Interestingly, in those participants taking lipid-lowering medications, there was no difference comparing estrogen treatment with placebo (both groups had a small decrease in thickness), indicating that lipid-lowering drugs and estrogen had similar beneficial effects on atherosclerosis that were not additive. There have been two other similar ultrasonography studies. A 2-year Dutch study did not achieve a significant difference comparing treatment with placebo, but the results were handicapped by a very high drop-out rate and problems with follow-up.[791] A German study that found no effect of HT enrolled women who already had increased intimal–media thickness, and the duration of the study was only 1 year.[792]

A meta-analysis of 23 randomized HT trials concluded that treatment reduced the risk of CHD events by 32% in younger women compared with older women (≥10 years since menopause or >60 years of age).[793] This is a conclusion that is less firm than at first apparent, because most of these trials were not designed to measure an end point of CVD. However, another meta-analysis by the same authors concluded that HT reduced overall mortality in women with an average age of less than 60.[794] There is a growing story that adequate estrogen exposure prior to the onset of clinical events provides protection against CVD.

The timing hypothesis originated in the hormone trials conducted in monkeys by the Wake-Forest group headed by Tom Clarkson and provides some of the initial support of the timing hypothesis.[795]

Key Points: Timing Hypothesis

- Estrogen treatment initiated immediately after menopause in monkeys inhibited progression of coronary artery atherosclerosis by about 70%. When treatment was delayed by 2 years (equivalent to about 6 years in women), there was no effect.[795]
- Next in line, according to strength of evidence in our view, would be he WHI reports of reduced CAC in estrogen-treated women and an increase in cardiac events only in the oldest women in the trials.[729,779] The problem of low event rates in younger women in the WHI was addressed by lumping together, in one HR, myocardial infarction, coronary death, coronary revascularization, and confirmed angina—the risk in women aged 50 to 59 years for all of these events was significantly reduced (HR = 0.66; CI = 0.45–0.96).[789] In addition, the WHI measured CAC in a substudy of the estrogen-only arm and found that women with bilateral oophorectomies who were not treated with estrogen had an increase in subclinical CHD.[796]
- Every woman has a trajectory of atherosclerosis development, the slope of which determines the age of onset for clinical events. Premenopausal women with lower estrogen levels have higher cardiovascular risk factors and develop more and earlier CHD.[797]
- The importance of premenopausal estrogen is also supported by Clarkson et al's monkey studies. Premenopausal monkeys with normal ovarian function have less progression of coronary artery atherosclerosis as compared with monkeys with impaired ovarian function.[795]
- The Mayo Clinic Cohort Study of Oophorectomy and Aging included 1,274 premenopausal women with unilateral oophorectomy (followed up for a median of 29.5 years) and 1,091 premenopausal women with bilateral oophorectomy (followed up for a median of 25 years) who had surgery from 1950 to 1987, compared with 2,383 matched women from the same population of women who had not undergone oophorectomy.[798] Women with bilateral oophorectomy before age 45 had about a 5-fold increase in risk of mortality for neurologic or mental diseases and experienced almost a 2-fold increase in mortality from CVD, increased risks of parkinsonism, cognitive impairment and dementia, and an increase in depressive and anxiety symptoms later in life (**Figure 22.7**).[799–802]
- The Nurses' Health Study compared, after 24 years of follow-up, ovarian conservation (13,035 women) and bilateral oophorectomy (16,345 women) at the time of premenopausal hysterectomy.[803] *An all-cause increase in mortality, CHD, and stroke was observed in those women who never used estrogen after surgery; this amounted to one additional death for every nine surgeries.*
- The results in observational studies strongly indicate that hormone treatment of young postmenopausal women reduces the risk of CHD. In the Nurses' Health Study, the reduction was approximately 50%.[725] The women in the Nurses' Health Study who were under age 60 when hormone treatment was initiated had a significant reduction in CHD risk compared with no effect in women over age 60.[804] A similar reduction was present in the observational arm of the WHI.[805] In fact, after adjustment for confounding influences in the WHI observational arm such as behavioral, dietary, physical activity, and cardiovascular risk factors, the RRs for cardiovascular events were 30% to 38% lower than in the clinical trials. These data were derived from populations of women usually treated with postmenopausal HT, women close to their natural age of menopause.

- In a primary prevention trial using ultrasound measurement of cIMT, estradiol-treated women had slower progression of atherosclerosis.[783] These same investigators demonstrated no effect of estrogen treatment in older women who had angiographic evidence of coronary atherosclerosis.[785]

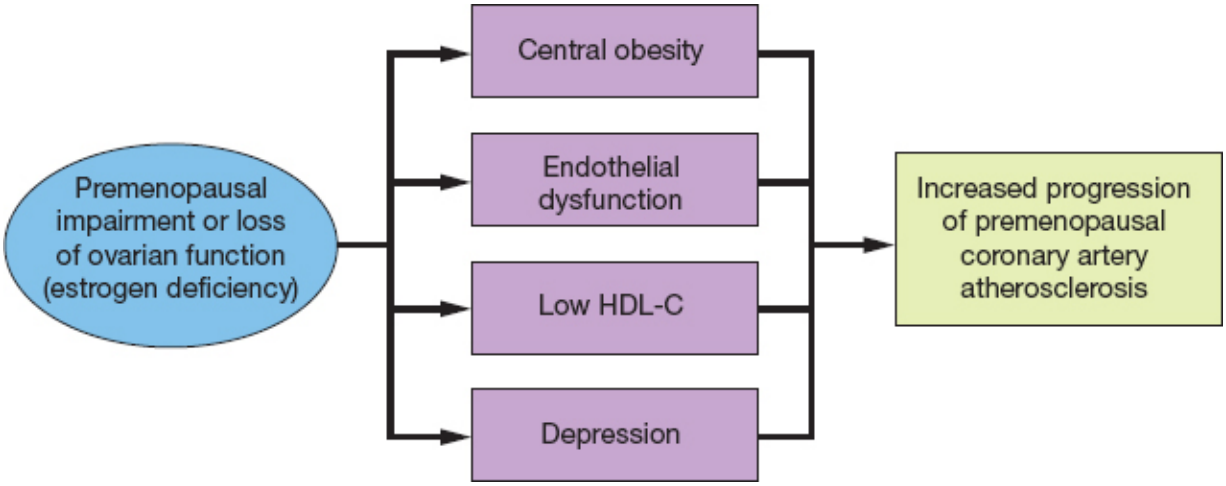


FIGURE 22.7

Primary Prevention Randomized Clinical Trials Addressing the Timing Hypothesis

KEEPS was a randomized, double-blind, placebo-controlled trial aimed at assessing the effects of early initiation of oral or transdermal HT on progression rates of subclinical atherosclerosis.[806] Women were eligible for enrollment if they were healthy, aged 42 to 58 years, between 6 and 36 months from their last menstrual period with no prior CVD events, a CAC score less than 50 Agatston units, and without exogenous estrogen exposure or lipid-lowering therapy for the past 90 days. Women were randomized to receive oral (o) CEE 0.45 mg/d or transdermal (t) E2 50 μg/d, each with 200 mg oral progesterone for 12 days per month, or placebo for 48 months. The primary end point was annual change in cIMT by ultrasonography, with secondary end points of changes in markers of CVD risk, including CAC scores (determined by CT scan of the chest).[806] Of the 727 randomized women, 89.3% had at least one follow-up cIMT, while 79.8% had a cIMT annually. The KEEPS trial found that the mean cIMT increase of 0.007

mm/y was similar among all three groups. Similarly, the percentage of subjects in whom CAC scores increased was not different. LDL and HDL levels improved, levels of CRP and SHBG increased with o-CEE, but IL-6 did not. Insulin resistance decreased with t-E2; there were no changes in blood pressure with either o-CEE or t-E2 use.[806] Thus, the KEEPS trial did not demonstrate a significant difference in cIMT (a measure of preclinical progression of atherosclerosis) among oral, transdermal, or placebo groups. In a follow-up of a subgroup of subjects (representative of the placebo, o-CEE, and t-E2 groups) 3 years after stopping HT from the KEEPS trial, the effects of cessation of HT on cIMT were analyzed.[807] There did not appear to be a "rebound" effect on cIMT progression upon discontinuation of o-CEE or t-E2.[807] Regardless of HT regimen, there was an overall increase in cIMT over time, which may be inherent to the aging process.[807] A secondary analysis of the KEEPS trial analyzed how oral versus transdermal HT affected epicardial and pericardial fat deposits, which have an association with the progression of coronary artery calcifications. Cardiac fat deposits were not impacted by o-CEE; however, an increase in pericardial fat was observed in t-E2. Clinical implications of these observations remain unclear, and future studies are needed to establish if indeed pericardial fat deposits are differentially affected by route of ET, and clinical consequences therefrom.

ELITE also assessed the effect of early administration of HT on the development/progression of atherosclerosis.[808] Six hundred and forty-three healthy postmenopausal women are stratified by years since menopause (early equal to <6 years or late [>10 years]) and randomly assigned to oral E2 1 mg/d plus vaginal progesterone 45 mg for 10 days per month for women with a uterus or placebo (including sequential vaginal gel for subjects with a uterus). The primary outcome was the rate of change in cIMT (measured every 6 months). Secondary outcomes included assessment of coronary artery atherosclerosis by cardiac CT scan (performed at the completion of study medication). Following 5 years, it was found that oral E2 with/without vaginal progesterone resulted in a significantly slower increase in cIMT in the early postmenopause group, compared to placebo.[808] In women who were greater than 10 years past menopause, cIMT progression rates were not different from placebo. Measures of CAC by CT, total stenosis, and plaque burden did not differ

between placebo groups and the estradiol groups for early or late menopause status.[808]

Thus, unlike KEEPS, results of the ELITE trial support the timing hypothesis in that early initiation (ie, closer to the timing of menopause) of HT was associated with more favorable cardiovascular outcomes. The differences between ELITE and KEEPS may, among many possibilities, relate to inherent differences in the studied populations or reflect differences in the choice and dose of estrogen formulations utilized.[463,809]

Key Points: Hormones and Coronary Heart Disease

- **The message from multiple secondary prevention trials is clear: Exogenous estrogen should be avoided in postmenopausal women with existing CHD, and there are no grounds for an expectation that such treatment will reduce subsequent cardiac events.**
- **Evidence from primary prevention clinical trials, while less clear, suggests that early initiation of estrogen may confer cardioprotective effects (as evident in the ELITE trial); however, additional studies are needed to establish consistency of such a benefit across populations and to clarify if such benefit may depend on the type and dose of estrogen formulation, given the discrepant findings between ELITE and KEEPS trials. Until clarity is attained, cardioprotection alone should not be used as an indication for prescribing HT.**
- **A reasonable goal is to maintain a healthy level of estrogen during the premenopausal years and in the early postmenopausal period.**
- **Experimental evidence in the monkey indicates that the beneficial effects of hormonal treatment are progressively diminished with increasing atherosclerosis.[463]**
- **In postmenopausal women, the vasodilatory effects of estrogen dissipate with increasing age.[809]**

VENOUS THROMBOSIS

Results from multiple studies indicate that postmenopausal HT increases the risk of VTE about 2-fold, mostly in the first year or 2 years of treatment,

a conclusion supported by the results from the canceled estrogen–progestin arm of the WHI.[766,810] The absolute risk in the WHI estrogen–progestin arm was 18 additional cases per 10,000 women per year. In the estrogen-only arm of the WHI, a smaller increase in deep vein thrombosis was observed, and an increase in pulmonary embolism was not statistically significant.[767,811] There are some notable observations in the WHI data on venous thrombosis. Most of the cases occurred in the first 2 years of exposure, and the risk was greatest in the women over age 70 and in women who are overweight. The risk was higher in women who were susceptible to venous thrombosis, specifically those with the Leiden mutation. This raises a very important question: Is it possible that the risk of venous thrombosis is very low in younger, normal postmenopausal women?

It should be emphasized that the risk of VTE appears to apply only to new hormone starters; women who have been on HT can be reassured that the evidence indicates that the increased risk of venous thrombosis is concentrated in the first 1 to 2 years of treatment.[658] The actual risk is very low because of the low frequency of this event. If the RR is increased 2-fold, this would increase the incidence of VTE by about two cases per 10,000 women per year of hormone use. Furthermore, venous thrombosis carries with it a very low risk of mortality, around 1%, and most of the fatal cases have followed venous thrombosis associated with trauma, surgery, or a major illness.[812]

VTE is a risk that is reduced with the use of statins and low-dose aspirin,[813,814] although it is not known whether statin and aspirin use would completely protect against the increased risk associated with postmenopausal use of HT.

Accruing data are reassuring regarding lesser VTE risk with the transdermal route of estrogen compared to oral use, a benefit that is attributed to avoidance of the first-pass hepatic effect with the nonoral route. For example, oral administration of estrogen compared with transdermal administration in male-to-female transsexuals is associated with a greater prothrombotic state and risk of venous thrombosis; however, this effect could be at least partly attributed to major differences in the estrogen doses.[815] It would be better to have evidence uninfluenced by dosage, and for this purpose, we can consider responses of APC resistance, recognized as a marker for venous thrombosis risk. In one randomized trial,

oral estrogen treatment increased APC resistance, but transdermal estrogen was no different than placebo.[40] Another randomized trial found that both routes of administration increased APC resistance; however, the increase with oral estrogen was about 4 times greater compared with transdermal estrogen.[39] A French case–control study concluded that there was a 4-fold increase in VTE with current use of oral estrogen, but no increase in risk with transdermal estrogen.[41] In addition, this study reported that oral estrogen treatment adds to the risk of VTE associated with obesity, but transdermal estrogen does not.[816] The French study also reported (although limited by small numbers) that transdermal treatment, in contrast to oral estrogen, does not further increase the risk of VTE associated with known prothrombotic conditions, such as factor V Leiden deficiency or prothrombin mutations.[42]

However, there are some problems with the French case–control study. There are wide CIs for the significant OR associated with oral estrogen treatment. Usually, this reflects small numbers, but the number of cases and controls in this study should allow greater precision. It is possible that this imprecise conclusion is influenced by the fact that the cases and controls differed significantly in several characteristics that influence the risk of VTE, specifically greater body weight and a positive family history of VTE. We know that a 2-fold increased risk of VTE is uniformly reported, including the data from the WHI.[810,811] It is very likely that the French estimate is higher compared with the usual 2-fold increased risk because of confounding differences between their cases and controls. **It is worth noting again that in the WHI, the cases of venous thrombosis were concentrated in the first years of exposure, in the oldest, and in the heaviest women in the study.**

The French case–control study found no increase in VTE risk associated with estrogen combined with progesterone or pregnane derivatives and an increase with norpregnane derivatives. The pregnane group includes synthetic progestins, such as MPA, chlormadinone, and cyproterone. The norpregnanes (progesterone without the 19-carbon) included two progestins, nomegestrol acetate and promegestone, that are not used in the United States. (Nomegestrol acetate is the progestin in Uniplant, a single-rod implant contraceptive, and combined with estradiol in an oral contraceptive.) However, can we make the conclusion that the norpregnanes

are thrombogenic? The CI in the norpregnane group was very wide, again apparently not due to small numbers, but this makes this conclusion shaky and suspect. Similar results were reported from the E3N French prospective cohort study, with an increased risk of VTE of 1.7 (CI = 1.1–2.8) associated with current users of oral therapy (an HR more in keeping with the usual 2-fold increase reported in the literature) and no increase with transdermal estrogen.[45] Again, an increase was observed with norpregnane progestins, this time with tighter CIs. In contrast, several other studies have demonstrated an increased VTE risk in women using medroxyprogesterone.[817]

In the French studies, oral hormone users used almost exclusively estradiol in doses that averaged 1.5 mg/d. Transdermal users most commonly used an estradiol dose of 50 μg or less daily. To legitimately compare oral and transdermal methods, one would have to be sure the two groups had similar blood levels, to account for the wide variation in metabolism and clearance among individuals. It is possible that the difference between the oral and transdermal groups represents differences in estrogen doses. Nevertheless, the French conclusions are supported by a very large case–control study (23,505 cases of VTE) using the UK General Practice Research Database.[305] The use of transdermal estrogen either alone or combined with a progestin was not associated with an increase in VTE, compared with about a 1.5-fold increase with oral estrogen alone and oral estrogen–progestin.

A greater safety with transdermal administration of estrogen with regard to VTE makes some sense because of the known lesser impact on clotting proteins when the first-pass liver effect is avoided. This is supported by transdermal estrogen's almost negligible effect on APC resistance when compared with oral therapy.[39,818] A randomized trial assessing the risk of recurrent VTE in women with a prior history of thrombosis being treated with an oral hormone regimen was canceled after 1 year when eight women in the treated group developed recurrent venous thrombosis compared with only one in the placebo group.[819] The eight women were studied retrospectively, and six of the eight had an inherited susceptibility to venous thrombosis. The numbers were not large, but the results are a strong argument for the recommendations detailed in Chapter 22. There is no argument that inherited abnormalities in the clotting scheme increase the

risk for VTE. The evidence is mixed for arterial thrombosis, but most of the evidence fails to find an association between specific inherited defects (thrombophilia) and arterial thrombosis, although this is still unsettled.[820–823]

If a patient has a close family history (parent or sibling, or child) or a previous episode of idiopathic thromboembolism, an evaluation to search for an underlying abnormality in the coagulation system is warranted before exposing the patient to exogenous HT. The following measurements are recommended, and abnormal results require consultation with a hematologist regarding prognosis and consideration for prophylactic treatment with an anticoagulant. The list of laboratory tests is long, and, because this is a dynamic and changing field, the best advice is to consult with a hematologist (**Table 22.8**). When a diagnosis of a hereditary thrombotic tendency is made, screening should be offered to other family members.

TABLE 22.8

Hypercoagulable Conditions	Screening Test(s)
Antithrombin III deficiency	Antithrombin III
Protein C deficiency	Protein C
Protein S deficiency	Protein S
Factor V Leiden mutation	Activated protein C resistance ratio
Prothrombin gene mutation	Prothrombin G mutation (DNA test)
Antiphospholipid syndrome	Hexagonal activated partial thromboplastin time
	Anticardiolipin antibodies
	Lupus anticoagulant β_2 glycoprotein antibodies
Hyperhomocysteinemia	Homocysteine level
Malignancy	Complete blood count (leukemias, lymphoma) Fibrinogen

Other risk factors for thromboembolism that should be considered by clinicians include an acquired predisposition, such as the presence of lupus anticoagulant or malignancy, obesity, immobility, or trauma. Varicose veins are not a risk factor unless they are very extensive, and, unlike arterial thrombosis, smoking either has no effect or at best is a weak risk factor for VTE. Raloxifene (and tamoxifen) shares with estrogen an increased risk for VTE.[215] The size of the risk is comparable for all three drugs, about a 2-fold increase.

Key Points: Hormone Therapy and Venous Thromboembolism

- **Observational studies support the clinical choice of a transdermal method for women who are at higher risk for VTE and for whom menopausal HT is being considered due to failure of symptom benefit from nonhormonal strategies.**
- **Although existing data are overall reassuring regarding safety of progestin regimens commonly used in menopause hormone regimens, an absence of good data does not allow making any statements with confidence regarding an absence of thrombogenic risk for the various progestins. However, it may be prudent to consider transdermal E2 with micronized progesterone (in women with a uterus) in those deemed at risk for VTE until RCTs confirm/refute the safety of alternative progestogens.[817] The clinician and patient can together consider a combination of HT (preferably transdermal administration) and chronic anticoagulation, in consultation with a hematologist.**
- **We recommend appropriate prophylactic anticoagulant treatment in hormone users anticipating immobility with hospitalization, especially if other risk factors (most notably, obesity) are present. Some patients may elect to discontinue hormone treatment 4 weeks prior to major surgery if extended immobility is to be expected, but this is an empiric, individual decision. HT can be resumed when the patient is ambulatory.**

BREAST CANCER AND MENOPAUSAL HORMONE THERAPY

Women and clinicians are regularly reminded about the threat of breast cancer, in the media, by advertisements, and by the experience of a friend or family member fighting this disease. Breast cancer is a major focus in the health concerns and care for postmenopausal women because it has an increasing frequency with age. About 95% of all breast cancers and 97% of breast cancer deaths in the United States occur in women over age 40.[824] Thus, there are good reasons why this medical condition is a prominent factor in clinical decision-making regarding postmenopausal HT.

The long-term use of postmenopausal HT has been challenged by data that have been interpreted to indicate that the risk of breast cancer is increased in hormone users. The debate and publicity over this issue have made decision-making very difficult for both patients and clinicians. **The most important unanswered question is whether postmenopausal HT initiates the growth of new breast cancers or whether the epidemiologic results reflect an impact on preexisting tumors.**

Biologic Plausibility

The most compelling reason to believe that long-term use of postmenopausal estrogen increases the risk of breast cancer is the inherent biologic plausibility. Factors known to increase a woman's exposure to estrogen are known to increase the risk of breast cancer; for example, there is a small decrease in risk with late menarche and a moderate increase in risk with late natural menopause.[825] In premenopausal women who are overweight, the risk of breast cancer is lower compared with normal weight individuals, and in postmenopausal women, excess weight is associated with either an unchanged or slightly increased risk.[826–828] This is attributed to an increase in total and free estrogen levels in postmenopausal women who overweight, in contrast to lower levels with increasing weight in premenopausal women. Postmenopausal women who are obese have later menopause, higher estrone production rates and higher free estradiol levels (lower SHBG), and a slightly greater risk for breast cancer.[829] Greater bone density, believed to be a marker for estrogen exposure, is also associated with an increased risk of breast cancer.[830–832]

Studies seeking a correlation between circulating levels of sex hormones and breast cancer have yielded conflicting results. In the Rancho

Bernardo cohort, no relationship between estrogen, androgen, and SHBG levels and the incidence of breast cancer could be demonstrated.[833] Using serum collected earlier in life, no differences in endogenous hormones could be detected in 51 women who subsequently developed breast cancer, including the various estrogens, progesterone, androstenedione, and even SHBG.[834] On the other hand, in a very large prospective study in Italy, estradiol, testosterone, and SHBG levels were higher in postmenopausal women who subsequently developed breast cancer.[835] In a British report, women who subsequently developed breast cancer had higher levels of estradiol.[836] Two North American prospective studies also found higher levels of estrogen in women who subsequently developed breast cancer, and most impressively, an increasing risk of breast cancer correlated with increasing levels of free estradiol.[837,838] In another study, women who developed breast cancer displayed higher levels of unbound, free estradiol and lower levels of SHBG.[839] In the Nurses' Health Study, an association was reported between an increased risk of breast cancer and higher levels of estradiol, estrone, and DHEA-S, whereas no association could be demonstrated with the percent free or bioavailable levels of estradiol, androstenedione, testosterone, or DHEA.[840] **The discrepancies among the various studies seeking a correlation between hormone blood levels and the risk of breast cancer reflect the fact that the differences are very small, and it is a struggle to achieve statistical significance.**

Overall, the biologic plausibility for an estrogen link with breast cancer is an impressive argument. This argument is further strengthened by the proven benefit of reducing the incidence of breast cancer with the antiestrogen, tamoxifen. However, establishing a clinically real cause-and-effect relationship with epidemiologic data requires more than the rationale of biologic plausibility.

Key Points: Postmenopausal Breast Cancer Risk

- **The risk of breast cancer is increased with increasing duration of lifelong exposure to estrogen.**

- **Postmenopausal women who are overweight have a slightly increased risk of breast cancer.**

Results From Observational Studies

In the past decade, a large number of case–control and cohort studies indicated a slightly increased risk of breast cancer with postmenopausal use of HT. Overall, most of these studies indicated a greater risk associated with estrogen–progestin compared with unopposed estrogen treatment.[841–857]

A Reanalysis of the World's Literature

Prior to the publications from the WHI, the 1997 report of a reanalysis of the world's literature was the most referenced article on this subject. A team of epidemiologists invited all investigators who had previously studied the association of postmenopausal hormone use and the risk of breast cancer (51 studies) to submit their original data for a collaborative combined reanalysis, an undertaking more rigorous than a standard meta-analysis. This analysis reached the following conclusions[858]:

- Ever users of menopausal hormones had an overall increased RR of breast cancer of 1.14.
- Current users for 5 years or more had an RR of 1.35 (CI = 1.21–1.49), and the risk increased with increasing duration of use.
- Current and recent users had evidence of having only localized disease (no metastatic disease), and ever users had less metastatic disease.
- There was no effect of a family history of breast cancer.

This was the first important indication that women with a positive family history of breast cancer do not have a further increase in risk with HT, a finding also reported in the WHI.[859] There were two other notable conclusions: All of the increase in risk was localized disease, and women who used HT and developed breast cancer had better survival rates than nonusers; these observations have been repeatedly confirmed.

The Million Women Study

The Million Women Study recruited 1,084,110 women between 1996 and 2001 from those invited by the UK National Health Service Breast Screening Programme to have screening mammography every 3 years (about half had ever used postmenopausal HT).[852] The study data were recorded from questionnaires returned prior to the initial mammography, and the women were followed to determine cancer incidence and death. The study is noteworthy for its large numbers and adjustments for the well-recognized factors associated with risk of breast cancer. No increase in the risk of breast cancer was measured in past users of any hormone preparation, regardless of the length of time since discontinuation, from less than 5 to 10 years or more (with the exception of discontinuation in the year previous to diagnosis), and regardless of the duration of use. Based on an average follow-up of 2.6 years (a very short exposure; indeed, the breast cancers were diagnosed on an average of 1.2 years after the study began), the RR for invasive breast cancer in current users of estrogen only was 1.30 (CI = 1.22–1.38) and for current users of estrogen–progestin was 2.00 (CI = 1.91–2.09).

There are many criticisms of the Million Women Study. For example, the study reported a lower risk of breast cancer for perimenopausal and postmenopausal women compared with premenopausal women despite the well-established fact that breast cancer risk increases with aging. There were many differences comparing users and nonusers, requiring multiple adjustments. Hormone use or nonuse was established at entry and not changed during follow-up despite multiple crossovers in treatment among the women. Validation of the questionnaire data was claimed based on information obtained from only 570 women. Breast cancer mortality was assessed after an average of 4.1 years of follow-up, based on a total of 517 deaths; however, breast cancer was diagnosed very rapidly (an average of 1.2 years), and deaths occurred swiftly (within an average of 1.7 years). Current users and past users were compared with the never users, and, although the risk of mortality was increased, it did not reach statistical significance (1.22; CI = 1.00–1.48). This finding was highlighted because it differed with a consistent story reported in the literature over a decade that hormone users had better survival rates. The Million Women Study

calculated their risk of mortality by dividing deaths from breast cancer by the total number of users or nonusers. When the data are recalculated appropriately by dividing deaths from breast cancer by the total number of cases of breast cancer in the user and nonuser groups, the results agree with the literature—**the risk of mortality was reduced about 27% in the hormone users.**

The Danish Nurse Cohort

The Danish Nurse Cohort of 10,874 women was established in 1993.[860] The results reflected a variety of hormone products and regimens, and an increased HR for breast cancer was associated with HT (HR = 2.42; CI = 1.81–3.26), with a 2-fold increase in breast cancer mortality. Stated simply, hormone users had a greater mortality rate from breast cancer because they had more breast cancers. Even though the case fatality rate was better (more favorable prognosis), the increased incidence produced a net effect of an increase in mortality.

Danish case–control and cohort studies are noted for their ability to accurately obtain information from the national registries. Nevertheless, there were important limitations to this study. The most glaring problem was that not all causes of death could be verified and a death in a woman with a diagnosis of breast cancer was assumed to be a breast cancer death. The authors state that this problem would be balanced by similar numbers in the user and nonuser groups, but this is an assumption. In this population of older women, one would expect deaths from other causes to outnumber deaths from breast cancer. This single assumption by the epidemiologists could have skewed the results.

In addition, the case fatality and breast cancer mortality calculations were adjusted only for age. The authors stated that a relatively small number of deaths precluded multiple adjusting. However, there are so many factors that influence the risk of breast cancer, including age of menarche, age at menopause, age at first full-term pregnancy, parity and age at diagnosis, use of mammography, presence of benign breast disease (specifically with atypical hyperplasia), body size, and alcohol intake How can we know that the results did not reflect an imbalance in some of these factors?

Hormone Therapy and Lobular Breast Cancer

A population-based, case–control study adds to the previous reports from this Seattle group of epidemiologists focusing on the relationship between postmenopausal HT and the histologic subtype of breast cancer.[861] The main conclusions are an increased risk of tumors of the lobular type or with a lobular component and an increase in the OR that appeared with 3 or more years of use with combined estrogen–progestin therapy. Similar results were reported in Swedish and German case–control studies.[855,862]

It is a logical conclusion that the results reflect increasing proportions of hormonally sensitive tissue. Lobular tumors are characteristically ER-positive and more hormone sensitive. If HT is affecting preexisting tumors, one would expect the hormonally sensitive lobular cancers to be detected earlier.

Key Points: Hormone Use and Breast Cancer

- **Case–control and cohort studies have identified an increased risk of breast cancer associated with HT, greater with combined estrogen–progestin regimens.**
- **The incident cases of breast cancer associated with HT use are predominantly ER-positive tumors, perhaps mostly tumors with lobular tissue.**
- **An increased risk of breast cancer is predominantly observed only in current users and is detected relatively rapidly.**

The Women's Health Initiative

The impression gained from the observational data concluding that exposure to estrogen–progestin was more harmful was reinforced when clinicians were confronted by the results in the prematurely stopped estrogen and progestin (CEE+MPA) arm of the WHI.[863] Invasive breast cancer was increased, 199 cases in the treated group and 150 in the placebo group (HR = 1.24; CI = 1.01–1.54). The absolute risk was four to six additional cancers per 10,000 women per year. The WHI performed

subgroup analyses focusing on how prior HT use influenced the risk of breast cancer found in the estrogen–progestin trial arm.[864] Prior hormone users totaled 4,311 participants (26%), with 42% reporting less than 2 years of use (17% used hormones 5–10 years previously and 26% >10 years before enrolling in the WHI study). Prior users had an increased HR compared to placebo (1.96; CI = 1.17–3.27) in contrast to no increase among never-users (1.02; CI = 0.77–1.36). The WHI concluded that this difference could reflect an increasing risk with cumulative exposure to HT.

Many of the factors associated with the risk of breast cancer were slightly but significantly more prevalent in the group of prior hormone users in the WHI, such as younger age, more education, lower body mass, more physical activity, smoking, alcohol use, VMS, and lower bone density. The overall risk of breast cancer in the treated estrogen–progestin group was the same as previously reported by the WHI (1.24; CI = 1.02–1.50).[863] However, after adjusting for the multiple factors recognized to influence the risk of breast cancer, *the HR was 1.20 and no longer statistically significant* (*CI = 0.94–1.53*). The placebo group failed to demonstrate an age-related increase in risk over the duration of the trial, and the treatment group and the placebo group differed in regard to breast cancer risk factors, creating a need for the investigators to perform multiple adjustments. Why did not the randomization of large numbers avoid this confounding problem? **The strength of the WHI conclusion is limited by the fact that the participants in the treatment and placebo groups differed considerably.**

Results in the second estrogen-only arm of the WHI, which too was prematurely stopped, failed to detect an increase in breast cancer risk associated with estrogen-alone use (RR = 0.80; 95% CI = 0.62–1.04).[865] Furthermore, a statistically significantly decreased risk of breast cancer was noted in the CEE group compared to placebo in the postintervention phase (HR = 0.77; 95% CI = 0.62–0.95).[866,867] In addition, there was a significantly lower mortality risk from breast cancer in the estrogen-treated group compared to placebo (HR = 0.37; 95% CI = 0.13–0.91).[867] This striking difference between the CEE+MPA versus CEE-alone arms of WHI led many to conclude that exposure to progestin (MPA) may be causative to the exaggerated breast cancer risk that was observed only in the CEE+MPA arm of WHI hormone trials. A longitudinal median of 20-year follow-up on the WHI cohort was published in 2020, wherein not only the earlier

observed risk reduction in breast cancer in the CEE-alone hormone trial persisted, but a lasting reduced mortality from breast cancer was also evident in postmenopausal participants of the WHI E-alone hormone trial.[868] Conversely, the slightly higher risk of breast cancer that was apparent at the termination of the WHI E+P trial was noted to persist at 20-year follow-up, although reassuringly there was no evidence of increased mortality in participants of the WHI E+P trial. Despite the discrepant incidence of breast cancer in the two WHI hormone trials, it must be emphasized that the populations participating in the two trials differed considerably, such that it is not appropriate to simply conclude that the differences in breast cancer risk can be attributed to the effects of progestin exposure. Even the WHI investigators cautioned clinicians to avoid comparing the two trial arms because the participants in the two arms differed noticeably.[768] In regard to breast cancer risk, women in the estrogen-only arm had a higher rate of previous exposure to hormones and longer durations of prior use. It is possible that earlier and greater use of HT before participation in the study identified those individuals with preexisting tumors who were then excluded from participation, accounting for the lower incidence of breast cancer in the treated group. **The breast cancer results in the WHI do not allow us to answer the important question whether exposure to estrogen–progestin has a greater risk of breast cancer or whether preexisting tumors respond differently to the various hormone regimens, accounting for differences in epidemiologic reports. This is further addressed later in this chapter.**

BREAST CANCER RISK AND DURATION OF HORMONE USE

A cohort study assessed the risk of breast cancer in postmenopausal Finnish women using oral, transdermal, and vaginal estrogen-only or estrogen–progestin products containing either estradiol or estriol.[869,870] The use of estradiol for 5 years or more and the use of estrogen–progestin for 3 years or more were associated with a statistically significant increased risk. The risk was similar when comparing oral and transdermal therapy. An increase was observed in both localized and metastatic diseases. A statistically significant increase was noted with carcinoma in situ.

Only 7% of Finnish postmenopausal women used HT for more than 5 years. This study reported an increase in breast cancer risk in this long-term user group of women. No increase in breast cancer risk was detected either in association with estriol given orally or with vaginal estrogen products. However, it is inappropriate to conclude that these formulations can be used without risk. To make this conclusion, users and nonusers of these formulations would have to be comparable in terms of breast cancer risk factors and in terms of bioequivalent blood levels of estrogen. Only then could a valid comparison be made. This study could not adjust for these factors.

The use of postmenopausal HT in Finland can be accurately recorded because all treatments must be prescribed and then paid for by the National Social Insurance Institution. However, the study is affected by an overwhelming problem: The results are questionable because of an inability to control for confounders. The risk was expressed as incidence ratios, calculated by dividing the observed number of cases by the numbers expected (based on the general statistics in Finland). Therefore, the study could not be controlled for confounders. Risk ratios less than 2.0 can easily be inaccurate because they can reflect confounding factors. It is well demonstrated that hormone users differ when compared to nonusers in terms of recognized risk factors for breast cancer. The differences also include a greater prevalence of mammography among hormone users. A good example can be found in the report from the Nurses' Health Study that, like the cohort from Finland, indicated an increased risk of breast cancer with long-term users of estrogen only.[871] The long-term HT users in the Nurses' Health Study had more bilateral salpingo-oophorectomies, more nulliparity, more benign breast disease, and greater alcohol consumption, and they were thinner—all factors that make a comparison of HT users to nonusers very difficult.

In order to minimize the problem of confounders, the Finnish report argued that "there are no socioeconomic differences between postmenopausal hormone therapy users and the general population in Finland," citing a previous report. This statement is not totally accurate. The previous report in 1999 was based on population surveys and measured only two things: length of education and rural versus urban living.[872] A lack of educational differences was present in Finnish women under the age of

55, but older postmenopausal women had more years of education. In addition, there were regional differences at all ages, with the current use of HT being most common in the Helsinki area (especially among older women). Therefore, the 1999 study does not imply a lack of differences in hormone users in Finland, in fact, just the opposite. Age information is not provided in the reports on breast cancer, but the longer term hormone users were probably an older group of women, and according to the 1999 Finnish report, they do differ when compared to the general population of Finland. Remember, this cohort study is not comparing users with nonusers. It compares users to general population statistics. Therefore, we cannot know whether the results of this study reflect long-term use of estrogen or whether the results reflect a greater prevalence of risk factors and mammography in the hormone-using group (see **Table 22.7**).

Hormone Therapy and Breast Cancer Outcome

Long-term use of HT increases the risk of breast cancer, yet cause-and-effect mechanisms are unclear. In the WHI trials, estrogen plus progestin use showed increased risk, while use of estrogen alone did not result in added risk for breast cancer. This disparity in results of the two WHI hormone trials raised concerns that progestin may be the culprit in causing breast cancer in hormone-using menopausal women. Most of the studies that have examined breast cancer mortality rates of women who had used postmenopausal HT at the time of diagnosis have documented improved survival rates.[720,731,739,873–882] Even a study that indicated a reduction in mammographic sensitivity also reported smaller, more differentiated tumors among the users compared with the nonusers.[336] Evidence indicates that hormone users develop smaller, better-differentiated (lower grade), and lower-stage tumors, evidence that is consistent with the effects on preexisting tumors and that surveillance/detection bias is not the only explanation for better survival.[851,881–899] Lower-grade tumors are present even when there is no difference in the prevalence of mammography comparing hormone users and nonusers or when the data are adjusted for the method of detection.[877,879,890,900] This is not a totally uniform story, in that at least one prospective study concluded that estrogen–progestin users had both lower and higher stage and grade tumors.[851] However, nearly all

reports indicate that more tumors in hormone users are detected by screening mammography, and when assessing outcomes in all cancers detected by mammography, hormone users have more ductal in situ tumors, more node-negative cancers, smaller tumors, and less invasive disease and, thus, better survival rates.[882,895]

In contrast, the WHI results in the estrogen–progestin arm indicated an earlier appearance of *invasive, lymph node–positive* tumors than previously reported in case–control and cohort studies. The WHI argued that the results (both the invasive breast cancers and the mammography findings) are consistent with stimulation of growth of established breast cancers (supported by no statistical difference in in situ tumors in the WHI trial) but at the same time a delay in diagnosis. This certainly challenges the idea that hormone users have better outcomes because of earlier detection. The WHI suggested that this disagreement could be because of a difference of mammography use in the observational studies. However, as pointed out, even studies that examined tumor characteristics and outcome in users and nonusers who have equally used mammography, lower-grade and lower-stage disease with a better outcome is identified in the users.[877,879,895] In addition, a prospective cohort study found little impact of hormone use on mammography specificity.[901]

Differing with many reports in the literature, the WHI concluded that their results suggested that invasive breast cancers diagnosed in women who use HT may have a worse prognosis, basing this conclusion on the differences observed in tumor size and spread of disease. As discussed previously, it is well recognized that the participants in the WHI represent an older postmenopausal population (average age 63 and an average of about 12 years since menopause in the estrogen–progestin arm). This older population is more likely to have preexisting occult tumors that would become detectable quickly after hormonal stimulation. In addition, breast tissue in older postmenopausal women may respond differently to hormone stimulation than breast tissue in women close to their menopause. It is possible that the WHI results reflect this older population who might have occult tumors that are in fact larger and more prone to respond to hormonal stimulation than tumors in younger women.

There is another problem with the WHI data on tumor size and stage of disease. The WHI reported that estrogen–progestin users had slightly larger

tumors (an average of 2 mm) and less localized disease. However, there are reasons both obvious and not apparent, why the WHI data disagree with the great bulk of the literature. First, no nodes were examined in nearly 10% of the subjects who developed breast cancer; information was missing on node involvement in 4.0% of the treated group and 4.7% of the placebo group and on tumor size in 6.5% of the treated group and 6.0% of the placebo group. Because case numbers were not large, a change in a few cases could change the conclusions. Next, the WHI investigators assumed that tumors less than 1 cm in size with no node information should be classified as localized disease, and those greater than 1 cm in size were not staged. According to the U.S. Surveillance, Epidemiology, and End Results (SEER) data, breast tumors 1 cm in diameter have a 20% incidence of positive nodes.[902] Finally, there is a major problem that is hard to explain. The WHI conclusion of less localized disease in hormone users is based on, once again, a difference in the placebo group, a surprisingly low incidence of positive nodes. There is a linear relationship between tumor diameter and the percent of cases with positive nodes.[902] The average tumor size in the placebo group was 1.5 cm, and according to US data, this should give about a 25% incidence of positive nodes, not the 15.8% that was reported.[902–905] Why is the placebo group different? Whatever the reason, it influences the conclusion.

In 2008, the WHI investigators had reported health outcomes at 3 years after the estrogen–progestin arm of the clinical trial was terminated.[906] This follow-up report had included 15,730 participants who were followed from July 2002 to April 2005 (95% of randomized women). No increase in cardiovascular events, including venous thrombosis, in the women treated with estrogen–progestin was observed in the follow-up period. There were 79 cases of invasive breast cancer in the treated group in the follow-up period compared with 60 in the placebo group, a difference that gave an HR of 1.27, but it was not statistically significant. There was no difference in cases of colorectal cancer or fractures and a nonsignificant decrease in endometrial cancer in the treated group. There was a greater rate of mortality in the treatment group in the follow-up period, but this difference was small and not statistically significant. This WHI follow-up report concluded that the trend of increasing breast cancer during the trial period did not extend into the follow-up period. However, in 2020, the WHI

investigators reported on 20 years of follow-up of participants of both estrogen plus progestin and estrogen-alone hormone trials.[868] Unlike findings at 3-year follow-up, the difference in breast cancer incidence between the estrogen plus progestin versus placebo groups differed significantly at 20 years median follow-up (annualized rate was 0.45% in the E+P arm vs 0.36% in the placebo arm; HR = 1.28; 95% CI = 1.13–1.45; $P < 0.001$). Reassuringly, despite the incidence of breast cancer being higher in estrogen plus progestin group, there was no significant difference in breast cancer mortality between E+P and placebo groups (annualized mortality rate was 0.045% in the E+P vs 0.035% in the placebo arm; HR = 1.35; 95% CI = 0.94–1.95; $P = 0.11$). Unlike findings of the WHI E+P hormone trial, the previously observed reduction in breast cancer incidence in the estrogen-alone hormone trial was noted to persist at a median of 20 years of follow-up (annualized rate was 0.30% in participants in the E-alone arm vs 0.37% in the placebo group; HR = 0.78; 95% CI = 0.65–0.93; $P = 0.005$). Furthermore, breast cancer–related mortality was also significantly lesser in postmenopausal participants of the estrogen-alone arm of WHI compared to placebo (annualized mortality rate in the E-exposed group was 0.031% vs 0.046% in the placebo group; HR = 0.60; 95% CI = 0.37–0.97; $P = 0.04$). In reporting this extended follow-up on WHI hormone trial participants, the WHI investigators rightly conclude that "the influence of menopausal hormone therapy on breast cancer remains unsettled with discordant findings from observational studies and randomized clinical trials."[868]

Key Points: Breast Cancer in Hormone Users

- **Lower grade and stage of disease account for the better survival rates in hormone users who develop breast cancer compared with nonusers.**
- **Hormone users who develop breast cancer usually have earlier detection of their tumors.**
- **The survival and detection results are consistent with an impact of HT on preexisting tumors.**

The Impact of Hormone Therapy on Breast Density and on Mastalgia

An increase in mammographic breast density occurs at a greater rate in postmenopausal hormone users who develop mastalgia.[907] According to the Postmenopausal Estrogen/Progestin Interventions (PEPI) and WHI clinical trials, about 25% to 30% of women receiving combinations of estrogen and progestin develop breast tenderness.[907,908]

The subject of greatest clinical relevance, in our view, is the connection between breast tenderness and breast density and ultimately an impact, if any, on the risk of breast cancer. Although the increase in new-onset breast tenderness is associated with a greater increase in mammographic breast density compared with women who do not develop mastalgia, it is worth noting that one study asking whether hormone-induced changes in breast density increase the risk of breast cancer could find no evidence that this was so.[909]

A report from the WHI concluded that new-onset breast tenderness in the canceled estrogen–progestin arm of the WHI was associated with an increased risk of breast cancer (HR = 1.48; CI = 1.08–2.03) when compared to women who did not develop mastalgia.[908] The WHI report gave the impression that this linkage was of sufficient magnitude that it should be a major clinical concern, but there are reasons to place it in a different perspective.

The WHI compared the numbers for sensitivity, specificity, and positive predictive value with the Gail model, implying clinical worthiness by their similarity. However, the positive predictive value of new-onset mastalgia in the WHI was only 2.7%, meaning that 97.3% of the women would be expected not to develop breast cancer! Furthermore, in the references cited by the WHI to support their use of the Gail model, one actually concluded that the Gail model is not particularly sensitive in identifying individuals at risk, and the other was a study of false-positive mammogram screening.[910,911] A positive predictive value of 2.7% is not clinically strong.

The WHI report appropriately acknowledges the increase in breast tenderness noted in some postmenopausal women treated with HT and the link between mastalgia and an increase in mammographic density; however, the WHI report discusses these subjects as if it has accepted that the

hormone-induced increase in density is associated with an increased risk of breast cancer. Let us consider these issues.

Increased density impairs the detection of breast masses.[912] A failure to detect masses because of high tissue density causes an increase in interval cancers (cancers that present between mammographic screenings; in other words, cancers diagnosed after a negative mammogram).[913] Difficulties in reading high-density mammograms also produce false-positive recalls (patients who are recalled for assessment and found not to have cancer). Being recalled for reassessment after an initial mammogram is a cause of significant psychological stress.[914] In addition, at least 25% of the overall cost of mammographic screening in one US program was attributed to investigations of false-positive readings.[911]

These two problems, an increase in interval cancers (a decrease in mammographic sensitivity) and an increase in false-positive recalls (a decrease in mammographic specificity), are consistent with a possible decrease in the detection of cancer. Thus, the concern with dense breasts in postmenopausal women is a reduced quality of mammograms that would decrease the ability to detect early breast cancers.

Factors that are associated with greater breast density are nulliparity, older age at first birth, and current use of postmenopausal HT.[915] Mammographically, dense breasts reflect a high proportion of stromal, ductal, and glandular tissue, associated with epithelial and stromal cell proliferation.[916] The likelihood of dense breasts in hormone nonusers decreases with advancing age and increasing body weight as glandular tissue is replaced by fat.[915] The link with nulliparity supports the contention that a full-term pregnancy early in life produces a change in structure in the breast that persists throughout life and is associated with resistance to proliferation.

Assessing the impact of breast density on the risk of breast cancer is complicated by two factors that produce heterogeneous data: (1) results from programs with biennial screening are less favorable when compared with annual screening and the available data are derived from both, and (2) results from recent years are better, reflecting improvements in technology. Nevertheless, high breast density (75% dense) on mammography in *hormone nonusers* is reported to be associated with a 4- to 6-fold increased risk of breast cancer.[917–920] **Although HT increases breast density in some**

women, it is not certain that the short-term increase in density with HT changes an individual's risk of breast cancer.

More current users of HT have denser breasts than nonusers.[915,921–924] In women younger than age 55, it is difficult to find any differences between hormone users and nonusers.[185] The impact is essentially limited to women older than age 55. The effect of HT on breast density occurs rapidly; thus, duration of use has no effect.[185] In the PEPI 3-year randomized trial, almost all increases occurred within the first year, with an increase in breast density observed in 8% of estrogen users and 19% to 24% of estrogen–progestin users and only 2% in the placebo group.[925] The users of estrogen–progestin combined regimens had a greater risk of developing denser breasts compared with estrogen-alone treatment (7- to 13-fold greater in the PEPI trial with no differences observed comparing MPA to micronized progesterone).[925] In the WHI, estrogen–progestin use increased density in an average of 6.0% of users in the first year, with attenuation in the second year to 4.9%.[926] In careful studies, the daily, continuous, combined estrogen–progestin regimens have been reported to have a greater effect than sequential regimens, with an increase in density occurring within the first months of treatment and then maintained with no change.[335,336,927–929]

Therefore, HT increases breast density mainly in older postmenopausal women, more women respond to combined estrogen–progestin regimens (especially the daily, continuous programs), and the effect occurs within the first months of use and remains stable with no changes or some attenuation with increasing duration of use. However, this effect is only seen in at most about 25% of estrogen–progestin users, but usually around 10% of hormone users; indeed, it should be emphasized that most women do not respond in this manner.

Overall, studies have suggested that hormone users experience a decrease in mammographic sensitivity with a lesser impact on specificity (false-recall rates). However, the studies are based on small numbers of interval cancers, and it is uncertain how real or how large this effect is because of the difficulty in controlling for confounding factors (eg, age, age at menopause, and time since menopause). If the effectiveness of breast cancer screening is reduced by postmenopausal HT, one would expect an adverse impact on breast cancer mortality. Instead, a study that indicated a reduction in mammographic sensitivity also reported smaller, more

differentiated (grade I) tumors among the users compared with the nonusers,[336] and most of the studies that have examined breast cancer mortality rates of women who had used postmenopausal HT, as reviewed earlier, have documented improved survival rates.

If breast density and breast cancer were a reflection only of hormone exposure, a strong preponderance of ER-positive tumors would be expected in women with increased density. However, women with increased density demonstrated equal increases in risk for both ER-positive and ER-negative breast cancers, and one study found a preponderance of ER-negative tumors in hormone users with dense breasts.[930,931] This suggests that other factors besides hormone exposure are involved in the relationship between density and breast cancer. For example, there is an association between breast density and family history of breast cancer, indicating an underlying genetic basis for both density and breast cancer.[932] In a case–control study that assessed the relationship between HT and breast density, leaner women were more likely to increase their breast densities with HT, but there was no association between the response to hormones and family history, late age at first birth, or history of benign breast disease; the study concluded that recognized risk factors influenced the response to HT only to a minor degree, suggesting again that unknown genetic factors are involved.[933] In a study designed to correlate histologic findings in dense breast tissue, an increase in fibrous stroma and type 1 lobules was observed to be more prevalent in hormone users, but these changes were also present in nonhormone users, and overall, there was no statistically significant difference between histologic features and breast density in women undergoing mastectomy for breast cancer.[934] If breast density in postmenopausal women were strictly related to the hormonal environment, a drastic reduction in the estrogen milieu of the breast should have a salutary impact on density. The MAP1 randomized trial evaluated the effect of letrozole treatment on breast density; no effect of AI administration on breast density was observed despite 1 year of treatment.[935]

A Swedish study looked at the type of progesterone and breast density, with estradiol and either NETA or DRSP. Because of its antiandrogenic and mineralocorticoid actions, DRSP was hypothesized to perform differently than NETA. One hundred and twenty healthy, naturally postmenopausal women were randomized to either 2 mg of DRSP or 0.5 mg of NETA;

either progestin was administered as a continuous regimen in combination with 1 mg of oral E2 for 6 months, and investigators chose to examine the impact of choice of hormone regimen on two recognized surrogates for breast cancer risk, mammography, and fine-needle aspiration biopsy; testing was performed at baseline and at 6 months following initiation of intervention. A statistically significant increase in breast density was noted in both groups, and the magnitude of this change from baseline was comparable in DRSP and NETA groups. Proliferation of breast epithelial cells also significantly increased in both groups but was slightly yet significantly more pronounced in the E2/DRSP compared to NETA group. The change in breast cell proliferation at 6 months compared to baseline for E2/DRSP was 2.5% versus 0.7% for E2/NETA ($P < 0.01$); while these differences were of statistical significance, clinical implications, if any, of this minimal differential in proliferative effects of two commonly utilized progestins are unclear.[936]

The combination of the LNG intrauterine contraceptive device and ET in postmenopausal women does not seem to increase breast density as assessed by mammography.[937,938] However, recent data utilizing magnetic resonance imaging (MRI) are suggestive of systemic effects of LNG-IUD as an increase in background parenchymal enhancement in breast MRI has been described in LNG-IUD users.[939]

The increase in breast density associated with HT appears in some studies to be a transient, reversible change, a change not consistent with a *persistent* effect on cellular proliferation. After discontinuing HT, it was reported that breast density rapidly decreases after HT is discontinued so that former users do not display an increase compared to never-users.[915,924,940,941] In a retrospective analysis, regression of hormone-induced abnormalities was found to occur within 2 to 3 weeks of cessation of treatment.[941,942] However, in a large randomized trial of 1,704 women aged 45 to 80 years, although suspension of HT for 1 or 2 months produced small but significant decreases in density, mammography recall rates of 10% to 12% were not affected.[943] Furthermore, a nonrandomized before and after study (but of only 47 women) detected no significant changes in mammographic density after a 4-week cessation of HT.[944] Besides discontinuing HT, another approach is to consider lower doses of hormones;

there is some evidence that low-dose treatment has little effect on breast density.[945]

Key Points: Breast Density and Hormone Use

- **Some women develop an increase in breast density with the current use of postmenopausal HT, more often associated with continuous, combined use of estrogen–progestin regimens.**
- **The older a postmenopausal patient, the greater the risk of developing an increase in breast density with HT.**
- **There is no strong evidence to indicate that new-onset breast tenderness or the increase in breast density with HT changes an individual's risk of breast cancer.**
- **The evidence to support a recommendation that HT should be discontinued for several weeks prior to mammography in women who have dense breasts is mixed, and the only randomized study found no impact of suspension of treatment on a mammography recall rate of about 10%. Nevertheless, this is a reasonable recommendation to consider on an individualized basis.**
- **In women who develop mastalgia and/or an increase in breast density with postmenopausal HT, consider a dosage reduction of the administered hormones.**
- **Systemic effects of LNG-releasing intrauterine contraceptive devices on breast tissue are plausible.**

The Effect of Hormone Therapy on Mammographic Screening

The impact of screening mammography has been established by multiple randomized trials: about a 28% reduction in breast cancer mortality in women aged 50 years and above.[946] At the same time, it is recognized that it is difficult for mammography to detect noncalcified masses, especially in dense breasts. This sensitivity problem has been improved by digital mammography, but not eliminated.

Does the hormonal effect on breast density impair mammographic screening? In other words, is there an increase in interval cancers and false-positive recalls in postmenopausal hormone users? In a review of seven studies, there were relatively few interval cancers in the user groups;

nevertheless, six of the seven studies reported decreased mammographic sensitivity in hormone users with a small increase in interval cancers in users compared with nonusers.[947] Excluding women under age 50, the RR for an interval cancer was summarized as 1.7 (CI = 1.2–2.4). American, Scottish, and Australian studies have indicated a 5% to 20% decrease in mammographic sensitivity in hormone users who have dense breasts.[948–951] A Finnish study concluded that women with the densest breasts, and using hormones, had the highest RR of breast cancer, but this conclusion was based on only four cases of cancer in women with dense breasts.[952]

The risk of false-positive recall (mammographic specificity) was investigated in five studies.[948,952–955] The rate of false-positive recall in nonusers ranged from 2.1% in the United Kingdom to as high as 14.7% in an American program; four of the five studies found a slight increase in the risk of false-positive recalls in hormone users. In a French study, mammographic sensitivity was reduced from 92% to 71% in users because of an incidence of interval cancers that was 3.5 times that of nonusers within the first year of the initial examination and 1.7 times greater during the following 2 years.[953] Most of the hormone users were on combined estrogen–progestin regimens. The false-positive recall rate was only slightly higher, 3.3% in users and 2.8% in nonusers. A prospective study of screening mammograms from Massachusetts General Hospital concluded that recall rates were essentially the same comparing hormone users and nonusers and that HT rarely causes a diagnostic dilemma.[954] However, in New Hampshire, increased breast density and use of HT independently increased the need for supplemental imaging.[955]

Treatment with either estrogen alone or estrogen–progestin in the WHI was associated with more abnormal mammograms compared with placebo.[866,956] The difference was about 12% with estrogen–progestin and 8% with estrogen alone, but remember the characteristics of the participants differed in the two arms of the clinical trial. Nevertheless, the higher prevalence with estrogen–progestin is consistent with the other studies in the literature. Overall, the studies have suggested a decrease in mammographic sensitivity with a small impact on specificity (false-recall rates).

Adding Ultrasound to Mammography

The American College of Radiology conducted a prospective, multicenter, randomized trial in 21 centers in the United States, with 2,725 women, designed to validate the performance of screening ultrasound in conjunction with mammography in women with dense breasts and at high risk for breast cancer.[957] Each patient underwent mammography and ultrasound in a randomized sequence. Forty cases of cancer were diagnosed, 12 on ultrasound alone, 12 on mammography alone, 8 suspicious with both techniques, and 8 with negative examinations. Adding ultrasound yielded an additional 4.2 cancers per 1,000 high-risk women. The false-positive rate for mammography alone was 4.4%, for ultrasound alone 8.1%, and for combined mammography plus ultrasound 10.4%. **Thus, adding ultrasound to mammography screening in high-risk women with dense breasts improved the sensitivity of screening but increased the rate of false-positive examinations. Breast cancer mortality was not an end point in this trial, but the fact that the cancers detected by ultrasound are usually asymptomatic, node negative, and not detected by mammography should yield a reduction in mortality.**

Ultrasound screening can detect cancers not seen on mammography, and its performance is not affected by dense breast tissue. Adding ultrasound to a screening program seems straightforward, but its impact on mortality reduction has not been measured in a large trial. In the single-center studies of screening ultrasound that have been published, cancers have been found only by ultrasound, and most are small, early-stage tumors. An Italian multicenter study reported that 29 cancers were found by ultrasound in 6,449 women with dense breasts and negative mammograms.[958]

The problem with all screening methods is a substantial rate of false positives. In the American study, 91.4% of suspicious ultrasound findings were benign.[957] The positive predictive value for ultrasound was only 8.6%, but the value for mammography was 14.7%. The crucial question is how many false positives are worth the gain in additional cancer diagnoses. In the American study, the gain was an additional 29% (the number of cancers detected only by ultrasound). In women with elevated risks, this seems worthwhile.

Combining MRI with mammography yields a very high sensitivity, and this is now recommended for women at very high risk for breast cancer. Breast MRI is the most sensitive technique, but it is very expensive,

requires the intravenous injection of contrast, and is not always tolerated by patients. Ultrasound has the advantage of being less expensive, easily tolerated, and widely available. Thus, the combination of ultrasound and mammography seems best for women of intermediate risk. Ultrasound has a disadvantage of not detecting ductal carcinoma in situ, which is detected by mammography and MRI.

In general, supplemental screening for dense breasts (either ultrasound or MRI) will identify more breast cancers (invasive cancers), but it may come at the cost of increased false-positive rates and biopsies.[959] What is not known, however, is if cancers identified from ultrasound and MRI have improved outcomes and reduced mortality.[959] **Further research studies are clearly needed.**

Key Points: Mammography Screening

- **There is sufficient evidence to support utilizing more than one screening technique (mammography, ultrasound, and MRI) for high-risk patients defined as a combination of factors that produces a 3-fold increase in risk, especially in women with radiographically dense breast tissue. Thus far, over 90% of cancers detected only on ultrasound have been in women with dense breasts. Therefore, it seems advisable to add ultrasonography to mammography for hormone users who develop dense breasts, and the density persists despite a short period without HT. In addition, digital screening mammography is superior to conventional film screening for women with dense breasts.**[960]
- **Hormone users who develop an increase in breast density have a small decrease in mammography sensitivity and an increase in false recalls. An adverse impact of this increase in breast density is not apparent in breast cancer mortality statistics in hormone users. Digital mammography is preferred for women with dense breasts.**
- **Ultrasonography should be added to mammography screening in hormone users who develop dense breasts with no regression after a short period without hormone treatment.**

The Effect of Progestins in Combined Regimens

Overall, studies support the conclusion that the RR of breast cancer is higher in users of combinations of estrogen and progestin. The effect is confined to ER-positive, PR-positive (ER+/PR+) tumors, mainly lobular cancers. **What if this conclusion reflects early detection of better-differentiated tumors, a consequence of a favorable response of preexisting tumors to estrogen–progestin exposure?**

Almost every study that has reported an increase in breast cancer risk with postmenopausal HT has found the increase within a few years. Remember that although the doubling time of breast cancer is variable, in general, a tumor doubles in size every 100 days. Thus, it takes a single malignant cell approximately 7 years to become detectable by mammography and 10 years to grow to a clinically detectable 1-cm mass.[961] The rapid finding of an increased risk within a few years of exposure to HT suggests that the epidemiologic studies are detecting preexisting tumors.

Older studies on the hormone receptor content in breast cancers diagnosed in hormone users were limited by small numbers. Furthermore, recent studies examining receptor status are likely to be more accurate in that receptor status assays have improved. In the Nurses' Health Study, the use of postmenopausal HT has been associated with a significant increase in ER+/PR+ breast cancer, but not in receptor-negative disease.[962] This relationship, greatest in lean women, was stronger and observed sooner with the use of estrogen–progestin, a significant increase with 5 or fewer years of combined use and no increase with 5 or fewer years of the use of estrogen alone. In a cohort of women from the area of Lund, Sweden, an increased risk of breast cancer was reported only in users of continuous combined estrogen–progestin, and this increase was observed within 2 years of use.[963] Other epidemiologic studies have reported a similar greater risk in current users of continuous, combined estrogen–progestin, concentrated in ER-positive disease.[847,850,853,964,965] Indeed, the use of HT is the greatest predictor of ER-positive disease.[966] In a retrospective study in the Northern California Kaiser program, only the current use of combined estrogen and progestin increased the odds of ER-positive tumors.[967]

E3N is a French prospective cohort study initiated in 1990, which concluded that it would be preferable to use progesterone or dydrogesterone because estrogen use with these two progestins was not associated with an increase in the RR of invasive breast cancer.[968,969] For any given progestin,

the route of administration of estrogen (oral or transdermal) had no effect on RR. A statistically significant increase in RR was associated with estrogen alone (RR = 1.29; CI = 1.02–1.65) and with progestins other than progesterone or dydrogesterone (RR = 1.69; CI = 1.50–1.91). The increased RRs seemed to rapidly dissipate after discontinuation of treatment; although this analysis was initially limited by small numbers, it was confirmed in a later follow-up.[970]

The French study argued that their results indicate that the "natural" progestins are safer than "synthetic" progestins. However, to accurately differentiate among various agents, one would have to be certain that the doses administered represented bioequivalent doses in terms of target tissue impact, something that would be difficult to do. Let us focus on the rapidity at which cases of breast cancer were identified. The use of estrogen combined with "other progestins" had an increased RR even with less than 2 years of exposure (RR = 1.37; CI = 1.07–1.72). In their earlier report, an increased RR was even apparent with less than 1 year of exposure of estrogen combined with synthetic progestins.[968] **The results in the French study could be due to earlier detection of preexisting tumors, an effect accelerated by specific progestins with greater potency.**

A follow-up report from the French study indicated that the increased risk of breast cancer was evident only in women with recent use of HT and not in past users.[970] Furthermore, the risk with short-term use was confined to hormone use with synthetic progestins for 2 years or fewer in the 3-year period immediately following menopause. With longer duration of hormone use, the risk was apparent even in those who initiated treatment years after the menopause. The logical conclusion is that this striking finding with short-term use early in the postmenopausal years reflects an impact of HT on preexisting tumors.

More recently, a study from England analyzed real-world data on nearly 100,000 women with a primary diagnosis of breast cancer between 1998 and 2018, and 457,498 female controls matched by age, general practice, and index date; relationships of HT use, duration of exposure, and type of HT with breast cancer were examined.[971] An increased rate of breast cancer was noted for current users of HT with less than 5 or greater than 5 years of hormone use (either estrogen alone or combination of estrogen and progestin) as well as for previous users of combination HT for more than 5

years. The authors have carefully placed their findings into practical counseling terms for patients and providers in indicating that there were approximately 3 to 8 extra cases per 10,000 women years for current estrogen-only users, 9 to 36 per 10,000 in current combination therapy users, and 2 to 8 per 10,000 for previous greater than 5-year combination HT users. This study also broke down the higher risk types of progestogens and can serve as a meaningful guide toward counseling patients on HT-related risks.

Molecular biology studies have attempted to gain clarity on the effects of estrogens and various progestins in HT formulations on breast cancer risk. In vitro studies using microarray analysis have profiled the gene network both up- and downregulated by estrogen.[972] Genes that are upregulated by estrogen are downregulated by estrogen–progestin treatment.[973] Comparing hormone users and nonusers, 276 genes were activated by hormone exposure (11 of the 13 women used estrogen–progestin and 2 used estrogen alone). All patients in this cluster were free of recurrence 5 years after diagnosis. In a cohort of 131 women, those patients exhibiting the gene profile associated with estrogen–progestin exposure preferentially benefited from tamoxifen treatment.[973] This Swedish study found that estrogen–progestin use altered the gene expression profile only in ER-positive cancers. Among the genes regulated, many were involved in either DNA repair or cell cycle regulation. For example, the p63 gene, involved in tumor differentiation, was overexpressed in estrogen–progestin users. Previous reports have found this gene to be expressed in normal tissue, partially expressed in ductal hyperplasia and not invasive cancers.[974]

It is well recognized that early pregnancy produces a mammary gland that is resistant to carcinogenesis. In rodents, this is accomplished by treatment with estrogen plus a progestin. The refractory phenotype that is produced is associated with progestin-induced changes in gene expression involved in cell proliferation.[975]

The PR is induced by estrogens at the transcriptional level and decreased by progestins at both the transcriptional and translational levels (probably through receptor phosphorylation).[976] The PR has two major isoforms, designated the A and B receptors.[977] The two forms are expressed by a single gene, a consequence of transcription from distinctly different promoters, in a complex system of transcription regulation.[978] Progestational

agents can elicit a variety of responses determined by target tissue production and activity of the two receptor forms with dimerization as AA and BB (homodimers) or AB (heterodimer).

PR-A and PR-B are expressed in various amounts in breast cancer and endometrial cancer cell lines. Studies indicate that the two receptors can be regulated independently; for example, the relative levels differ in the endometrium during the menstrual cycle.[979] Tissue specificity with the PR is influenced by which receptor and which dimer is active, and in addition, the transcriptional activities of PR-A and PR-B depend on target cell differences, especially in promoter context. In most cells, PR-B is the positive regulator of progesterone-responsive genes, and PR-A inhibits PR-B activity. Thus, repression of human ER transcriptional activity (as well as glucocorticoid, mineralocorticoid, and androgen transcription) is dependent on the expression of PR-A.[980,981] The PR-A and PR-B have different molecular functions, affecting different genes, and, therefore, target tissue response to progesterone will be influenced by the differential expression of each receptor and the ratio of their concentrations, as well as the target tissue context of adaptor proteins.[982,983]

PR-A–positive breast cells exhibit more aggressive growth, and PR-A isoforms are dominant in the absence of progesterone. Even without its ligand, PR-A can exert gene regulation in ER-positive breast cell lines.[984] In the absence of progesterone, PR-A upregulates genes known to be associated with invasion and poor prognosis, including those genes that provide resistance to apoptosis. In the presence of progesterone, PR-B is a stronger regulator of gene transcription. The breasts of normal women express equal amounts of PR-A and PR-B.

PR-A excess and breast cancer are linked. ER-positive tumors with a higher rate of recurrence are rich in the PR-A isoform.[984] As breast cancers become less differentiated, metastatic tumors become dominated by either PR-A or PR-B. PR-A–rich tumors with a low PR-A:PR-B ratio do poorly and respond less well to tamoxifen.[985] PR-A excess is also present in breast tissue from women with the *BRCA* mutations.[986]

Thus, PRs are not just passive markers of estrogen activity. ER+/PR+ tumors are well differentiated and have better outcomes. In the absence of progesterone, the unliganded PR-A can adversely influence the cell biology of ER-positive tumors. Cells rich in PR-A are more likely to be invasive,

poorly differentiated, and aggressive. In monkeys, the breast levels of PR-A were unchanged after 3 years of treatment with conjugated estrogens alone.[987] Treatment with conjugated estrogens and MPA produced a decline in PR-A levels, producing a 10-fold beneficial change in the PR-A:PR-B ratio. It is possible that the exposure of an ER-positive tumor to estrogen–progestin treatment can prevent an unfavorable PR-A:PR-B ratio, promoting the beneficial actions of PR-B. In addition, progestins may activate androgen receptors, a factor that has been demonstrated to inhibit growth and cause apoptosis in breast cancer cells.[988,989]

In a series of in vitro experiments, estradiol and its catechol metabolites induced neoplastic transformation in human breast epithelial cells.[990] This, of course, would be consistent with a genomic impact of estrogen that initiates breast cancer, an effect earlier than a promoting influence on already-established cancers. However, it is difficult to transfer in vitro effects on cell lines to the in vivo situation, and this is especially true with breast tissue that is bathed in a complicated and large collection of stimulating and inhibiting substances. Furthermore, the cells in the in vitro experiments were negative for both ER and PR. These receptor-negative malignant cells may well be something different than the receptor-positive tumors associated with postmenopausal HT.

Favorable effects of progestin exposure are reflected in the studies of the association between endogenous hormone levels and the risk of breast cancer. A pooled analysis of nine prospective studies of postmenopausal women concluded that the risk of breast cancer increases with increasing concentrations of all endogenous estrogens and androgens, including estradiol, estrone, estrone sulfate, androstenedione, DHEA, DHEA-S, and testosterone.[991] The overall increase in breast cancer risk was about 2-fold comparing the lowest endogenous levels in postmenopausal women with the highest levels. Women who ultimately develop breast cancer do not have different blood levels of progesterone.[834] Postmenopausal women who are overweight have an increased risk of breast cancer, and an analysis that adjusted for the increase in circulating estrogens associated with obesity concluded that the increasing risk with increasing body weight is the result of the increase in estrogens.[992]

In contrast to the endometrium, epithelial cell proliferation in the normal breast and in ER-positive tumors reaches its peak during the

progesterone-dominant luteal phase of the menstrual cycle.[963,993–995] This observation has been the driving force behind the argument that progesterone (progestins) is the major hormonal mitogen in the breast. However, studies do not support a major role for an adverse progestational influence. In animal models, it is estrogen that is the major inducer of proliferation and not progesterone. Indeed, evidence indicates that with increasing duration of exposure, progesterone can limit breast epithelial growth as it does with endometrial epithelium.[996–998] In vitro studies of normal breast epithelial cells reveal that progestins inhibit proliferation.[999] The story with human breast tissue specimens removed after the patients were treated with estradiol and progestin is more confusing, indicating, on one hand, that progestins inhibit in vivo estradiol-induced proliferation[996,998,1000] and, on the other hand, markers of epithelial and stromal cell proliferation were higher in women being treated with estrogen–progestin.[183,1001] Nevertheless, progestins have been demonstrated to decrease antiapoptotic protein expression,[1002] and apoptosis in breast tissue is higher in the luteal phase than in the follicular phase.[1003] Conversely, research comparing human breast cancer cell lines to noncancerous cells has demonstrated that progestogens differentially affect breast cell proliferative activity.[1004,1005] A study by Courtin et al analyzed the effects of estradiol (E2) alone, E2 + progesterone (P4), and E2 + MPA on cellular proliferation and apoptosis in breast cancer cells, as well as normal human breast cells.[1006] Treatment with E2 alone in all cell types resulted in increased cell proliferation. In normal human breast cells, the addition of P4 blocked estradiol's proliferative effect and also resulted in an increased number of apoptotic cells. When normal cells were treated with E2+MPA, however, there was little effect on cellular proliferation, and the number of apoptotic cells was decreased. In MCF-7 and T-47D breast cancer cell lines, MPA did not induce cellular proliferation, and neither MPA nor P4 affected apoptosis in these cells. Microarray studies revealed induction of different sets of genes in hormonally treated cells, compared to control cells. E2+MPA modified genes in a distinctly different pattern from E2+P4. In a study by Sweeney et al, it was found that MPA combined with E2 stimulated proliferation in long-term estrogen-deprived MCF-7 (MCF-7:5C) cells, while E2 alone resulted in cell death.[1007] Additional support for progestogens' role in breast cancer comes from studies analyzing MPA's

effects on estrogen-metabolizing enzymes in breast cancer cells. Using T-47D and MCF-7 (breast cancer cells), it was demonstrated that E2+MPA increased the expression of estrogen-activating enzymes but not the expression of estrogen-inactivating enzymes.[1007] This increase was greater than cells treated with E2 alone. Although there was an increase in estrogen-activating enzymes, there was no associated increase in cell proliferation. It is important to note, however, that locally increased estrogen levels can be seen in the breast cancer cell milieu, and this high-estrogen environment facilitates cancer cell growth.[1007] Thus, MPA may exert its carcinogenic effect via induction of a local state of estrogen excess. However, as mentioned earlier, these in vitro models must be interpreted with caution, as what happens in vivo is influenced by many other factors.

In the postmenopausal monkey model, greater breast cell proliferation was observed after 30 months of treatment with estrogen–progestin compared with estrogen alone.[1008] In this same model, the administration of progesterone produced no differences in proliferation markers, but adding MPA to estrogen increased breast proliferation by about 30% compared with placebo.[1009,1010] However, in this 2-month study, the administration of progesterone inexplicably lowered the blood levels of estradiol and estrone by 30% to 50%, in contrast to no effect with MPA. Thus, the tissue results may reflect estrogen differences, not progestin differences. Nevertheless, the monkey experiments do not detect a beneficial effect of MPA. A 2-year monkey study recorded lower levels of p53, a tumor suppressor gene, and lower levels of caspase-3, an enzyme involved in apoptosis with use of MPA[1011] Given the marked similarities in macaques to human gene coding sequences, this primate serves as a more reliable model for studying the effects of menopausal HT on breast cancer acquisition.

A prospective study of premenopausal women in Italy found that higher progesterone levels in the luteal phase were associated with a reduction in breast cancer risk.[1012] However, a nested case–control analysis based on the Nurses' Health Study could find no influence of progesterone levels on breast cancer risk.[1013] In this study, women with the highest levels of total and free estradiol in the early follicular phase had about a 2-fold increase in breast cancer risk, predominantly ER+/PR+ tumors, and a similar increase in risk was associated with higher levels of total and free testosterone and androstenedione. There was no association with luteal estradiol levels, and

the authors speculated that this is because early follicular phase levels reflect nonovarian target tissue levels and also that progesterone downregulation of ERs may occur in the breast during the luteal phase.

Although it is not a uniform story, it is possible that favorable breast tissue effects of progestins translate into better differentiation and earlier detection of preexisting tumors. Supporting data can be found in two important American studies. A retrospective cohort study in the Southern California Kaiser program found a reduction in breast cancer case mortality that was significant only among women with breast cancer who were users of estrogen–progestin, not with estrogen alone.[1014] An increase in lower-grade, lower-stage, and ER-positive cancer was found only in current users of estrogen–progestin. In a study remarkable for its size, 374,465 women screened in six US mammography centers.[851] These data are consistent with a beneficial effect of estrogen–progestin treatment.

Breast cancer mortality was recorded in the Collaborative Breast Cancer Study Cohort, a prospective cohort of 12,269 postmenopausal women from Wisconsin, Massachusetts, and New Hampshire.[1015] Women were followed for an average of 10.3 years after breast cancer diagnosis. After adjusting for BMI, smoking, and history of mammography screening, compared with nonusers, mortality from breast cancer was lower among current users of estrogen–progestin and an even greater effect, a 40% reduction, with 5 or more years of use. These are striking data. The strength of the study is the large size of the cohort. Indeed, this is the strongest evidence thus far published that the use of estrogen–progestin is associated with the development of less aggressive breast cancers. Even in studies that adjusted for the prevalence of mammography screening, breast cancers in hormone users were smaller, had fewer positive axillary lymph nodes, and were of lower-grade disease. More recently, a 15-year prospective cohort study published in 2020 provided additional evidence toward the relationship of type and duration of HT and breast cancer risk. Participants included a total of 75,398 postmenopausal women (31,439 with hysterectomy and 43,959 with intact uteri) for whom information on HT use was available at study baseline[1016] as well as at a follow-up survey undertaken in 2004 and through 2011.[1017] In estrogen-only users, at baseline, the risk of breast cancer was not increased in current users of ET (HR = 1.05, 95% CI = 0.95–1.16); however, estrogen use was associated with an increased risk of breast

cancer in women continuing to use estrogen through 2004 (HR = 1.35, 95% CI = 1.04–1.75). In combination (E+P) hormone users, ever use of E+P at baseline was associated with an increased risk for breast cancer (HR = 1.54, 95% CI = 1.44–1.64); with ongoing use of E+P, there was a doubling in this risk with 10 or more years of use, and this exaggerated risk persisted in those who continued E+P through 2004 (HR = 1.80, 95% CI = 1.39–2.32). Of note, no association was seen in women who discontinued E+P before 2004 (HR = 1.14, 95% CI = 0.99–1.30). Based on this large population-based longitudinal study spanning 15 years of follow-up, it appears that while short-term use of estrogen alone may not confer increased risk (consistent with findings from WHI E-alone trial), with long-term use, excess risk may be apparent. Similar to findings from the WHI E+P trial, an increased risk in breast cancer was evident with estrogen plus progestin combination use, and this risk was noted to exaggerate with ongoing long-term HT use.

The following evidence supports a beneficial impact of progestins on preexisting tumors:

- **An increase in ER-positive tumors is seen sooner with estrogen–progestin treatment, and greater risk is observed with continuous, daily estrogen–progestin use.**
- **Genes upregulated by estrogen are downregulated by estrogen–progestin therapy.**
- **Genes that are activated by estrogen–progestin are involved in DNA repair and cell cycle regulation.**
- **Progestins decrease breast tissue levels of PR-A, causing a beneficial change in the PR-A:PR-B ratio that is associated with better differentiation and outcome.**
- **A reduction in breast cancer case mortality has been reported with estrogen–progestin use and not estrogen alone.**

Prevalence of Breast Cancer and Hormone Therapy

Multiple reports have documented a decline of breast cancer incidence in the United States that paralleled the decrease in use of menopausal HT

following the publications from the WHI hormone trials.[1018–1021] A similar decline was documented in France, Scotland, Switzerland, and Australia.[1022–1025] The decline was partially influenced by a decrease in screening mammography in the United States, but the correlation with hormone use exists even when the examined population includes only women screened with mammography. A similar pattern was evident in the WHI in the years following the cancelation of the estrogen–progestin arm as well as among the women in the observational arm, despite no change in the frequency of mammography in the WHI population.[1026]

This decrease in prevalence is consistent with the uniform findings in case–control and cohort studies of an increase in breast cancer risk only in current users, with a rapid reduction after cessation of treatment. An impact on existing tumors is supported by the other side of the coin, apparent in breast cancer statistics derived from the area around Geneva, Switzerland. Beginning in 1997, the peak breast cancer incidence in the Geneva area moved to a younger group of women (ages 60–64), with an increase occurring only in stage I and II diseases with ER-positive tumors in hormone users.[1027]

As discussed previously, the 20-year follow-up study of WHI hormone trial participants provided valuable insights into long-term effects of a relatively short-term exposure (during the course of WHI hormone trials) to estrogen plus progestin and estrogen alone.[1017] As was suggested by initial results of the respective WHI hormone trials, at a median of 20-year follow-up, differences in breast cancer incidence persisted in participants of the two WHI hormone trials. The incidence of breast cancers was significantly higher in participants assigned to estrogen plus progestin versus placebo at a median 20 years of follow-up (annualized rate was 0.45% in the E+P arm vs 0.36% in the placebo arm; HR = 1.28; 95% CI = 1.13–1.45; $P < 0.001$). However, despite the exaggerated risk of developing breast cancer in estrogen plus progestin group, there were no significant differences in breast cancer–related mortality between E+P and placebo groups. Not only did the previously observed reduction in breast cancer incidence in the estrogen-alone hormone trial persist at a median of 20 years of follow-up (annualized rate was 0.30% in participants in the E-alone arm vs 0.37% in the placebo group; HR = 0.78; 95% CI = 0.65–0.93; $P = 0.005$), but the risk of breast cancer–related mortality was also significantly lesser in

participants of the estrogen-alone arm of WHI compared to placebo (HR = 0.60; 95% CI = 0.37–0.97; *P* = 0.04).[1026]

The national decline in prevalence and the WHI results are both consistent with an impact of HT on preexisting tumors. If HT is affecting preexisting tumors, one would expect small, undetectable tumors to stop changing (at least temporarily) when women discontinue HT. This response would be consistent with the effects being reported, a decrease in ER-positive tumors in younger postmenopausal women. The data most likely primarily reflect existing cancers just below the detection limit in 2002 that slowed or stopped their growing.

The choice of estrogen used in the estrogen-alone arm of the WHI (CEE) has been suggested as one factor that may explain the favorable effects seen on the breast in the E-alone hormone trial. The CEE formulation contains a mixture of multiple estrogens, and each estrogen type not only preferentially binds the two ERs (ER-α and ER-β) but may also exert differential actions depending on the target tissue.[1028,1029] In studying the effects of 11 equine estrogens (in CEE preparations) on the transcriptional activity of ER-α and ER-β, it was found that many of the equine estrogens preferentially bind ER-β. ER-β activation can inhibit ER-α activity on cell proliferation.[1030–1032] The potential SERM-like properties of CEE have also been demonstrated in breast cancer cells treated with CEE and estradiol, where CEE and estradiol were noted to have distinct effects on gene expression.[1033] Furthermore, it has been demonstrated that several estrogenic compounds in CEE act as partial estrogen agonists; thus, like SERMs, the differences in binding and downstream cell signaling may afford CEE with specific tissue manifestations that are unlike estradiol's purely stimulatory effects (ie, manifestation of ER antagonistic effects).[1033,1034] This inhibition induced by equine estrogens may in part explain the decreased risk of breast cancer in the WHI estrogen-alone study; however, additional research is needed before definitive conclusions can be made. The theory that CEE may reduce the risk of breast cancer is supported by 20-year follow-up data from WHI discussed earlier that showed a significantly reduced risk of breast cancer in participants of WHI E-alone hormone trial.[1035]

Lastly, the SERM BZA paired with a CEE may further allow for favorable effects on breast tissue; BZA/CEE also has the added benefit of

avoiding a progestin.[231]

Key Points: Breast Cancer Prevalence and Hormone Use

- **A decrease in breast cancer prevalence paralleled the decrease in hormone use following the publicity generated by the WHI publications.**
- **The decrease in prevalence is consistent with the removal of hormonal effects on small undetectable tumors.**

Hormone Therapy and the *BRCA* Mutations

Women with either *BRCA1* or *BRCA2* germline mutations are advised to undergo bilateral prophylactic oophorectomy after completion of childbearing because of a high lifetime risk (~90%) for developing breast or ovarian cancer. This surgery reduces the risk of ovarian cancer by about 90% and the risk of breast cancer by about 50%. These relatively young women must consider the postoperative consequences of surgical menopause in their decision-making. In a cohort of 462 women with *BRCA1/2* mutations from 13 medical centers in North America and Europe, the incidence of breast cancer was compared in 155 of the women who had undergone bilateral prophylactic oophorectomy with 307 women who did not have the operation.[1036] The women who had oophorectomy had a 60% reduction in the risk of developing breast cancer.

HT of any type did not alter the reduction in breast cancer experienced by the women undergoing oophorectomy. Thus, short-term use (several years) of HT did not have an adverse effect on the beneficial reduction in breast cancer risk following prophylactic oophorectomy. In a later follow-up of this group of women, 93 (60%) of the women who underwent oophorectomy used HT.[1037] The average length of follow-up was 2.6 years (>5 years in 16%) in the surgically treated group and 4.1 years (>5 years in 33%) in the nonoophorectomized group. There was no hint of a

difference in breast cancer reduction comparing hormone users and nonusers. The findings were similar in 34 women who used a combination of estrogen and progestin, but the power of this finding was limited by the small number in this category.

A case–control study of 472 postmenopausal women with a *BRCA1* mutation found that women who used HT after prophylactic oophorectomy, either estrogen only or combined estrogen–progestin, not only did not have an increased risk of breast cancer, but hormone use was actually associated with a decreased risk.[1038] The findings were the same regardless of duration of use, or if it was current or past use. This conclusion is encouraging but limited by the fact that 68% of the tumors in the study were ER-negative, making the ER-positive tumors (that are more likely to be influenced by hormone use) relatively small in number. More recently, HT-related risk for breast cancer in *BRCA1* mutation previvors (without prior history of cancer) who had undergone risk-reducing oophorectomy was examined in a prospective multicenter, multinational cohort study.[1039] Participants were enrolled between 1995 and 2017, with a mean follow-up of 7.6 years. The use of HT was assessed based on questionnaires administered every 2 years. The study included 872 *BRCA1* mutation carriers (mean age 43 ± 8.5 years). Over a mean postoophorectomy follow-up of 7.6 years (range, 0.4–22.1), the use of HT (ever use, any type vs never use) was not associated with an increased risk of breast cancer (HR = 0.97, 95% CI = 0.62–1.52; *P* = 0.89). The results of this study offer reassurance for premenopausal *BRCA1* mutation carriers, considering risk-reducing oophorectomy regarding the relative safety of HT.

Women who are *BRCA* carriers face difficult decisions. **The experience thus far indicates that HT can be used safely for several years.** Continuing follow-up of these patients may extend this period of safety even longer. A *TSEC* (CEE paired with an SERM BZA) may be particularly suitable HT option in this population, given its efficacy for symptom control and skeletal benefit while having neutral effects on the breast and potential of BZA for blockade of breast cancer cell proliferation, as has been demonstrated in vitro.[231,232,1033] However, future studies are needed to establish both safety and efficacy of this newer class of menopausal hormonal regimen in breast cancer survivors as well as those who are at risk for breast cancer, such as *BRCA1/2* carriers.

Prophylactic oophorectomy in women with *BRCA* mutations reduces the risk of breast cancer by about 50%. Thus far, hormone use after prophylactic oophorectomy has not diminished the beneficial reduction in breast cancer risk.

Hormone receptor status of breast cancer cells itself, regardless of hormone use, may be relevant to future prognosis in carriers of *BRCA* mutation. A multicenter, retrospective cohort study examined the impact of hormone receptor status on clinical behavior and outcomes of breast cancer in a cohort of young *BRCA* mutation carriers (aged ≤40 years, n = 4,709) diagnosed with invasive breast cancer; 2,143 (45.5%) had hormone receptor–positive and 2,566 (54.5%) hormone receptor–negative breast cancers.[1040] At a median follow-up duration of 7.9 years, compared to patients with hormone receptor–negative disease, those with hormone receptor–positive cancers experienced a significantly higher rate of distant recurrences (13.1% vs 9.6%, $P < 0.001$), but significantly lesser incidence of a second primary breast cancer (9.1% vs 14.7%, $P < 0.001$). The 8-year disease-free survival, however, was comparable in patients with hormone receptor–positive and hormone receptor–negative disease.

Summary: Postmenopausal Hormone Therapy and Breast Cancer

Key Points

- The WHI agrees with case–control and cohort studies indicating that current use of HT has a slightly increased risk of breast cancer.
- The increased risk is observed sooner with the use of combined estrogen–progestin regimens.
- The increased risk with HT is confined to ER-positive tumors, mainly lobular cancers.
- Epidemiologic data indicate that a positive family history of breast cancer or other risk factors should not be contraindications to the use of postmenopausal HT.
- Women who develop breast cancer while using postmenopausal HT have a reduced risk of dying from breast cancer compared with never-users. This is probably because of two factors: (1) increased surveillance and early detection and (2) an effect on preexisting tumors so that tumors appear at a less virulent and less aggressive stage.

- The most important unanswered question in regard to breast cancer is whether postmenopausal HT initiates the growth of new breast cancers or whether the epidemiologic findings reflect an impact on preexisting tumors. A summary of the wide range of evidence supports a favorable effect of HT on preexisting tumors.
- Epidemiologic studies find an increased risk within a few years of hormonal exposure.
- Breast cancer associated with estrogen–progestin therapy is ER-positive, lower-grade, lower-stage disease with better survival rates.
- Epidemiologic studies find an increased risk only in current users; 5 years after discontinuation, the risk returns to baseline.
- The observed rapid decrease in breast cancer prevalence in mid-2000 to 2010s coincides with a decrease in the use of menopausal HT after the release of results of the WHI hormone trials.

Postmenopausal HT may be associated with a small increase in the risk of breast cancer. Of course, even a small increase in risk for breast cancer is frightening for patients to contemplate. It is helpful to remind patients of the risk of lung cancer associated with smoking (RR = 10–20), a risk magnitude that provides perspective on the possible risk associated with HT. It is also worth pointing out that the reported risk with HT is even smaller than that associated with recognized risk factors, such as a positive family history, being overweight after menopause, and alcohol intake. In our view, because the literature is sufficiently strong, it is appropriate to share with patients an alternative explanation for the epidemiologic reports regarding breast cancer and postmenopausal HT. It is helpful to emphasize the possibility that the studies reflect an effect of HT on preexisting tumors and that hormone users who develop breast cancer have a reduced risk of dying of breast cancer because their tumors are better differentiated, more localized, and smaller. Contrary to the prevailing belief, estrogen–progestin exposure may cause greater differentiation and earlier detection of preexisting tumors, resulting in better outcomes.

ENDOMETRIAL NEOPLASIA

There are two different types of endometrial cancer. The more common form, *endometrioid* carcinoma, develops slowly from a precursor lesion in response to estrogen stimulation. This type is less aggressive, is better differentiated, and responds to progestational treatment. In contrast, the uncommon form (perhaps 10–20%) develops rapidly, usually in older women, with a histologic pattern that is more characteristic of serous or clear cell carcinomas, in a background of atrophic endometrium.

Estrogen normally promotes mitotic growth of the endometrium. Abnormal progression of growth through simple hyperplasia, complex hyperplasia, atypia, and early carcinoma has been associated with unopposed estrogen activity, administered either continuously or in cyclic manner. **Only 1 year of treatment with unopposed estrogen** (**0.625-mg conjugated estrogens or the equivalent**) **will produce a 20% incidence of endometrial hyperplasia, largely simple hyperplasia.** In the 3-year PEPI trial, 30% of the women on unopposed estrogen developed adenomatous or atypical hyperplasia.[108,111,112] Some 10% of women with complex hyperplasia progress to frank cancer, and complex hyperplasia is observed to antedate adenocarcinoma in 25% to 30% of cases. **If histologic evidence of atypia is present, 20% to 25% of these cases will progress to carcinoma within a year.**[1041]

Multiple case–control and cohort studies have estimated that the risk of endometrial cancer in women on ET (unopposed by a progestational agent) is increased by a factor of somewhere from b.i.d. to 10 times the background incidence of 1 per 1,000 postmenopausal women per year.[1042,1043] **The risk increases with the dose of estrogen and with the duration of exposure** (reaching a 10-fold increase with 10–15 years of use, perhaps an incidence of 1 in 10 with very long-term use) **and lingers for up to 10 years after estrogen is discontinued.**[1044–1046] The risk of cancer that has already spread beyond the uterus is increased 3-fold in women who have used systemic estrogen for a year or longer.[1044,1047] Although most endometrial cancer associated with estrogen use is of low grade and stage, and associated with better survival (probably because of early detection), the overall risk of invasive cancer and death is increased. The risk of endometrial hyperplasia and cancer is not reduced by the administration of unopposed estrogen in a cyclic manner (a period of time each month without treatment).[1042,1048]

Dose as well as duration of estrogen exposure are both relevant to endometrial risk. A short-term study (2 years) indicated that estrogen-only treatment in one-half the usual standard dose of estrogen (in this case, 0.3 mg esterified estrogens) was not associated with an increased incidence of endometrial hyperplasia compared with a placebo group.[1049] In a similar 2-year study, endometrial stimulation with the transdermal delivery of a very low dose of estradiol, 14 μg/d, also did not differ compared with placebo.[1050] However, **we have learned that long-term exposure to low levels of estrogen can also induce abnormal endometrial growth** (**it just takes longer**)**, and, in our view, lower dose ET requires either ongoing endometrial assessment, perhaps annually, or the addition of a progestin to the treatment regimen.** This is supported by a case–control study from Washington that contained 18 cases and 9 controls who had exclusively used only 0.3 mg/d of unopposed conjugated estrogens.[1051] The use of this half-dose estrogen was associated with an overall 5-fold increased risk of endometrial cancer, reaching an RR of 9.2 in current users for more than 8 years' duration. Although limited by small numbers, the conclusion is logical and consistent with our understanding of the importance of duration of exposure to any increased level of endometrial estrogen stimulation. In a randomized trial, endometrial hyperplasia was increased after 2 years of treatment with 0.3 mg conjugated estrogens without a progestin.[114]

The risk of endometrial excessive proliferation is reduced by the addition of a progestational agent to the treatment regimen.[108,112] Although estrogen promotes the growth of endometrium, progestins inhibit that growth. This counter effect is accomplished by progestin-induced reduction in cellular receptors for estrogen and by induction of target cell enzymes that convert estradiol to the excreted metabolite estrone sulfate. As a result, the number of ER complexes that are retained in the endometrial nuclei is decreased, as is the overall intracellular availability of the powerful estradiol. In addition, progestational agents suppress estrogen-mediated transcription of oncogenes.

Reports of the clinical impact of adding progestin in sequence with estrogen include both the reversal of hyperplasia and a diminished incidence of endometrial cancer.[1052–1057] The protective action of progestational agents operates via a mechanism that requires time in order

to reach its maximal effect. For that reason, the duration of exposure to the progestin each month is critical. Studies indicate that in estrogen users, the *minimal* requirement for progestin exposure is for a period of 10 days each month.[1058–1060] More recently, this recommendation has been extended to 12 to 14 days of progestin exposure each month. **About 2% to 3% of estrogen-using women per year develop endometrial hyperplasia when the progestin is administered for less than 10 days monthly.**

Important unanswered questions are the following: What is the actual incidence of endometrial cancer in very long-term users of postmenopausal HT, and are there differences among the various regimens and routes of administration? A case–control study from Seattle reported that the use of combined estrogen–progestin (essentially all sequential and oral) for 5 years or more was associated with an increased RR of endometrial cancer, even with 10 to 21 days of added progestin per month.[1061] However, the increased risk was confined to those women who had been previously exposed to unopposed estrogen treatment; it is important to remember that **after discontinuing unopposed estrogen treatment, the risk of endometrial cancer lingers for up to 10 years, even if a subsequent regimen includes a progestin.** In the Swedish prospective cohort in Uppsala, a reduced risk of mortality due to endometrial cancer was observed in women receiving an estrogen–progestin combination; however, there were only two deaths, precluding statistical significance.[723] A case–control study from Los Angeles found no increased risk of endometrial cancer with the continuous, combined estrogen–progestin regimen or when at least 10 days of progestin were provided in a sequential regimen.[1060] **Epidemiologic studies have suggested that continuous, combined estrogen–progestin regimens provide superior protection against endometrial cancer. Long-term sequential regimens still carry a small increase in the risk of endometrial cancer.**[145,1062,1063] **In our view, periodic endometrial surveillance (annual sonohysterogram and/or endometrial biopsy) is recommended in estrogen users exposed only intermittently to progestin treatment.**

It is not an uncommon perception that protection against endometrial cancer requires periodic “shedding” of the endometrium. However, we know that at least one-third and up to one-half of the functioning endometrium are not lost during withdrawal bleeding, and it has not been

established that endometrial shedding is essential to protect against cancer.[1064] It is just as logical to believe that prevention of growth with the development of atrophic endometrium is protective. Case–control studies have indicated that not only is the excess risk associated with unopposed estrogen prevented by continuous, combined estrogen–progestin regimens, but with increasing duration of use, the risk of endometrial cancer is lower than that in never users.[1062,1065] In a small number of women who developed hyperplasia on a sequential regimen, conversion to continuous, combined treatment produced a return to normal endometrium, and in 345 women who completed 5 years of treatment with a continuous, combined regimen, not a single case of hyperplasia was detected.[129]

The WHI reported a 21% decrease in endometrial cancers in the canceled estrogen–progestin arm after 5 years of this clinical trial, although this difference was not statistically significant.[1066]

The lowest daily dose of progestin that protects the endometrium has not been established. Currently, the sequential program with conjugated estrogens uses 5 or 10 mg MPA, and the combined daily method uses 1.5 or 2.5 mg. A 2-year study has indicated that 1.5 mg MPA combined with 0.3 or 0.45 mg conjugated estrogens effectively prevents endometrial hyperplasia.[114] The dose of norethindrone that is comparable with 2.5 mg MPA is 0.25 mg.[115] The French E3N cohort study has demonstrated that endometrial safety effects vary by the type of progestin; the risk of endometrial cancer in estrogen users was higher when micronized progesterone and dydrogesterone were used compared to other progestin formulations.[1067]

Although the protective effect of progestin is considerable and predictable, it is unwise to expect all patients on estrogen–progestin therapy to never develop endometrial cancer. Appropriate monitoring of patients cannot be disregarded. Although routine assessments are not cost-effective, interventions directed by clinical responses are prudent and necessary. Greater surveillance is warranted in women on sequential estrogen–progestin regimens.

A relevance of obesity and insulin resistance for endometrial hyperplasia and cancer is increasingly recognized.[1035,1068] This relationship is independent of exogenous hormone use and underscores the need for

greater vigilance toward the risk for endometrial pathology in populations who are obese.

OVARIAN CANCER

Prospective cohort studies concluded that the risk of fatal ovarian cancer is increased with long-term estrogen use.[1069–1075] In addition, some case–control studies reported a small increase in risk in *ever users* that was higher with long duration of use.[1076] However, by no means is it certain if this association between menopausal hormone use and ovarian cancer is real. A pooled analysis of 12 case–control studies could find no consistent evidence for an association between ovarian cancer and ET.[1077] A meta-analysis concluded that there is a 14% increased risk of ovarian carcinoma among ever users of HT and that this risk increased to 27% with more than 10 years of hormone use.[1078] However, existing data included in this meta-analysis are subject to multiple potential biases. Among the six studies included in the analysis of duration of use, only one reported a statistically significant increase in risk with 10 or more years of hormone use. Another meta-analysis concluded that there was no clear evidence of an increased risk of ovarian cancer with ET and no effect of increasing duration of hormone use.[1079]

Individual studies have been hampered by relatively small numbers, but the lack of a uniform and consistent association argues against a major impact of postmenopausal estrogen treatment on the risk of ovarian cancer. In a relatively large case–control study, no indication could be found for an association between postmenopausal HT and the risk of epithelial ovarian cancer, even with long-term treatment.[1080] Another case–control study reported a slightly increased risk, but it was not statistically significant.[1081] And another case–control study could find no increase in risk with ever use, past use, or long duration of use (and no differences comparing various estrogens and regimens).[1082] In a comparison of users and nonusers of HT in the state of Washington, the risk of epithelial ovarian cancer was increased among current and recent users of estrogen only, but not in past users or in users of estrogen–progestin.[1083]

The canceled estrogen–progestin arm of the WHI reported an increase in ovarian cancer that was not statistically significant (HR = 1.58; CI = 0.77–3.24), prompting this statement: “The possibility of an increased risk of ovarian cancer incidence and mortality remains worrisome and needs confirmation.”[1066] The Kaplan–Meier curves suggested an increasing effect over time, but this, too, was not statistically significant. There were no differences reported in histologic type, stage, or grade (but the small numbers made it essentially impossible to assess subcategories).

All of the studies found it difficult to control for most of the factors that influence the risk of ovarian cancer. This is because there are multiple factors, and information regarding each factor is not readily available.

Factors that decrease the risk of ovarian cancer

- Use of steroid hormone contraceptives
- Pregnancy and parity; a greater effect with a recent pregnancy and pregnancy at older age[1084,1085]
- Breastfeeding[1086]
- Hysterectomy and tubal ligation[1087]
- Nonsteroidal anti-inflammatory drugs (NSAIDs)[1088]

Factors that increase the risk of ovarian cancer

- Increasing BMI[1089,1090]
- Infertility[1091]
- Family history of ovarian and breast cancer[1074]

Mixed reports on risk

- Alcohol intake[1092,1093]
- Cigarette smoking[1094–1096]

Because of the many factors that influence the risk of ovarian cancer, case–control and cohort studies have found it difficult (in fact, impossible) to match cases and controls. Hormone users usually have used more oral contraceptives, have had fewer children, and are more educated and thinner. Adjustments have been made only for major factors, such as oral

contraceptive use. The technique of meta-analysis is especially hampered by these confounding issues.

A major problem has been the impact of endometrioid cancers, an ovarian cancer that logically can be expected to be influenced by ET. In many of the studies, the overall results are swayed by the increase in endometrioid cancers, a cancer that could originate in hormonally stimulated endometriosis.[1097] An accurate analysis requires a separate consideration of endometrioid cancers, but this is difficult because the small numbers do not allow effective subcategorization.

An Australian case–control study reported a statistically significant increase only in the 18 cases with endometrioid cancer.[1098] A Swedish case–control study reported a small but significant increase in risk with unopposed estrogen and with sequential estrogen–progestin, but 49% of the cases were endometrioid cancers.[1076] In a cohort report from the Breast Cancer Detection Demonstration Project, only endometrioid cancer was significantly increased.[1070] In the WHI, there were two endometrioid cancers in the treated group and none in the placebo group.

It should also be noted that in one randomized trial, a case–control study, and two retrospective cohort analyses, no detrimental effect on prognosis after surgery for ovarian cancer could be detected in patients subsequently treated with hormones.[1099–1102] A nested case–control study of postmenopausal hormone-using women in the WHI-OS had examined for a relationship between circulating estrogens and estrogen metabolites at study baseline in relation to incident ovarian and endometrial cancers (serous and nonserous types).[1103] Fifteen estrogens and estrogen metabolites were quantified in baseline blood samples utilizing stable isotope dilution liquid chromatography with tandem mass spectrometry (LC–MS/MS). There was no evidence of a relationship between circulating estrogens nor estrogen metabolites with overall risk for ovarian cancer nor with serous ovarian or endometrial cancers. Interestingly, however, unconjugated estradiol levels were positively associated with nonserous ovarian cancer risk; the likelihood for nonserous ovarian cancer was 3-fold higher in women with unconjugated estradiol levels in the fifth quintile versus those with levels in the first quintile (OR 3.01, 95% CI = 1.17–7.73). This work offers insights into a heterogeneous endocrine milieu of hormone users and allows novel

insights into etiologic heterogeneity across histologic subtypes of ovarian cancer.

Overall, there is an indication that ever users of HT, no matter what formulation, progestin, or treatment regimen, have a small increase in the risk of epithelial ovarian cancers. The data are consistent with a promotional effect on existing malignancies because the risk diminishes after discontinuation of treatment. It is not difficult to review the epidemiologic data and conclude that there is no uniform story, that there are studies with both positive and negative results, and that most of the studies struggled with limited power because of small numbers and all of the studies are affected with confounding because of the difficulties in assessing and controlling for risk factors. The case–control and cohort studies inconsistently controlled for level of education, parity, oral contraceptive use, BMI, tubal ligation, and family history of ovarian and breast cancer (not a single study controlled for all the known risk factors!). It is a real possibility that there exists an increased risk for the hormonally sensitive ovarian cancer of the endometrioid type, and studies should carefully segregate this cancer for separate analysis. It is appropriate to emphasize the weak associations and the mixed story, but at the same time, the seriousness of the specific relationship dictates that the association between postmenopausal HT and the risk of ovarian cancer remains an unresolved issue.

COLORECTAL CANCER

Several observational studies show a reduced risk of colorectal cancer in those taking HT.[1104–1113] The effect is greatest in current users, and most studies have not indicated an increased effect with increasing duration of use; for example, the Nurses' Health Study (which found a 34% reduced risk in current users) could not demonstrate an added benefit with longer duration of hormone use.[1114] A reduction in fatal colon cancer has also been documented in current users.[1107,1115] In addition, there appears to be a reduced risk of polyps, especially large polyps, among current and recent

hormone users. A reduced risk of colorectal cancer has also been reported with a high intake of phytoestrogens.[488,1116]

The canceled estrogen–progestin arm of the WHI reported a statistically significant 44% reduction in incidence of colorectal cancer, and this was achieved within only a few years of estrogen–progestin therapy.[622] This result in the estrogen–progestin arm was not without concern, however, in that the hormone-treated group had more advanced disease. Indeed, the conclusion was largely because of a difference in localized disease, 10 cases in the treated group and 36 in the placebo group. The results suggest that already-present cancers were influenced by HT to reach a more advanced stage, but that estrogen–progestin treatment reduced the risk of new colonic cancers. Unlike the combination regimen arm of WHI, there was no significant difference in the occurrence of colorectal cancer among hormone users or placebo group in the estrogen-alone WHI trial.[1117] However, it must be appreciated that the E-alone WHI trial had two important problems when contrasted with the E+P trial: a very high drop-out rate and about 6,000 fewer participants. Furthermore, interpretability of WHI results must be confined to older postmenopausal women, an age group where carcinogenetic events are likely already underway. Analysis of the California Teacher study for risk of invasive colon cancer also revealed a decreased risk in postmenopausal women taking HT.[1118] In another case–control study, both oral and transdermal HTs reduced the risk for developing colorectal cancer.[1119]

While the mechanisms underlying decreased colorectal cancer risk in HT users remain unclear, a few hypotheses have been put forth. The estrogen-induced change in the bile (a decrease in bile acids with an increase in cholesterol saturation) favors gallstone formation but may reduce the promotion (by bile acids) of colonic cancer. Other possible mechanisms include a direct suppressive effect of hormones on mucosal cell growth and an effect on beneficial mucosal secretions. The colon contains only ER-β, and the reduction in the risk of colonic cancer associated with postmenopausal ET may reflect an antiproliferative activity of the ER-β. Obesity is a recognized risk for colorectal cancer, and body mass has also been suggested as an effect modifier in the relationship between HT and colon cancer.[1120] **Despite a lack of clarity on the exact mechanisms whereby HT may confer risk mitigation against colon**

cancer, this potential for benefit deserves greater attention; colorectal cancer ranks third in women, both in incidence and mortality, and is more prevalent than cancers of the uterus or ovary.[824] However, it should be noted that data supporting benefits of HT against colon cancer are not uniform, and until clarity is attained, there is no place for use of HT for the prevention of colon cancer.

LUNG CANCER

The leading cause of cancer mortality in American men and women is lung cancer; 87% of the deaths occur in smokers, and there are twice as many deaths from lung cancer in women as with breast cancer, annually.[824] In a post hoc analysis that combined data from 0 to 4 years of follow-up with the treatment period in the canceled estrogen–progestin arm of the WHI, the incidence of non–small cell lung cancer, the type that accounts for about 80% of cases of lung cancer, was nonsignificantly increased, but the number of deaths and the number of poorly differentiated and metastatic tumors were increased in the treatment group.[1121] The cases were essentially limited to past and current smokers and to women over age 60. Although the WHI was not designed to assess lung cancer, and chest imaging was not part of the study protocol, the results are provocative and concerning.

There is reason to believe lung cancer might be a target tissue for estrogen; at the same time, there is evidence to indicate that the impact is not uniformly detrimental and may even be protective. ERs are present in normal and non–small cell lung cells.[1122] Case–control studies have indicated a decrease in risk for lung cancer and specifically for non–small cell tumors.[1123–1127] Two studies even reported a protective effect in hormone users against lung cancer, especially in smokers.[1128,1129] One study reported decreased survival in women with lung cancer who used HT,[1130] but others did not detect a decreased survival in patients with lung cancer with a history of HT.[1131,1132] The Nurses' Health Study found an increase in lung cancer mortality in women who underwent early bilateral oophorectomy and did *not* use estrogen.[803] Gene expression is stimulated in non–small cell lung cancer cells by estrogen, and proliferation of these cells is reduced by an estrogen antagonist.[1133,1134] In the Rancho Bernardo cohort study, there

was no significant association between hormone use and lung cancer; however, there was a suggestion that women over age 55 had a small nonsignificant increase in lung cancer; no such increase was noted in younger women using hormones (although not statistically significant, the results with stratification by age are similar to the WHI findings).[1135] **The overall data, including the WHI analysis, suggest that HT initiated in older women with a history of smoking may promote the growth of existing lung cancers. The WHI evidence in women under the age of 60 is reassuring, and case–control and cohort data that reflect hormone use in a younger population than in the WHI indicate that estrogen is associated with some protection against lung cancer.**

CERVICAL CANCER

Any association between postmenopausal HT and cancer of the uterine cervix has not been extensively studied. Evidence from one cohort study and one case–control study is reassuring and indicates that the postmenopausal use of estrogen does not increase the risk of cervical cancer.[1136,1137] Indeed, these studies observed protection against cervical cancer in the estrogen users, but this may reflect detection bias (more examinations and Pap smears in estrogen users). Another case–control study suggested an increased risk in cervical adenocarcinomas, but there were only 13 cases.[1138] In a follow-up report of 120 women treated for stage I and II cervical cancers, no associations with HT as regard to survival or recurrence were observed.[1139]

MALIGNANT MELANOMA

The possibility of a relationship between exogenous hormones and cutaneous malignant melanoma has been the subject of many observational studies. Accurate evaluation utilizing the Royal College of General Practitioners and Oxford Family Planning Association prospective cohorts and accounting for exposure to sunlight did not indicate a significant difference in the risk of melanoma comparing users of oral contraceptives

to nonusers.[1140,1141] Results with the use of postmenopausal ET have not indicated a major impact. A slightly increased risk with long-term use of estrogen was noted in one case–control study (a conclusion based on 10–20 cases and not achieving statistical significance), whereas other case–control studies could find no association with postmenopausal estrogen treatment.[1142–1146] Others have reported slight increases in the risk of malignant melanoma associated with the use of exogenous estrogen, but all failed to reach statistical significance.[1136,1142,1147] In an analysis of cancer incidence in a Swedish cohort of women prescribed menopausal HT, no increase in malignant melanoma was observed.[874] On the adverse side, a Dutch case–control study reported a significant 42% increase in melanoma risk in postmenopausal hormone users, but it was based on only 33 cases and there was no consideration of sun exposure.[1148] In post hoc analyses of the two WHI trials, HT did not affect the incidence of melanoma.[540] More recently, associations between the use of oral contraceptives and menopausal HT and melanoma risk were examined in women participating in the European Prospective Investigation into Cancer and Nutrition (EPIC), a prospective cohort study in 10 participating European countries initiated in 1992. Among postmenopausal women, ever use of HT was not associated with melanoma risk (HR = 1.14, 95% CI = 0.97–1.43).[1147] **At this time, no solid evidence exists to suggest an increase in risk for cutaneous malignant melanoma with the use of HT.**

METABOLIC EFFECTS

Severe hypertriglyceridemia and pancreatitis can be precipitated by the administration of oral estrogen to women with elevated triglyceride levels.[1149,1150] In women with triglyceride levels between 250 and 500 mg/dL, estrogen should be provided with great caution, and a nonoral route of administration is strongly advised in those being considered for HT. **The triglyceride response to estrogen is rapid, and a repeat level should be obtained in 2 to 4 weeks. If levels are substantially increased, HT must be discontinued. A level greater than 500 mg/dL represents an absolute contraindication to estrogen treatment.** Triglyceride levels in the normal range were not affected by progestins in the PEPI trial.[111] An exaggerated

triglyceride response to estrogen might be attenuated by a progestin, especially a progestin of the 19-nortestosterone family, and, therefore, the daily, combination method of treatment could be considered for women with slightly elevated triglycerides. **However, the treatment of choice is transdermal estrogen, a route of administration that does not affect triglyceride levels; indeed, triglyceride levels markedly elevated in response to oral therapy return to normal when the route of administration is changed to transdermal administration.**[48,51]

Although physiologic and epidemiologic evidence indicates that estrogen use increases the risk of gallbladder disease, the overall impact is not great. The Nurses' Health Study indicated that oral ET may carry a 1.5- to 2.0-fold increased risk of gallbladder disease.[1151] The risk of cholecystectomy appeared to increase with dose and duration of use and to persist for 5 years or more after stopping treatment. Other observational studies also reported increased risks of cholecystectomy in past and current users of estrogen.[782,1152,1153] At least two case–control studies concluded that estrogen use is not a risk factor for gallstone disease in postmenopausal women, although the statistical power was limited by small numbers.[1154,1155] A cross-sectional study of gallstone disease could detect no association with postmenopausal hormone treatment.[1156] In the HERS clinical trial, the RR of gallbladder disease was 1.38; however, this did not achieve statistical significance.[780,1157] The risk of gallbladder disease and gallbladder surgery was significantly increased in both the estrogen–progestin and estrogen-only WHI hormone trials.[1158] This amounted to an increase of 20 to 30 cases per 10,000 per year in this older population of postmenopausal women. The routine, periodic use of blood chemistries is not cost-effective, and careful monitoring for the appearance of the symptoms and signs of biliary tract disease suffices. It is not certain that this potential problem is limited to oral therapy. Nonoral routes of estrogen administration have been reported to inconsistently increase biliary cholesterol saturation (a lithogenic response).[1159,1160] In the Million Women Study in the United Kingdom, the risk of gallbladder disease was actually lower with transdermal estrogen compared with oral estrogen, but the many problems with this observational cohort make it difficult to allow a confident statement.[1161]

Weight Gain

Weight gain in midlife is common, and lifestyle remains the dominant contributor to this occurrence; specifically, the balance of dietary intake and exercise is tilted toward excessive caloric intake because of a decline in physical fitness and the age-related decrease in basal metabolic rate. Despite common perception, the weight gain in women around menopause is not due to the hormonal changes associated with menopause.[1160–1164] Likewise, postmenopausal HT cannot be blamed for weight gain. The large Rancho Bernardo prospective cohort study and the randomized PEPI clinical trial documented that HT with or without progestin does not cause an increase in body weight.[1165,1166] In fact, in the PEPI trial, the hormone-treated groups actually gained less weight than the placebo group. In the 2-year clinical HOPE trial assessing the efficacy of lower estrogen–progestin doses, hormonal treatment was associated with lesser increases in body weight and body fat compared with placebo.[1167]

After menopause, there is an increase in abdominal fat and total body fat that is associated with an increase in insulin resistance, a consequence of the decrease in estrogen levels.[1168] Postmenopausal ET maintains the premenopausal body habitus, preventing the increases in abdominal fat, insulin resistance, blood pressure, and diabetes mellitus associated with estrogen deficiency.[1169] Estrogen (with or without progestin) prevents the tendency to increase central body fat with aging.[618–621,1170] This would inhibit the interaction among abdominal adiposity, hormones, insulin resistance, hyperinsulinemia, blood pressure, and an atherogenic lipid profile that results in the metabolic syndrome. An excellent randomized trial in Denmark documented less weight gain with HT because of a smaller increase in fat mass.[1171] In a substudy of the WHI, assessments of body composition by dual-energy x-ray absorptiometry (DXA) indicated that estrogen–progestin users had less fat and greater lean mass.[1172] This same salutary effect on central body fat has also been observed with tibolone treatment.[1173] **Rather than causing body weight gain, therefore, postmenopausal HT reduces the increase in insulin resistance and abdominal fat usually seen with aging, with a beneficial impact on the risks of hypertension, diabetes mellitus, and dyslipidemia.**

PRESENTATIONS REQUIRING CLINICAL JUDGMENT

Patients With Endometrial Cancer, Endometrioid Tumors, and Endometriosis

Gynecologic oncologists have reported that HT can be safely considered in patients who have had stage I and II adenocarcinoma of the endometrium without fear of an increased risk of recurrence or a decrease in disease-free interval.[1174–1177] In a matched cohort of 249 women with stage I, II, and III endometrial cancers with a long follow-up, there was no indication of an increase in recurrent disease with HT.[1178] Similar negative results were reported in a Turkish case–control study.[1179] The only randomized trial, organized by the Gynecologic Oncology Group, closed prematurely because of recruitment difficulties following the publicity associated with the WHI.[1180] Nevertheless, a total of 1,236 patients with stage I or II endometrial cancer were randomized to either estrogen-only or placebo, and although the participants constituted a low-risk group, the recurrence rate was low, 14 recurrences with 5 deaths in the treatment group and 12 recurrences and 9 deaths in the placebo group. If a high-risk tumor is ER and PR negative, it seems reasonable to allow immediate initiation of HT. Because the latent period with endometrial cancer is relatively short, a period of time under observation (5 years) without evidence of recurrence would increase the likelihood of long-term safety on an estrogen program. **We recommend that HT be avoided in patients with high-risk tumors that are receptor-positive until 5 years have elapsed. The combination of estrogen–progestin is recommended in view of the potential protective action of the progestational agent. A similar approach makes sense for patients previously treated for endometrioid tumors of the ovary. In view of the fact that adenocarcinoma has been reported in patients with pelvic endometriosis and on unopposed estrogen and that estrogen alone may allow for recurrence of endometriosis, the combined estrogen–progestin program is also advised in patients with a prior history of endometriosis.**[1181–1186]

Should a Postmenopausal Woman Who Has Had Breast Cancer Use Hormones?

The argument that postmenopausal HT should not be given to women who have had breast cancer is a reasonable one. It is based on the recognition of a large body of evidence that indicates that breast cancer is often a hormone-responsive tumor. The overriding fear of many clinicians (and patients) is that metastatic cells are present (perhaps being controlled by various host defense factors) that will be susceptible to stimulation by exogenous hormones.[1187] However, many women who have had breast cancer are aware of the benefits of postmenopausal hormone treatment and are asking clinicians to help make this risk–benefit decision. In addition, some women suffer from such severe hot flushing and vaginal dryness that they are willing to consider hormonal treatment. Tibolone treatment of breast cancer survivors is relatively contraindicated as discussed earlier in this chapter.

The rate of recurrent breast cancer in hormone users has been reported in multiple case series with more than 1,000 breast cancer survivors.[1188–1204] It is reassuring that the recurrence rates in these reports are not different from the expected rate of breast cancer recurrence. In one series, 25 and then 77 women with breast cancer ranging from in situ to stage III disease received estrogen–progestin therapy for 24 to 82 months; the recurrence rate was not greater than that expected.[1191,1192] From this group of patients, 41 breast cancer survivors receiving HT had the same outcomes when compared with 82 women selected from a cancer registry and not taking hormones.[1192] In a report from Australia, 90 women with a history of breast cancer who were given a combination of estrogen and progestin had lower mortality and recurrence rates; however, the dose of progestin was very high (which in itself can be therapeutic), and treatment was not randomized.[1196] In a follow-up of 319 women treated with estrogen after treatment for localized breast cancer, only one patient developed recurrent disease.[1197] In a matched-controlled series of 277 breast cancer survivors, there was no difference in the estrogen-treated group and the control group for recurrent disease.[1204] A series with 114 women who received hormone treatment had a low rate of recurrence.[1193] These patients have had both positive and negative nodes and positive and negative ER status. Although the results conform to an incidence of recurrent disease no greater than expected, the outcomes can reflect biases in clinician and patient decision-

making that can only be overcome with a proper long-term, randomized clinical trial.

A case–control study of HT after breast cancer actually found a significant reduction in risk of recurrent disease, breast cancer mortality, and total mortality in hormone users.[1205] Again, these are reassuring observational data that HT after breast cancer has no adverse impact on recurrence.

A US trial at the University of Texas M.D. Anderson Cancer Center provided estrogen to randomized women who had been treated for localized stage I and stage II breast cancers with either ER-negative or ER status unknown tumors.[1206] After 5 years of follow-up, 56 women in the trial receiving estrogen were compared with 243 women with comparable disease not receiving estrogen; there was no adverse effect of estrogen treatment on disease-free survival.[1207]

A multicenter, large case–control study of women younger than 55 years with breast cancer concluded that the use of oral contraceptives or postmenopausal HT either before or after diagnosis did not increase the risk of the first breast cancer or recurrent breast cancer.[1208] This negative finding was not changed by duration of use or age of oral contraceptive use or by BMI, duration of use, or type of postmenopausal hormone use (estrogen only or combined estrogen–progestin).

A longitudinal national cohort study analyzed over 2,000 women with a history of early-stage invasive ER-positive breast cancer taking either vaginal estrogen or systemic HT. Neither vaginal nor systemic HT was associated with increased risk of recurrence or mortality.[1209] An increase in recurrence was, however, noted on subgroup analysis of vaginal hormone users who were also on an AI (HR = 1.39, 95% CI = 1.04–1.85); mortality risk was not increased, and these authors advised caution when considering vaginal ET for early-stage breast cancer patients who are on AIs as adjuvant therapy.

The HABITS Trial

“Hormonal replacement therapy After Breast cancer—Is it Safe?” (HABITS) began in multiple centers in Sweden in May 1997, to compare breast cancer survivors treated for at least 2 years with HT with treatment other than hormones. A similar trial was initiated in Stockholm. Because

recruitment was slower than anticipated, the two trials agreed in February 2002 to pool their patients and to use a joint safety and monitoring committee. In October 2003, the safety committee recommended that the trial be discontinued because there were 26 women in the treated group with new breast cancers compared with 7 in the nontreated group. The HABITS trial was terminated in December 2003.[1210] Confronted with this outcome, the Stockholm investigators decided to cancel their trial as well, even though the HR in the Stockholm patients was 0.82 (CI = 0.35–1.9).

HABITS was a randomized but not placebo-controlled trial in which HT was compared to management without hormones in women with menopausal symptoms who had been previously treated for stage I or II breast cancer. Concomitant use of tamoxifen treatment was allowed in the HABITS patients, but not of AIs. HT consisted of the variety of products and methods on the Swedish market, but not tibolone. Most of the treated women used products with the relatively high dose of 2 mg estradiol. After 4 more years of follow-up of 442 women, there were 39 cases of new breast cancer in women using HT compared with 17 in the nontreated group, for an HR of 2.4 (CI = 1.3–4.2).[1211]

It is important to appreciate some significant concerns related to the study design and methodology in HABITS. The treated and nontreated groups of women were very different in terms of characteristics and behaviors. More of the women in the treated group had hormone receptor–positive cancers (62.3%) compared with the nontreated group (54.5%). Protocol deviations occurred; 11 women in the treated group never received hormones, whereas 43 in the nontreated group did receive hormones. There was a very wide range of exposure times, ranging from 0 to 80 months. About one-third of the women who received hormones changed products during the study. The method of analysis of the HABITS data was intent to treat and, thus, the impact of these differences cannot be ascertained.

Analysis of the new breast cancers in HABITS (either local recurrences or contralateral cancers) indicated statistically significant increases only in hormone receptor–positive cancers. However, when adjusted for use of HT before diagnosis of the original breast cancer, use of tamoxifen, and hormone receptor status, the HR was 2.2 with a CI that included 1 (1.0–5.1), which, by definition, while close, is not statistically significant.

The Stockholm trial reported in 2005, after a median follow-up of 4.1 years, 11 new breast cancers in the treated arm and 13 new breast cancers in the nontreated arm.[1212] Why there is difference between the Stockholm trial and HABITS? The HABITS investigators suggest that their patients had more node-positive disease and thus “probably” had more women with subclinical disease that would be stimulated by HT. Another possibility was more protection with higher tamoxifen use in the Stockholm trial, although the HABITS trial could detect no impact of tamoxifen. The HABITS investigators believe that another possible explanation was the greater use of norethindrone and NETA in HABITS compared with the use of MPA in Stockholm. All of these explanations are speculations; the difference between the two trials remains and calls into question the reliability and accuracy of the data.

The cancelation of HABITS and the Stockholm trials made it impossible for the English and Italian trials to continue recruitment, and they were also canceled. Thus, the scientific community was left with many questions, but without ongoing efforts to elucidate answers. In our view, the existing data on the risk of breast cancer recurrence or new-onset cancers related to HT are far from being definitive.

Although intuitively it seems that the risk/benefit ratio would be more favorable in the presence of negative nodes, negative receptors, and small tumors, are negative ER and PR assessments by themselves sufficient to conclude that the cancer is not sensitive to hormones? Moreover, if the patient is in the high-cure category, does it make any difference what the receptor status is? The answers to these questions are not known. Receptor status is not absolute; it is always a relative measure and can change over the course of disease progression.

Patients and clinicians have to incorporate all of the previously mentioned considerations into medical decision-making. However, when all is said and done, patients have to take an unknown risk if they want the benefits of hormone treatment; the prescribing clinicians too take an unknown medical–legal risk. Some patients who are burdened by severe menopausal symptoms that remain unresponsive to nonhormonal interventions may and do choose to take estrogen, judging the benefits to their quality of life with hormone use to be worth the unknown risk. Until definitive data are available from

clinical trials, clinicians should support patients in this decision. Other patients will prefer to avoid any unknown risks. These patients, too, deserve support in their decision.

IMPLICATIONS OF HORMONE THERAPY FOR WOMEN WITH DIABETES MELLITUS

Estrogen can improve the metabolic changes associated with diabetes. Indeed, in prospective studies of postmenopausal women with type 2, non–insulin-dependent diabetes mellitus, estrogen-only or estrogen–progestin therapy improved all glucose metabolic parameters, including insulin resistance, the lipoprotein profile, and measurements of androgenicity.[631,632,1066,1213–1217] One study, however, could detect no impact with transdermal administration.[1215] These changes should reduce the risk of CVD, and in a very large cohort of 24,420 women from the Northern California Kaiser Permanente Diabetes Registry, current use of HT reduced the risk of myocardial infarction, but in women with a recent heart attack, an increased risk of a recurrent myocardial infarction was observed in hormone users (again a difference between primary prevention and secondary prevention).[1218] Tibolone also has a beneficial impact in short-term studies on insulin resistance in normal women and in women with non–insulin-dependent diabetes mellitus.[283,307] Raloxifene, an SERM, has no effects on glucose metabolism or insulin sensitivity in normal women but exerts a modest improvement in insulin resistance in women who are hyperinsulinemic.[1219,1220]

IMPLICATIONS OF HORMONE THERAPY FOR WOMEN WITH LIVER DISEASE

In an evaluation of liver chemistries in a group of patients with primary biliary cirrhosis, standard HT doses produced no adverse changes over a period of 1 year.[1221] Estrogen treatment, either oral or transdermal, has not been associated with worsening cholestasis in women with primary biliary cirrhosis.[1222,1223] We recommend measurement of liver chemistries after 1

month of treatment and every 6 months, with continuing HT in the absence of deterioration.

A French cohort study concluded that HT protects against the progression of hepatic fibrosis from chronic hepatitis C.[1224] Most individuals with hepatitis C virus infection develop chronic disease, a major cause of worldwide morbidity and mortality from liver fibrosis. The time course is relatively slow, taking years to progress from infection to cirrhosis. Progression is increased by consumption of alcohol, excess body weight, diabetes, and the degree of fatty degeneration in the liver. The severity of liver fibrosis is greater in men, and progression in women accelerates around age 60. In vitro and animal experiments have documented a beneficial effect of estrogen on the development of fibrosis, an effect that is consistent with the data in the French study finding greater progression of fibrosis after menopause and amelioration with HT. Another French study, a retrospective survey, reported a greater rate of fibrosis progression with hepatitis C in postmenopausal and nulliparous women and a lower rate in postmenopausal women treated with HT compared with nontreated women.[1225]

Liver fibrosis from hepatitis C infection is not the result of viral destruction of hepatic cells. Fibrosis is a response to the inflammatory activity incited by the virus. By now, it is well known that estrogen can suppress the secretion of pro-inflammatory cytokines. Because of the prevalence of hepatitis C infection, these French reports are very important. Many clinicians are reluctant to prescribe HT to women with a history of liver disease. However, as long as liver enzymes are normal, there is no reason to withhold treatment, and these French studies indicate that ET is beneficial. Postmenopausal HT should be discussed when women present with a history of hepatitis C infection.

The lesson learned from the earlier-mentioned conditions is that estrogen-alone and estrogen–progestin treatment including contraception is acceptable as long as liver enzyme function is normal. This caveat is also true for women who have undergone organ transplantation surgery.[1226]

HT should be avoided in the setting of chronically impaired liver function.

HORMONE TREATMENT IN THE PRESENCE OF UTERINE LEIOMYOMAS (FIBROIDS)

Uterine leiomyomas are monoclonal tumors that retain sensitivity to both estrogen and progestin (see Chapter 3); therefore, it is appropriate to be concerned over whether leiomyomas will grow in response to postmenopausal HT. As assessed by vaginal ultrasonography, the number and size of uterine leiomyomas increased in women being treated with an intramuscular depot form of estrogen–progestin therapy.[1227] However, the hormonal dose in this study was relatively high, certainly higher than standard regimens. At the end of 1 year, women with small asymptomatic fibroids administered with a daily combination of 0.625-mg conjugated estrogens and 2.5-mg MPA had no sonographic evidence of growth in contrast to an increase in size observed with transdermal estradiol (50 μg) and 5-mg MPA daily (a response that probably reflects the effect of a higher progestin dose).[1228] In follow-up studies with standard doses of estrogen–progestin or tibolone, ultrasonography detected no changes in uterine or myoma volumes.[1229–1231] Clinical experience indicates that fibroid tumors of the uterus almost always are not stimulated to grow by the commonly utilized postmenopausal doses of estrogen and progestin. Tibolone and raloxifene also do not stimulate myoma growth.[320,1232,1233] Interestingly, however, a vulvar leiomyoma with growth stimulated by estrogen–progestin treatment has been reported.[1234] A case–control study could find no statistically significant increase in the risk of uterine sarcomas associated with ET.[1235] **Nevertheless, in women with known fibroids, periodic surveillance by pelvic examination and TVUS scans is prudent.**

IMPLICATIONS OF HORMONE THERAPY FOR WOMEN WITH SLEEP APNEA

The low prevalence of sleep apnea in premenopausal women and the increased frequency after menopause suggest a hormonal link. In careful studies, however, postmenopausal HT had no significant adverse effect on sleep-disordered breathing in women with more than mild obstructive sleep apnea.[1236,1237] And other sleep laboratory studies found that estrogen

treatment reduced difficulties with sleep-disordered breathing.[1238–1240] The slight rise in basal body temperature induced by a progestational agent may be sufficient to disrupt the quality of sleep in some women, a problem that may be more noticeable with a sequential regimen and with nighttime administration.

IMPLICATIONS OF HORMONE THERAPY FOR WOMEN WITH ASTHMA

In some women, changes in asthma activity have been noted to correlate with the phases of the menstrual cycle. The impact of postmenopausal HT on asthma activity has not been well investigated, but there is an indication that estrogen has an adverse effect. A worsening in spirometry assessment was detected in asthmatics after ET; however, the difference was judged to be subclinical, and the patients did not report any changes in their perceptions of symptoms.[1241] A similar study could detect no adverse effects with either discontinuation or reinitiation of estrogen treatment.[1242] And another study concluded that ET improved asthma and decreased the need for glucocorticosteroid treatment.[1243] In a prospective assessment of a cohort of women, the use of postmenopausal HT (estrogen with or without progestin) was associated with a 50% increase in the risk of developing adult-onset asthma, and the risk was greater with long-term use and higher doses of estrogen.[1244] Similar results were reported in the French E3N cohort study, except an increased risk was observed only in estrogen-alone users.[1245] In the Nurses' Health Study, newly diagnosed asthma was increased about 2-fold by HT.[1246] Because hormonal changes may precipitate asthmatic activity (eg, catamenial asthma), attention should be directed to the symptomatic pattern and consideration given to the daily, continuous, combined regimen.

MENOPAUSAL HORMONE THERAPY, DEMENTIA, AND COGNITION

The WHIMS analyzed the effects of HT on cognition and on risk of dementia in postmenopausal women participating in the WHI hormone trials. Contrary to earlier assumptions that menopausal ET should offer cognitive benefit, the WHIMS concluded that estrogen–progestin and estrogen-only therapy actually increased the risk for dementia in women aged 65 years and above and did not prevent mild cognitive impairment.[1247–1250] However, the only statistically significant finding in the estrogen–progestin arm was increased dementia (vascular dementia, not Alzheimer disease) in older women (22 cases in the treated group and 10 cases in the placebo group) aged 75 years and above and who had been exposed to a relatively short term of estrogen–progestin therapy. The estrogen-only arm of the WHI contained more women who are obese with preexisting CVD, and the trend for an increase in dementia likely reflected an effect in older women with established atherosclerosis. A 2019 randomized placebo-controlled trial noted a faster decline in immediate list recall and a slower decline in story recall in ET use. However, like the WHI/WHIMS trials, average age was more than 10 years from menopause.[1251] Both *timing* and *duration* hypothesis, similar to ones proposed for cardiovascular effects of HT, emerged in the wake of WHIMS, raising questions that outcomes may differ for those women who initiate HT early in the course of menopause and in those who following early initiation continue to use HT for longer durations; hypotheses proposed that unlike WHIMS, women initiating HT proximate to final menses and who then continue to use hormones for prolonged periods may be protected against dementia. The WHI report recognized that these hypotheses could not be tested in this clinical trial because of the older age of the study participants and remoteness of hormone initiation from the onset of menopause. A prospective study of a homogeneous population in Utah (thus minimizing, if not eliminating, the healthy user bias) concluded that a reduction in the risk of Alzheimer required long-term treatment, initiated at least 10 years before symptoms of dementia appear.[1252] Thus, any favorable effects of HT on cognition and on the risk of Alzheimer disease, if any, appear to be limited to women who initiate treatment close to onset of menopause. However, KEEPSCog, an ancillary study to KEEPS that examined the timing hypothesis as regards the effects of HT initiated within 3 years of the onset of menopause, similarly failed to identify cognitive benefit.[1253]

OTHER CONDITIONS

Close surveillance is indicated for some patients with seizure disorders and migraine headaches. Patients with migraine headaches often improve with strategies that minimize fluctuations in circulating hormone levels that can serve to trigger headaches. Transdermal route of estrogen administration is preferable, given a stable hormone profile in comparison to following oral ingestion. Conditions that do not represent contraindications include controlled hypertension, smoking, and varicose veins. The belief that estrogen is potentially harmful with each of these clinical situations is derived from old studies of high-dose oral contraceptives. Estrogen in appropriate postmenopausal doses is acceptable in the presence of these conditions.

No other cancers (in addition to those mentioned previously) are known to be adversely affected by HT. Postmenopausal HT can be administered to all patients with a history of cervical, ovarian, or vulvar malignancies.
Highly unusual anecdotal happenings include the following:

- Provocation of chorea by ET in a woman with a history of Sydenham chorea[1254]
- Exacerbation of pulmonary leiomyomatosis by ET[1255]
- Psychiatric symptoms in response to estrogen in patients with acute intermittent porphyria[1256]
- Idiosyncratic ocular symptoms associated with estrogen[1257]
- Sudden deafness and tinnitus with commencement of HT[1258]
- Resolution of an infection with *Trichomonas vaginalis* after discontinuation of estrogen–progestin therapy[1259]
- Successful treatment of Sjögren syndrome with tibolone[1260]

BEYOND SYMPTOM CONTROL

Some Additional Benefits of Hormone Therapy

Estrogen Therapy and Autoimmune Diseases

Rheumatoid Arthritis

No clear conclusion is apparent from the studies of effects of estrogen on rheumatic diseases, especially rheumatoid arthritis. Some have indicated that exogenous estrogen, either in oral contraceptives or as postmenopausal therapy, protects against the onset of rheumatoid arthritis, whereas other studies find no such effect.[1261–1264] Existing data are hampered by small numbers. In a randomized, placebo-controlled, clinical trial, maintenance of standard serum estradiol levels was associated with improvements in some measurements of disease activity in patients with rheumatoid arthritis.[1265] Reassuringly, there has been no evidence that postmenopausal HT aggravates rheumatoid arthritis or causes a flare in disease activity. **Postmenopausal HT can be safely considered in symptomatic postmenopausal women with rheumatoid arthritis. HT can additionally be considered as a fracture risk reduction strategy in appropriately selected patients** (skeletal effects of HT are discussed in the section on osteoporosis)**.**

Systemic Lupus Erythematosus

In the Nurses' Health Study, the use of postmenopausal estrogen was associated with approximately a 2-fold increase in systemic lupus erythematosus (SLE), an observation based on 30 cases in past and current users of estrogen.[1266] In a follow-up of 60 postmenopausal women with stable SLE, no adverse effects of HT could be detected.[1267] Patients with SLE develop early atherosclerosis, and those treated with glucocorticoids are especially at greater risk for osteoporosis,[1268] but there is a concern that exogenous estrogen will increase flares and stimulate thrombosis because of an existing hypercoagulable state in these patients. Importantly, no increase in arterial or venous thrombosis was observed with postmenopausal HT in a longitudinal study of a large cohort of US women with SLE.[1269] **Postmenopausal HT can be considered in patients with stable or inactive disease, without renal involvement, or high antiphospholipid antibodies, and transdermal route for estrogen administration is advised.**

Estrogen Therapy and Osteoarthritis

Osteoarthritis is the most common form of arthritis in older people, and its prevalence increases rapidly in women after menopause. Increasing severity of osteoarthritis of the knee has been reported to be associated with increasing bone density and the current use of postmenopausal HT in middle-aged women.[1270] However, estrogen treatment reduced osteoarthritis in a monkey model, and a cross-sectional study concluded that current users of estrogen had a reduced prevalence of osteoarthritis of the hip, and there was protection against the severity of osteoarthritis, with a greater effect with longer duration of use.[1271,1272] Arthritic complaints are a major side effect of the low estrogen state induced in women with breast cancer treated with AIs, and osteoarthritis develops more frequently in women with the lowest levels of estrogen.[1273,1274] Because there are no known treatments that modify the course of osteoarthritis, this potential benefit of postmenopausal HT deserves study in appropriately designed randomized clinical trials.

Estrogen Therapy and the Oral Cavity

Oral complaints are common among postmenopausal women. The administration of estrogen provides significant relief from oral discomfort, burning, bad taste, and dryness.[1275] ET is also associated with a reduction in periodontal disease, including gingival inflammation and bleeding.[1276,1277] These changes may reflect epithelial responses to estrogen by the oral mucosa, in a manner similar to that of the vaginal mucosa. Oral alveolar bone loss (which can lead to loss of teeth) is strongly correlated with osteoporosis, and the salutary effect of estrogen on skeletal bone mass (discussed later in the section on osteoporosis) is also manifested on oral bone.[1278,1279] In the Leisure World Cohort, tooth loss and edentia were significantly reduced in estrogen users compared with nonusers (with a reduced need for dentures), and this beneficial effect was greater with increasing duration of estrogen use.[1280] Approximately a 25% reduced risk of tooth loss in current users of estrogen was observed in the Nurses' Health Study.[1281]

Estrogen Therapy and the Larynx

Professional singers have used HT to prevent what they view as unwanted voice changes associated with menopause.[1282] In prospective studies, objective voice analyses have documented a more androgenic change in voice in the early postmenopausal years with a lesser change associated with estrogen treatment; although slightly attenuated by the addition of a progestin, the overall effect of estrogen treatment is to preserve voice quality.[1283–1285] Laryngeal cytology demonstrated epithelial maturation in women on estrogen treatment, and these women reported better voice quality and fewer voice changes compared with a control group.[1286]

Estrogen Therapy and Vision

There is some evidence that ET improves visual acuity (or lessens the visual deterioration during the early postmenopausal years), perhaps due to a beneficial effect on lacrimal fluid.[1287,1288] An increased prevalence of keratoconjunctivitis sicca (dry eyes) in menopausal and postmenopausal women, with symptoms of scratchiness, burning, and photophobia, is recognized by ophthalmologists.[1289] Although reports concluded that there was no effect or even a worsening of dry eyes with HT, a clinical trial indicated relief from dry eye symptoms with the use of topical estrogen eye drops.[1290–1294]

There is evidence that postmenopausal ET protects against cataracts.[1295–1299] Estrogen-alone or estrogen–progestin treatment also lowers intraocular pressure in postmenopausal women with normal eyes or glaucoma.[1293,1300–1302] In the Nurses' Health Study, current use of estrogen–progestin, but not estrogen alone, was associated with a reduced risk of glaucoma.[1303] In a retrospective study of female veterans with open-angle glaucoma, HT tended to older at the diagnosis of glaucoma.[1304] There is modest and inconsistent evidence that the risk of age-related macular degeneration is reduced in postmenopausal hormone users.[1305–1310]

Estrogen Therapy and Age-Related Hearing Loss

Demineralization of the cochlear capsule occurs with aging and metabolic bone diseases, such as cochlear otosclerosis. This demineralization is associated with neural hearing loss. Postmenopausal women (age 60–85 years) who have lower than average femoral neck bone mass have an

increased risk of having a hearing loss.[1311] This association between femoral neck bone mass and age-related hearing loss suggests that prevention of bone loss with ET might also be exerted on the cochlear capsule. In addition, estrogen may have beneficial effects on cochlear blood flow and central nervous system auditory neurons. Hearing impairment in a Turkish family was associated with an inactivating mutation for ER-β.[1312] Mouse knockout studies indicate that ER-β is important for the prevention of age-related hearing loss.[1313] Studies have documented better hearing levels in estrogen users, with an indication that the addition of a progestin attenuated the favorable effect of estrogen.[1314,1315] Interestingly, however, older age at menopause and longer duration of postmenopausal HT were associated with a higher risk of hearing loss.[1316]

HOW LONG SHOULD POSTMENOPAUSAL HORMONE THERAPY BE CONTINUED?

The answer to this question is relatively straightforward. Periodic reassessments of risk-to-benefit ratio must be undertaken in hormone-using women, and **duration of therapy should be guided by the principles of "net benefit" and "do no harm."** Clarity on persistence of the indication for which HT was initiated in the first place and overall risk profile of the user should be periodically assessed, and a woman should continue their menopausal hormone regimen if the potential for benefit outweighs that of harm.[1317] The symptom, metabolic, and skeletal effects of hormones revert early following discontinuation, with longer times needed for others may take years (eg, dissipation in breast cancer risk) after discontinuation.

Resurgence in menopausal symptoms after discontinuing HT is not uncommon, and resulting disruption in quality of life has been reported in at least 25% of previously treated women and, in one Swedish study, 70%.[1318,1319] It seems intuitively advantageous to encourage a tapering, gradual discontinuation program to minimize recurrence of menopausal symptoms, although randomized trials comparing gradual discontinuation with abrupt cessation found no benefit with a tapering regimen.[1320–1323] Neither the recurrence rate nor the severity of menopausal symptoms differs comparing the two methods.

SHOULD WOMEN REMOTE FROM MENOPAUSE BE STARTED ON HORMONE THERAPY?

The positive impact of HT on the bone has been demonstrated even in women older than age 65.[1324,1325] This is a strong argument in favor of treating women remote from menopause who have never been on estrogen and who cannot take or afford the other alternatives for bone preservation. Estrogen treatment that is not begun until after age 60 can with long-term use achieve bone densities nearly but not totally comparable with those in women taking estrogen from menopause, and estrogen use between the ages of 65 and 74 has been documented to protect against hip fractures.[1326,1327] **Adding a hormonal regimen to women over the age of 60 is, however, not a trivial consideration, given the known risks of thromboembolism, stroke, and cognitive deterioration that were evident in the WHI hormone trials.** This judgment requires the conclusion that a relatively youthful and vigorous older woman has something to gain from the choice of hormone treatment. While patients with osteoporosis may qualify, alternative effective strategies are available to minimize fracture risk, which may prove to be safer alternatives to HT in the older adults. The primary and secondary prevention trials reviewed in this chapter have strongly indicated that estrogen administered to women with established atherosclerosis is associated with an increased risk of arterial thrombosis. The mechanism, as reviewed in earlier in this chapter, is presumed to be the creation of a prothrombotic environment by the stimulation of metalloproteinase enzyme activity in unstable atherosclerotic plaques. This effect is enhanced by the production of 27-hydroxycholesterol in atherosclerotic sites, a cholesterol metabolite that competitively inhibits estrogen's beneficial actions within blood vessels. Statin treatment is known to stabilize atherosclerotic plaques rapidly, within 3 months. Although there are no studies to support this recommendation, it seems reasonable to consider initiating statin treatment for several months before starting ET in older women; such a consideration requires a thorough discussion on alternative options and on the net balance of risks versus benefits of HT remote from menopause onset, toward shared decision-making. In 2017,[1328] after review of existing data on benefits versus risks of HT, the United

States Preventive Services Task Force (USPSTF) recommended against postmenopausal women taking HT (combined E+P or E alone) for the sole purpose of preventing chronic conditions. **The USPSTF recommendations were revised in 2022 and stood firm in advising against postmenopausal women taking combined HT for the sole purpose of preventing chronic conditions**.[1329]

Older women who have been deficient in estrogen for many years often experience side effects when standard doses of estrogen are initiated. Breast tenderness can be especially disturbing. Because of these side effects and the experience in the WHI with its older population, it is better to start older women with lower doses, and transdermal products that deliver low amounts of estrogen must be considered preferentially. The benefits from initiating HT in aging women must be balanced against risks for harm, and a thorough clinician–patient dialogue must place existing data in perspective, including findings from the WHI hormone trials.

CAN THE DIET PRODUCE VARIATIONS IN SYSTEMIC ESTROGEN LEVELS?

Oral estrogens have an extensive first-pass metabolism, both in the gastrointestinal tract and the liver. This metabolism consists chiefly of sulfation and hydroxylation. The cytochrome P-450 system catalyzes the hydroxylation of estrogen, and antioxidants can inhibit this action. Flavonoids (eg, naringenin and quercetin) are present in high concentrations in fruits and vegetables, and grapefruit juice inhibits estrogen metabolism, producing an increase in bioavailability that is consistent with an inhibition of hydroxylation.[1330,1331] This raises the possibility that dietary interactions with food products could produce a clinical impact. There is great variability within individuals and between individuals in the pharmacokinetics of exogenously administered estrogen. It is possible that this variability partially reflects the dietary habits of individuals and not intrinsic metabolism.

An effect of alcohol ingestion by premenopausal women was not demonstrated on circulating levels of estrone, estradiol, DHEA-S, or SHBG in a cross-sectional study that depended on a questionnaire to assess alcohol

intake.[1332] However, when alcohol is administered under experimental conditions, circulating estrogen concentrations are raised to high levels.[1333,1334] In a prospective cohort study of premenopausal women in Italy, higher estradiol levels were correlated with an increased alcohol intake over a 1-year period of time.[1335] In the past decade, the gut microbiome has emerged as an important variable capable of influencing estrogen metabolism, the metabolic and carcinogenic milieu, as well as modifying interactions between dietary factors and hormones.[1336]

CLINICAL APPROACH TO POSTMENOPAUSAL HORMONE THERAPY

We hope that the readers can appreciate that menopause is a normal life event, which, just like puberty, may be challenging for some, and that for many women who are challenged by menopause-related bother, menopausal HT can bring about marked improvement in quality of life. Furthermore, with long-term use, menopausal HT may offer health benefits that extend beyond symptom control. Menopausal HT should be considered for symptomatic women traversing the menopause transition and early menopause as they consider their paths for successful aging; the decision to initiate HT should be made after weighing individualized risks against patient's symptom burden and indicated benefits. **It is important to appreciate that the attitude and beliefs of the clinician have a major influence on the treatment-related decisions made by patients.** As beneficial as the impact of HT may be, we must also emphasize the large improvement in health to be gained by lifestyle changes that include cessation of smoking, attention to diet and exercise, control of body weight, and attention to stress reduction.

It is the task of an epidemiologist to derive study conclusions based on research data. It is the obligation of a clinician to make a judgment whether the epidemiologist's conclusions have clinical meaning. For example, an epidemiologist may conclude that estrogen reduces coronary artery calcification and point out that a randomized clinical trial has not proved that such a reduction lowers the risk of CHD. However, it is appropriate for a clinician, knowing the correlation between coronary artery calcification

and CHD, to conclude that estrogen reduction of coronary calcification will translate into less CHD. **Medical judgments require more than absolute evidence from randomized trials, and medical judgments frequently do not have the luxury of postponing clinically meaningful decisions until data are conclusive.**

Long-term use of menopausal HT is not precluded by the results reported by the WHI. Protection against osteoporotic fractures, reduction in incidence of colorectal cancers and possibly new-onset diabetes mellitus, and a possibility of primary prevention of CHD are some of the long-term benefits, provided HT is initiated for the right patient at the right time. Once HT is initiated, it is incumbent that prescribers remain attentive to interval changes in the user's health profile and periodically weigh hormone use–related benefits against the known hormone-related risks of VTE, stroke, and breast cancer (from estrogen and progestin use). Prescribers should additionally remain receptive to alternative proven therapies (eg, nonhormonal formulations such as Brisdelle and fezolinetant for vasomotor control, and statins and incretins for metabolic benefit) and to support beneficial lifestyle modifications. It remains the clinician's responsibility to weigh any purported benefit against HT-related risks for each patient such that potential for benefit from HT outweighs any risk for harm for each and every patient at all time.

The WHI agrees with 30+ years of research

- CHD: potential for protection in young postmenopausal women
- Stroke: no increase in early postmenopausal, healthy women
- VTE: 2-fold increase in the first years of use, concentrated in those with preexisting risk factors
- Cancer: slightly increased risk of breast cancer or an effect on preexisting tumors; reduction in colorectal cancer
- Osteoporosis: reduction in vertebral and nonvertebral fractures
- Diabetes mellitus: reduction in new-onset diabetes

A theme has emerged from the epidemiologic confusion of the past few decades. It takes healthy tissue to allow effective response to estrogen and maintenance of health. Experimental evidence in primates and in women

indicates that as cells (endothelial, neurons) age and as atherosclerosis sets in, the potential for net benefit from menopause HT lessens and net risk increases.[463,809,1252] Toward maximizing benefit, therefore, initiation of indicated HT should begin closer to the onset of menopause.

The most effective and appropriate method to help in decision-making is to identify the specific goals and objectives of the individual patient—*let your patient be your guide*. Once an individual's objectives are identified, choices from multiple treatment options can be reviewed. Postmenopausal health and HT are subjects receiving enormous attention and research; therefore, decision-making should be at least an annual event, incorporating new knowledge as it appears. Approached in this manner, the terms "short term" and "long term" and the imposition of time limits for therapy become meaningless. Clinician and patient together make an annual clinical judgment that is appropriately directed to accomplishing the individual patient's goals. **The guiding principle is the *right* drug in the *right* dose for the *right* patient at the *right* time, and for the appropriate duration according to an individual patient's needs and tailored to the individual's unique risk profile.**

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