CHAPTER 14

Menopause and Aging

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Epidemiology

- *The age of menopause has been constant over several centuries and is influenced by genetic, ethnic, and environmental variables.*
- *The prediction of the age of menopause based on anti-müllerian hormone (AMH) trajectories is possible but impractical.*

Menopause is defined by the last menstrual period. Because cessation of menses is variable and many of the symptoms thought to be related to menopause may occur prior to the cessation of menses, there is seldom a precise timing of this event. Other terms used are *perimenopause*, which refers to a variable time beginning a few years before and continuing after the event of menopause, and *climacteric*, which merely refers to the time after the cessation of reproductive function. While the terms *menopausal* and *postmenopausal* are used interchangeably, the former term is less correct because "menopausal" should only relate to the time around the cessation of menses.

As life expectancy increases beyond the eighth decade worldwide, particularly in developed countries, an increasing proportion of the female population is postmenopausal. With the average age of menopause being at 51 years old, more than one-third of a woman's life is now spent after menopause. Here symptoms and signs of estrogen deficiency merge with issues encountered with natural aging. As the world population increases and a larger proportion of this population is made up of individuals over 50, medical care specifically directed at postmenopausal women becomes an important aspect of modern medicine. Between the years 2000 and 2005, the world population older than 60 years old increased from 590 million to 1 billion. In the United States, the number of women entering menopause will almost double in the 30 years between 1990 and 2020 (Table 14.1).[1]

Age of menopause, which is a genetically programmed event, is subject to some variability. The age of menopause in Western countries (between 51 and 52 years old)[2,3] is thought to correlate with general health status.[4-6] Socioeconomic status is associated with an earlier age of menopause.[2] Higher parity, on the other hand, has been found to be associated with a later menopause.[7] Smoking has consistently been found to be associated with menopause onset taking place 1 to 2 years earlier.[3,8] While body mass has been thought to be related to age of menopause (greater mass with later menopause),[9] the data have not been consistent. Malnourishment and vegetarianism have both been found to be associated with earlier onset of menopause.[10,11] However, physical and athletic activity has not been found consistently to influence the age of menopause.

There also appear to be ethnic differences in the onset of menopause. In the United States, African-American and Hispanic women have been found to have menopause approximately 2 years earlier than white women.[12,13] Although parity is generally greater around the world than in the United States, the age of menopause appears to be somewhat earlier. Malay women have menopause at approximately age 45, Thai women at age 49.5, and Filipina women between the ages of 47 and 48.[14-16] Indian women have also been reported to have menopause by age 46.2 years.[17] Women in countries at higher altitude (Himalayas or Andes) have been shown to have menopause 1 to 1.5 years earlier.[18,19] Because the average age of menopause in the United States is 51 to 53 years with an age distribution weighted toward white women, menopause prior to age 40 is considered premature. Conversely, by age 58, 97% of women will have gone through menopause.

The primary determinate of age of menopause is genetic. Based on family studies, heritability for the age of menopause averaged 0.87—suggesting that genetics explain up to 87% of the variance in menopausal age.[20] Prediction models for the age of menopause have been based on the downward trajectory of values of AMH with age, as shown in several studies, noted below. In a recent review of the literature, maternal age of menopause does contribute somewhat to values of AMH in the prediction model, but AMH is thought to the most valuable marker.[21]

Multiple genic loci have been identified by genome-wide association studies, which are associated with the age of natural menopause as well as ovarian insufficiency.[22,23] In a meta-analysis of 22 genome-wide association studies, candidate genes identified appear to be involved in DNA replication and damage repair, hormone production and action, and immune function.[23] These include *EXO1*, *HELQ*, *U1MC1*,

Abstract

With the increase in life expectancy, a woman may now expect to spend one-third or more of her life after menopause. Thus the understanding of the physiology of menopause and aging and possible management strategies assumes great significance for women's health. This review will first discuss the epidemiology of menopause, early or premature menopause, and the effects of menopause on various organ systems and diseases that occur after menopause. This will be followed by a consideration of various therapies for the symptoms of menopause, osteoporosis, and various preventative strategies for women after menopause. Hormonal and nonhormonal therapies will be discussed.

Key words

Menopause
premature ovarian insufficiency
estrogens
androgens
gonadotropins
AMH
inhibin
vulvovaginal atrophy
osteoporosis
coronary disease
stroke
venous thromboembolism
mortality
prevention
hormone therapy
nonhormonal treatment

Table 14.1 US Population Entering the Postmenopausal Years, Ages 55 to 64

Year	Population
1990	10.8 million
2000	12.1 million
2010	17.1 million
2020	19.3 million

Modified From US Bureau of the Census: *Current Population Reports: Projections Of The Population Of The United States 1977 To 2050*, Washington, Dc, 1993, US Government Printing Office.

FAM175A, *FANCI*, *TLK1*, *POLG*, *MCM8*, and *PRIM1* associated with DNA repair, and *IL11*, *NLRP11*, and *PRRC2A* in the immune function domain. Nevertheless, in spite of these advances, the mechanisms of action of these genes and their interactions with environmental factors and possible gonadotoxic factors, which may affect ovarian reserve and reproductive lifespan, remain to be determined.

Premature Ovarian Failure

- *Premature ovarian failure (POF) or insufficiency occurs in up to 10% of young amenorrheic women and has multiple etiologies, but is often idiopathic.*
- *Treatment is dependent on presenting symptoms.*
- *Spontaneous pregnancies may occur and long-term management should include estrogen replacement.*

POF is defined as hypergonadotropic ovarian failure occurring prior to age 40. It has been suggested that women with POF should be referred to as having premature ovarian insufficiency (POI) to more effectively reflect its heterogeneous nature.[24] In practice, both these terms are used interchangeably. POF has occurred in 5% to 10% of women who are evaluated for amenorrhea[25]; thus, the incidence varies according to the prevalence of amenorrhea in various populations. Estimates of the overall prevalence of POF in the general population range between 0.3% and 0.9% of women.[26,27]

Throughout life, there is an ongoing rate of atresia of oocytes (see Chapter 8). Because this process is accelerated with various forms of gonadal dysgenesis due to defective X chromosomes, one possible etiology of POF is an increased rate of atresia that has yet to be explained. A decreased germ cell endowment or an increased rate of germ cell destruction can also explain POF.[24] Nevertheless, some 1000 (of the original 2 million) primary follicles may remain.[28,29] While most of these oocytes are likely to be functionally deficient, occasionally spontaneous pregnancies occur in young women in the first few years after the diagnosis of POF.

There are several possible etiologies of POF (Box 14.1). Defects in the X chromosome may result in various types of gonadal dysgenesis with varied times of expression of ovarian failure. Even patients with classical gonadal dysgenesis (e.g., 45,XO) may undergo a normal puberty, and occasionally a pregnancy may ensue[30-33] as a result of genetic mosaicism. Very small defects in the X chromosome may be sufficient to cause POF.[34] Familial forms of POF may be related to either autosomal-dominant or sex-linked modes of inheritance.[35-37]

Box 14.1 Causes of Premature Ovarian Failure/Insufficiency

Genetic
Enzymatic
Immune
Gonadotropin defects
Ovarian insults
Idiopathic

Mutations in the gene encoding the follicle-stimulating hormone (FSH)-receptor (e.g., mutation in exon 7 in the gene on chromosome 2p) have been described,[38] but these are extremely rare outside of the Finnish population in which these mutations were originally described.

An expansion of a trinucleotide repeat sequence in the first exon on the *FMR1* gene (Xq 27.3) leads to fragile X syndrome, a major cause of developmental disabilities in males.[39] The permutation in fragile X syndrome has been shown to be associated with POF.[40,41] There is a spectrum in findings based on the number of repeats in the premutation, and women with an "intermediate" number of repeats may have a lower ovarian reserve, which is often identified during an investigation for infertility.

Type 1 blepharophimosis/ptosis/epicanthus inversus syndrome, an autosomal-dominant disorder due to mutations in the forkhead transcription factor FOXL2, includes POF.[42] Triple X syndrome has been associated with POF, and so has dystrophic myotonia, although the mechanism underlying this relationship is unclear.[43]

Under the category of enzymatic defects, galactosemia is a major cause of POF that is related to the toxic buildup of galactose in women who are unable to metabolize the sugar. Even in women with fairly well-controlled galactose-free diets, POF tends to occur.[44,45] Another enzymatic defect linked to POF is 17α-hydroxylase deficiency. This rare condition manifests differently from the other causes discussed here because the defect in the production of sex steroids leads to sexual infantilism and hypertension.[46-48]

Because of the prevalence of autoimmune disorders in women, the degree to which autoimmunity may be responsible for POF is unclear. One study has suggested an association in 17.5% of cases.[49] Virtually all autoimmune disorders have been found to be associated with POF, including autoimmune polyendocrinopathies like autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy, which is caused by mutations in the autoimmune *(AIRE)* gene on 21q22.3.[50] The presence of the thymus gland appears to be required for normal ovarian function as POF has been associated with hypoplasia of the thymus.[51] In patients who have undergone ovarian biopsy as part of their evaluation, lymphocytic infiltration surrounding follicles has been described, as well as the resumption of menses after immunosuppression.[52-55]

Immunoassays using antibodies directed at ovarian antigens have been developed and have demonstrated positive findings in some patients with POF,[56] although the relevance of these findings remains unsettled. Ovarian autoantibodies could also conceivably be a secondary phenomenon to a primary cell-mediated form of immunity. Specific enzymes such as 3β-HSD may also be the target of ovarian autoimmunity.[57] From a practical standpoint, screening for the common autoimmune

disorders is appropriate in women found to have POF. Although relatively rare, as many as 2% to 4% of women with POF have antiadrenal antibodies,[58] and may be at risk for adrenal failure. Commercial antibodies to 21-hydroxylase are available and agree with other assays for adrenal cortex antibodies.[59] It has been suggested that screening women using dehydroepiandrosterone sulfate (DHEAS) also may be useful to detect signs of adrenal insufficiency.

More from a theoretical standpoint, abnormalities in the structure of gonadotropins, in their receptors, or in receptor binding could be associated with POF. While abnormal urinary forms of gonadotropins have been reported in women with POF,[60] these data have not been replicated. Abnormalities of FSH-receptor binding, as mediated by a serum inhibitor, have been described.[61] A genetic defect that may lead to alterations in FSH receptor structure was mentioned previously.[38]

Under the category of ovarian insults, POF may be induced by ionizing radiation, chemotherapy, or overly aggressive ovarian surgery. Although not well documented, viral infections have been suggested to play a role, particularly mumps.[62] A dose of 400 to 500 rads is known to cause ovarian failure 50% of the time,[63,64] and older women are more vulnerable to experiencing permanent failure. A dose of approximately 800 rads is associated with failure in all women.[64,65] Ovarian failure (transient or permanent) may be induced by chemotherapeutic agents, although younger women receiving this insult have a better prognosis.[65-67] Alkalyzing agents, particularly cyclophosphamide, appear to be most toxic.[68]

By exclusion, the majority of women are considered to have idiopathic POF because no demonstrable cause can be pinpointed. Among these women, small mutations in genes lying on the X chromosome, or yet to be identified autosomal genes, may be the cause.

Management of Primary Ovarian Failure/Insufficiency

Evaluation of women under age 30 who have POF should include screening for autoimmune disorders and a karyotype; detailed recommendations for screening of such women are available.[69] In addition, vaginal ultrasound may be useful for assessing the size of the ovaries and the degree of follicular development, which, if present, may signify an immunological defect.

Treatment usually consists of estrogen replacement. If fertility is a concern, the most efficacious treatment is oocyte donation. Various attempts at ovarian stimulation are usually unsuccessful, and the sporadic pregnancies that may occur are just as likely to occur spontaneously (~5%) as with any intervention.[70,71] These spontaneous pregnancies are frequently encountered while receiving estrogen replacement. Noting irregular or unscheduled bleeding (while receiving hormonal treatment [HT]) is important as a sign of endogenous sex steroid production. Serum AMH has been used to characterize women with ovarian insufficiency to determine where they may be in the spectrum of ovarian failure.[72] However, AMH levels cannot help predict the chance of a spontaneous pregnancy. It has been shown in a large cohort of women (n = 358) followed for POF, that spontaneous ovarian function may ensue in 24% of women, usually within a year of the diagnosis. In this longitudinal follow-up, 4.4% of women had spontaneous pregnancies.[73]

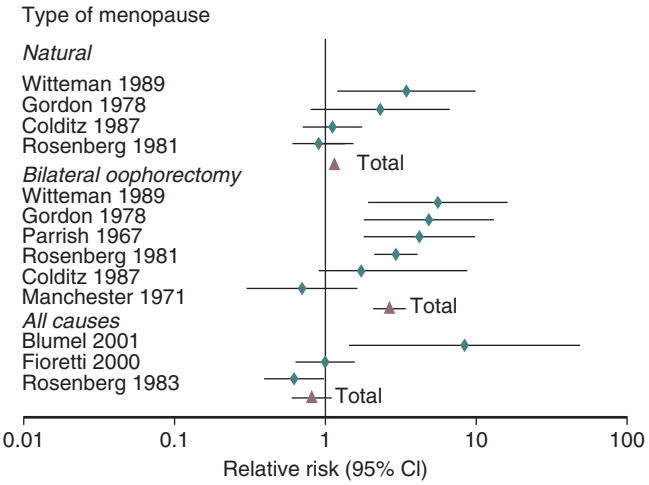


FIGURE 14.1 Effect of type of "early" menopause on cardiovascular disease. Data taken from a meta-analysis. *(From Atsma F, Bartelink ML, Grobbee DE, et al: Postmenopausal status and early menopause as independent risk factors for cardiovascular disease: a meta-analysis.* Menopause *13[2]:265–279, 2006 [review]. See reference 68 for data sources.)*

It has been well established that POF as well as bilateral oophorectomy prior to the usual age of menopause is associated with an increased risk[74] of cardiovascular disease (CVD) as well as increased mortality (Fig. 14.1). CVD mortality specifically is increased twofold to fourfold with early oophorectomy, and observational studies have suggested that using HT reduces this risk. A recent meta-analysis of women with POI suggested an increased risk of all-cause mortality, relative risk (RR): 1.39 (1.1 to 1.77).[75] Early estrogen intervention has been shown to decrease all-cause mortality, which will be discussed later. Accordingly, unless there are contraindications, estrogen should be considered in all young women with POF, at least until the age of natural menopause.

Menopausal Transition (Perimenopause)

- *Great variations in hormonal and menstrual findings occur around the final menstrual period.*
- *This is best described by STRAW+ 10, a workshop designed to describe these changes*
- *Prospective data have been generated by the Study of Women Across the Nation (SWAN) to describe the temporal changes of increasing FSH and decreasing estradiol around menopause.*

A workshop was convened in 2001 to build a consensus on describing various stages of the menopausal transition.[76] Ten years later, another workshop was convened to update the staging system with more recent data.[77] The Stages of Reproductive Aging Workshop + 10 (STRAW + 10) simplified bleeding criteria for the early and late menopausal transition and modified criteria for the late reproductive stage (stage –3) and the early postmenopausal stage (stage +1; Fig. 14.2). Then the late reproductive stages were expanded to include information on decreasing levels of AHM and inhibin B to reflect recent longitudinal data on fluctuating hormonal levels at the time of menopause, which will be described in more detail below.

Menarche FMP (0)

Stage	–5	–4	–3b	–3a	–2	–1	+1a	+1b	+1c	+2
Terminology	REPRODUCTIVE				MENOPAUSAL TRANSITION		POSTMENOPAUSE			
	Early	Peak	Late		Early	Late	Early			Late
					Perimenopause					
Duration	variable				variable	1–3 years	2 years (1+1)		3–6 years	Remaining lifespan
PRINCIPAL CRITERIA										
Menstrual cycle	Variable to regular	Regular	Regular	Subtle changes in flow/ length	Variable length Persistent ≥7-day difference in length of consecutive cycles	Interval of amenorrhea of ≥60 days				
SUPPORTIVE CRITERIA										
Endocrine FSH AMH Inhibin B			Low Low	Variable* Low Low	↑ Variable* Low Low	↑ >25 IU/L† Low Low	↑ Variable Low Low		Stabilizes Very low Very low	
Antral follicle count			Low	Low	Low	Low	Very low		Very low	
DESCRIPTIVE CHARACTERISTICS										
Symptoms						Vasomotor symptoms Likely	Vasomotor symptoms Most likely			Increasing symptoms of urogenital atrophy

* Blood draw on cycle days 2–5 ↑ = elevated.
† Approximate expected level based on assays using current international pituitary standard.[67–69]

FIGURE 14.2 The Stages of Reproductive Aging Workshop + 10 staging system for reproductive aging in women. *AMH*, Anti-Mullerian hormone; *FSH*, follicle-stimulating hormone. *(Modified from Harlow SD, Gass M, Hall JE, et al: Executive summary of the stages of reproductive aging workshop + 10: addressing the unfinished agenda of staging reproductive aging.* J Clin Endocrinol Metab *97[4]:1159–1168, 2012.)*

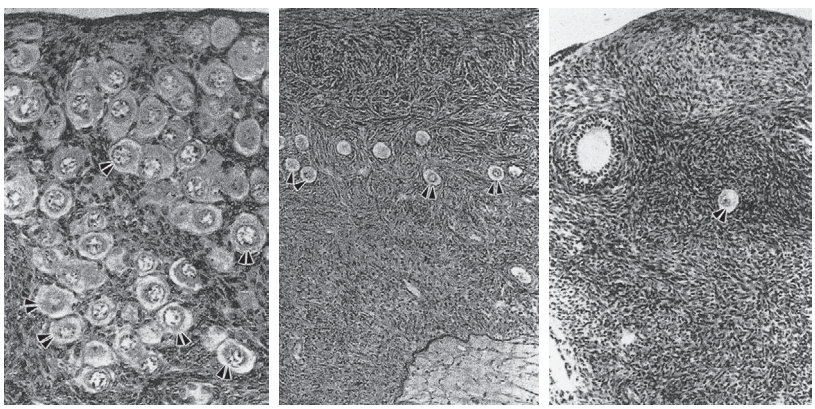


FIGURE 14.3 Photomicrographs of the cortex of human ovaries from birth to 50 years of age. Small nongrowing primordial follicles *(arrows)* have a single layer of squamous granulosa cells. *(Modified from Erickson CF: An analysis of follicle development and ovum maturation.* Semin Reprod Endocrinol *4:233–254, 1986.)*

The ovary changes markedly from birth to the onset of menopause (Fig. 14.3).[78] The greatest number of primordial follicles is present in utero at 20 weeks' gestation and undergoes a regular rate of atresia until around the age of 37. After this time, the decline in primordial follicles appears to become more rapid between age 37 and menopause (Fig. 14.4) when no more than a thousand follicles remain.[28] These remaining follicles are primarily atretic in nature.

Types of Ovarian Changes

Although perimenopausal changes are generally thought to be endocrine in nature and result in menstrual changes, a marked diminution of reproductive capacity precedes this period by several years. This decline may be referred to as *gametogenic ovarian failure*. The concept of dissociation in ovarian function is appropriate. Gametogenic failure is signified by reduced early follicular phase inhibin secretion, rising serum FSH levels, reduced antral follicle counts on ultrasound, decreased levels of AMH, and a marked reduction in fecundity. These changes may occur with normal menstrual function and no obvious endocrine deficiency, however, and they may occur in some women as early as age 35 (10 or more years before endocrine deficiency ensues).

Recent longitudinal data obtained from the Study of Women Across the Nation (SWAN) have shown that estrogen

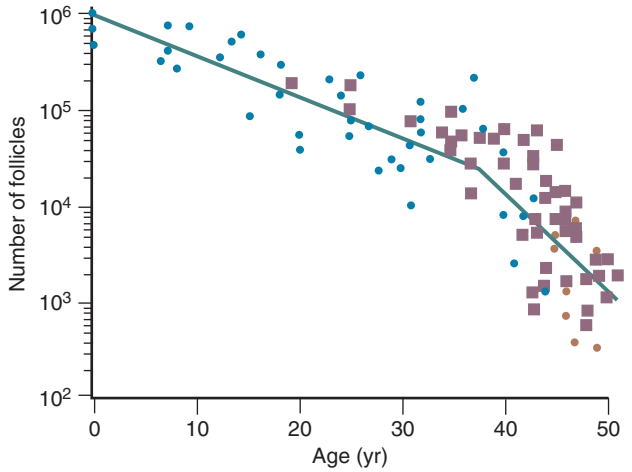


FIGURE 14.4 The age-related decrease in the total number of primordial follicles *(PFs)* within both human ovaries from birth to menopause. As a result of recruitment (initiation of PF growth), the number of PFs decreases progressively from about 1 million at birth to 25,000 at 37 years. At 37 years, the rate of recruitment increases sharply, and the number of PFs declines to 1000 at menopause (about 51 years of age). Note: The different colors and shapes in the graph represent different studies. *(Modified from Faddy MJ, Gosden RJ, Gougeon A, et al: Accelerated disappearance of ovarian follicles in mid-life: implications for forecasting menopause.* Hum Reprod *7:1342–1346, 1992.)*

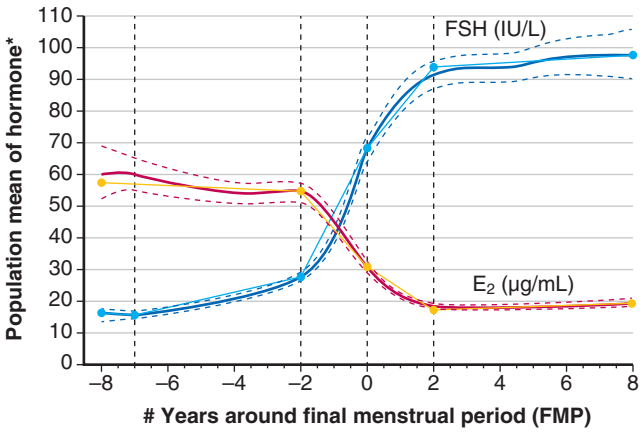


FIGURE 14.5 Adjusted population means (95% confidence interval) for segmented mean profiles of follicle-stimulating hormone and estradiol across the final menstrual period in the Study of Women's Health Across the Nation (n = 1215). E_2, Estradiol; *FSH*, follicle-stimulating hormone. *(Modified from Randolf J: Change in follicle-stimulating hormone and estradiol across the menopausal transition: effect of age at the final menstrual period.* J Clin Endocrinol Metab *96:746–754, 2011.)*

levels begin to decline 2 years before the last menstrual period (Fig. 14.5).[80] Older data had shown that this only occurred during the last 6 months.[81] The rise in FSH levels occurs several years before menopause but increases substantially in the last 2 years, and then stabilizes to steady-state levels 2 years after menopause.[80] These study levels then decrease in the late menopause (seventh decade).[80] There is also a very slow decline in androgen status (i.e., androstenedione and testosterone), which cannot be adequately detected at the time of the perimenopause.

Products of the granulosa cell are most important for the feedback control of FSH. As the functional capacity of the follicular units decrease, secretion of substances that suppress FSH also decrease. Most notably, inhibin B levels are lower in the early follicular phase in women in their late 30s (Fig. 14.6).[81,82] Indeed, FSH levels are higher throughout the cycle in older ovulatory women than in younger women (Fig. 14.7).[83]

The functional capacity of the ovary is also diminished as women enter into the perimenopause. With gonadotropin stimulation, while estradiol (E_2) levels are not very different between younger and older women, total inhibin production by granulosa cells is decreased in women over age 35.[84] From a clinical perspective, subtle increases in FSH on day 3 of the cycle, or increases in the clomiphene challenge test, correlate with decreased ovarian responses to stimulation and decreased fecundability.[85,86]

Although there is a general decline in oocyte number with age, an accelerated atresia occurs around age 37 or 38 (see Fig. 14.4).[28] While the reason for this acceleration is not clear, one possible theory relates to activin secretion. Because granulosa cell-derived activin is important for stimulating FSH-receptor expression,[87] the rise in FSH levels could result in more activin production, which, in turn, enhances FSH action. A profile of elevated activin with lower inhibin B has been found in older women (Fig. 14.8).[88] This autocrine action of activin, involving enhanced FSH action, might be expected to lead to accelerated growth and differentiation of granulosa cells. Further, activin has been shown to increase the size of the pool of preantral follicles in the rat. At the same time, these follicles become more atretic.[89]

Clinical management of women in the perimenopause should address three general areas of concern: (1) irregular bleeding; (2) symptoms of menopause, such as hot flushes; and (3) the inability to conceive.

Treatment of irregular bleeding is complicated by the fluctuating hormonal status. Estrogen levels may be higher than normal in the early follicular phase[80] and progesterone secretion may be normal, although not all cycles are ovulatory. For these reasons, short-term use of an oral contraceptive (usually 20 μg ethinyl estradiol) may be an option for otherwise healthy women who do not smoke to help them cope with irregular bleeding.

Early symptoms of menopause, particularly vasomotor changes, may occur as the result of fluctuating hormonal levels. In this setting, an oral contraceptive again may be an option if symptoms warrant therapy. Alternatively, lower doses of estrogen used alone may be another option.

Reproductive concerns often require more aggressive treatment because of decreased cycle fecundity. Once day 3 FSH levels increase and AMH levels are lower than the established normative data (usually less than 0.4 ng/mL), the prognosis for pregnancy is markedly reduced. A more detailed discussion of AMH levels may be found in the next section.

Hormonal Changes with Established Menopause

Depicted in Fig. 14.9 are the typical hormonal levels of postmenopausal women compared with those of ovulatory women in the early follicular phase.[90] The most significant

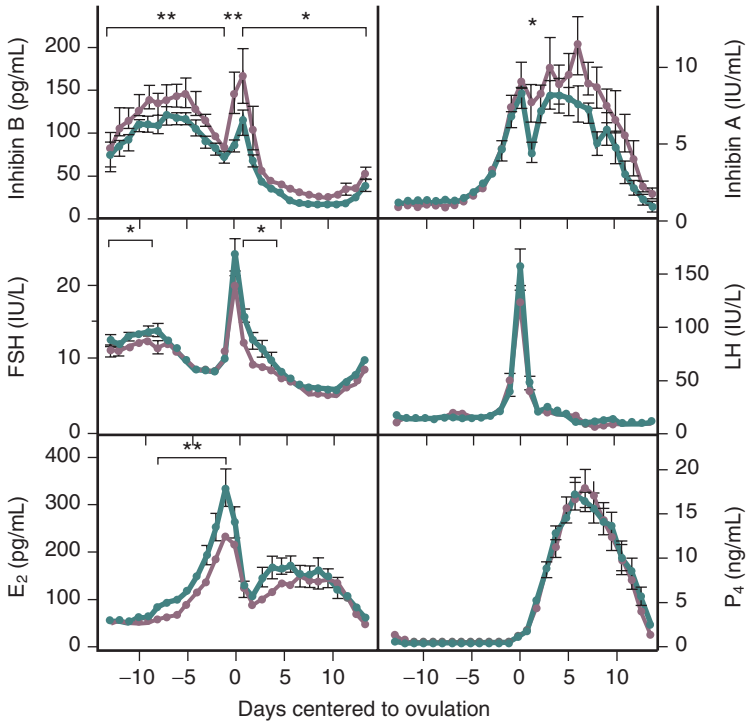


FIGURE 14.6 Mean inhibin B, follicle-stimulating hormone *(FSH)*, estradiol *(E_2)*, inhibin A, and progesterone *(P4)* levels in cycling women 20 to 34 years old *(purple)* and 35 to 46 years old *(green)*. Hormone levels are depicted as centered to the day of ovulation (*, $P < .04$; **, $P < .02$) when comparing the two age groups. *LH*, Luteinizing hormone. *(Modified from Welt CK, McNicholl DJ, Taylor AE, Hall JE: Female reproductive aging is marked by decreased secretion of dimeric inhibin.* J Clin Endocrinol Metab *84:105–111, 1999.)*

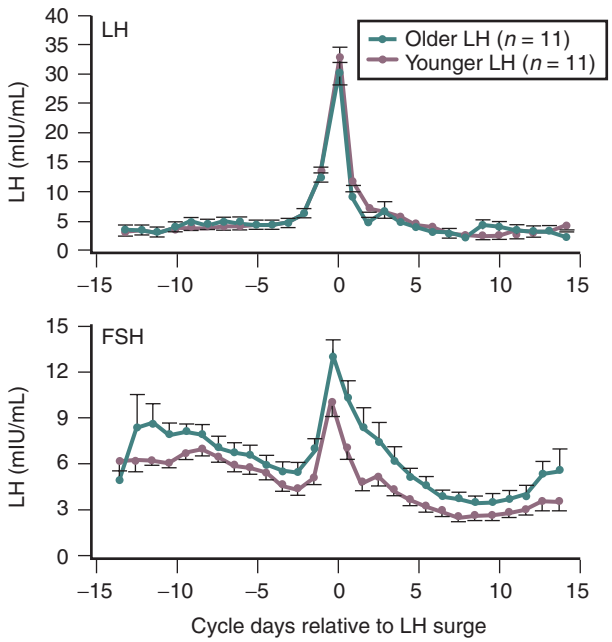


FIGURE 14.7 The daily serum follicle-stimulating hormone *(FSH)* and luteinizing hormone *(LH)* levels throughout the menstrual cycle of two groups (older and younger) of 11 women each (mean ± SE). The gonadotropin secretion pattern in normal women of advanced reproductive age is shown in relation to the monotropic FSH rise. *(Modified from Klein NA, Battaglia DE, Clifton DK, et al: The gonadotropin secretion pattern in normal women of advanced reproductive age in relation to the monotropic FSH rise.* J Soc Gynecol Investig *3:27–32, 1996.)*

findings are the marked reductions in E_2 and estrone (E_1). Serum E_2 is reduced to a greater extent than E_1. Serum E_1, on the other hand, is produced primarily by peripheral aromatization from androgens, which decline more slowly, principally as a function of age. Levels of E_2 average 15 pg/mL and range from 10 to 25 pg/mL, but are 10 pg/mL or less in women who have undergone oophorectomy. Serum E_1 values average 30 pg/mL, but may be higher in obese women because aromatization increases as a function of the mass of adipose tissue.

Estrone sulfate (E_1S) is an estrogen conjugate that serves as a stable circulating reservoir of estrogen, and levels of E_1S are the highest among estrogens in postmenopausal women. In premenopausal women, values are usually above 1000 pg/mL; in postmenopausal women, levels average 350 pg/mL.

Apart from elevations in FSH and luteinizing hormone (LH), other pituitary hormones are not affected. The rise in FSH, beginning in stage –3 as early as age 38 (see Fig. 14.2), fluctuates considerably until approximately 4 years after menopause when values are consistently greater than 20 mIU/mL. Specifically, growth hormone (GH), thyroid-stimulating hormone, and adrenocorticotropic hormone (ACTH) levels are normal. Serum prolactin levels may be very slightly decreased because prolactin levels are influenced by estrogen status.

Both the postmenopausal ovary and the adrenal gland continue to produce androgen. The ovary continues to produce androstenedione and testosterone but not E_2,[91,92] and this production has been shown to be at least partially dependent on LH. Androstenedione and testosterone levels are lower in women who have experienced bilateral oophorectomy, with

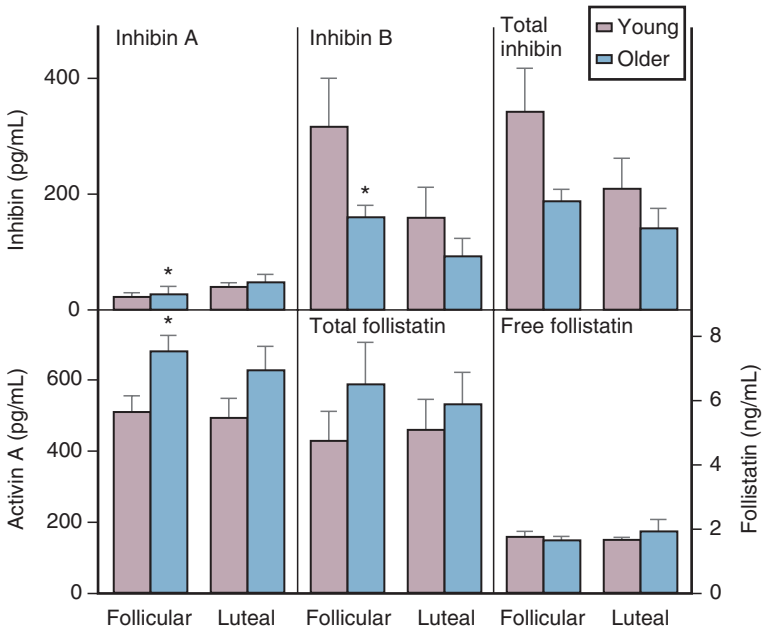


FIGURE 14.8 Mean concentrations of gonadal proteins from the same subjects. Total inhibin is a derived number from the sum of inhibin A and inhibin B. *, Group differences; $P < .05$. Net increase in stimulatory input resulting from a decrease in inhibin B and an increase in activin A may contribute in part to the rise in follicular phase follicle-stimulating hormone of aging cyclic women. *(Modified from Reame NE, Wyman TL, Phillips DJ, et al: Net increase in stimulatory input resulting from a decrease in inhibin B and an increase in activin A may contribute in part to the rise in follicular phase follicle-stimulating of hormone of aging cyclic women.* J Clin Endocrinol Metab *83:3302–3307, 1998.)*

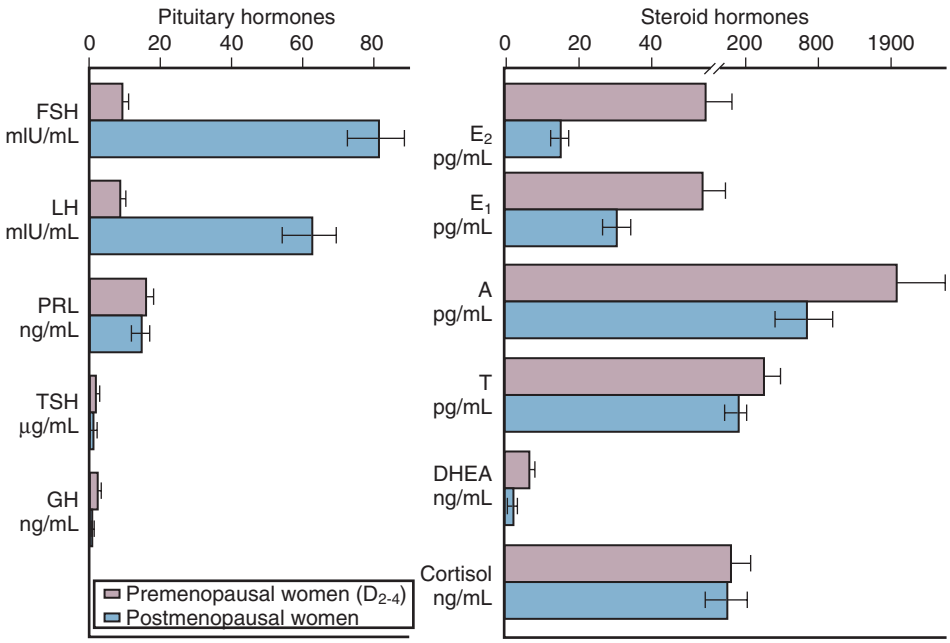


FIGURE 14.9 Circulating levels of pituitary and steroid hormones in postmenopausal women compared with levels in premenopausal women studied during the first week (days 2 to 4 [D_{2-4}]) of the menstrual cycle. *A*, Androstenedione; *DHEA*, dehydroepiandrosterone; E_1, estrogen; E_2, estradiol; *FSH*, follicle-stimulating hormone; *GH*, growth hormone; *LH*, luteinizing hormone; *PRL*, prolactin; *T*, testosterone; *TSH*, thyroid-stimulating hormone. *(Modified from Yen SSC: The biology of menopause.* J Reprod Med *18:287, 1977.)*

values averaging 0.8 ng/mL and 0.1 ng/mL, respectively. The adrenal gland also continues to produce androstenedione, dehydroepiandrosterone (DHEA), and DHEAS; primarily as a function of aging, these values decrease somewhat (adrenopause), although cortisol secretion remains unaffected. Some data suggest that much "ovarian" testosterone production may actually arise from the adrenal.[93] Most likely, this production is by indirect mechanisms due to the adrenal supplying precursor substrate (DHEA and androstenedione).

Although DHEAS levels decrease with age (approximately 2% per year),[94] recent data have suggested that levels transiently rise in the perimenopause before the continuous decline thereafter (Fig. 14.10).[95] This interesting finding from the SWAN study also suggested that DHEAS levels are

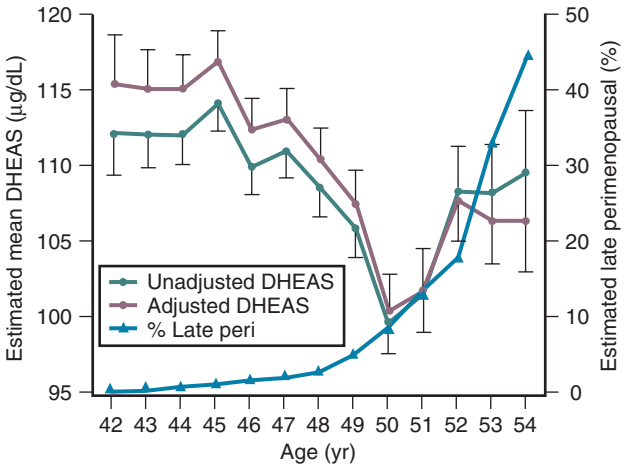


FIGURE 14.10 Mean (±SE) circulating dehydroepiandrosterone sulfate *(DHEAS)* at each year of age of the entire study population before and after adjustment for age, current smoking, menopausal status, log body mass index *(BMI)*, ethnicity, site, and the interaction between ethnicity and log BMI. Also shown is the percentage of women at each year of age who have transitioned to late perimenopausal status. *(Modified from Lasley BL, Santoro N, Randolf JF, et al: The relationship of circulating dehydroepiandrosterone, testosterone, and estradiol to stages of the menopausal transition and ethnicity.* J Clin Endocrinol Metab *87: 3760–3767, 2002.)*

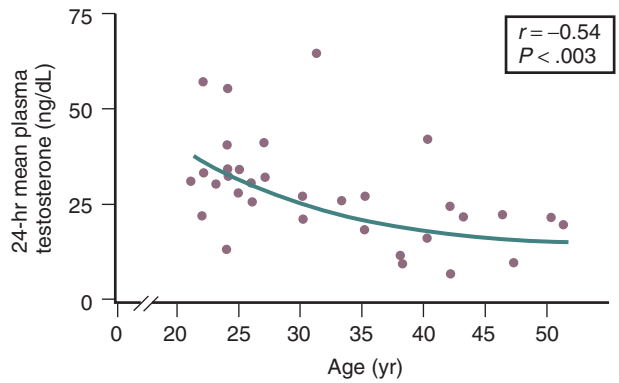


FIGURE 14.11 The 24-hour mean plasma total testosterone *(T)* level compared with age in normal women. The regression equation was T (nmol/L) = 37.8 × age (years)$^{-1.12}$ (r = –0.54; P < .003). *(Modified from Zumoff B, Strain GW, Miller LK, et al: Twenty-four hour mean plasma testosterone concentration declines with age in normal premenopausal women.* J Clin Endocrinol Metab *80:1429–1430, 1995.)*

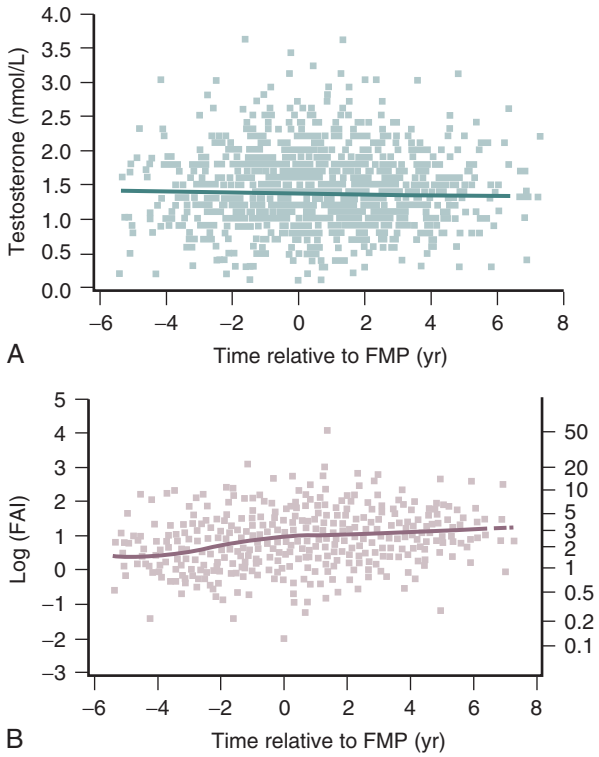


FIGURE 14.12 (A) Linear regression model: observed testosterone and fitted levels of mean T across the menopausal transition. (B) Double logistic model: observed free androgen index *(FAI)* and fitted levels of mean FAI across the menopausal transition. The left and right axes show FAI levels on the log and antilog scales, respectively. The horizontal axis represents time (years) with respect to first menstrual period *(FMP)*; negative (positive) numbers indicate time before (after) FMP. *(From Burger HG, Dudley EC, Cui J, et al: A prospective longitudinal study of serum testosterone, dehydroepiandrosterone sulfate, and sex hormone-binding globulin levels through the menopause transition.* J Clin Endocrinol Metab *85:2832–2838, 2000.)*

highest in Chinese women and lowest in African-American women.[95]

Testosterone levels also decline as a function of age, which is best demonstrated by the reduction in 24-hour mean levels (Fig. 14.11).[96] Because of the role of the adrenal in determining levels of testosterone after menopause,[93] adrenalectomy or dexamethasone treatment results in undetectable levels of serum testosterone. Compared with total testosterone, the measurement of bioavailable or "free" testosterone is more useful in postmenopausal women. After menopause, sex hormone-binding globulin (SHBG) levels decrease, resulting in relatively higher levels of bioavailable testosterone or a higher free androgen index (Fig. 14.12).[97]

In women receiving oral estrogen, bioavailable testosterone levels are extremely low because SHBG levels are increased. How this relates to the decision to begin androgen therapy in postmenopausal women will be discussed later in this chapter.

Elevated gonadotropin (FSH-LH) levels arise from reduced secretion of E_2 and inhibin as described earlier. Estrogen is important in controlling the production of gonadotropin-releasing hormone (GnRH) mRNA in type 1 neurons.[98,99] In addition, the increase in gonadotropins observed at menopause appears to be enhanced by substance P,[100] as well as by tachykinins produced in hypertrophied neurons,[101,102] which result from the decrease in E_2.

Unlike the rodent, where there is evidence for a hypothalamic factor involved in ovarian senescence,[5,104,105] no such clear evidence exists for women. The hypothesis proposed by Wise suggested that the effects of aging in the brain affect neurotransmitter systems that regulate GnRH, disrupting ovarian folliculogenesis and ultimately promoting senescence. Thus the accelerated follicular loss that is apparent in the late 30s is postulated to be due to age-related desynchronization in the rhythmicity of GnRH secretion.[105]

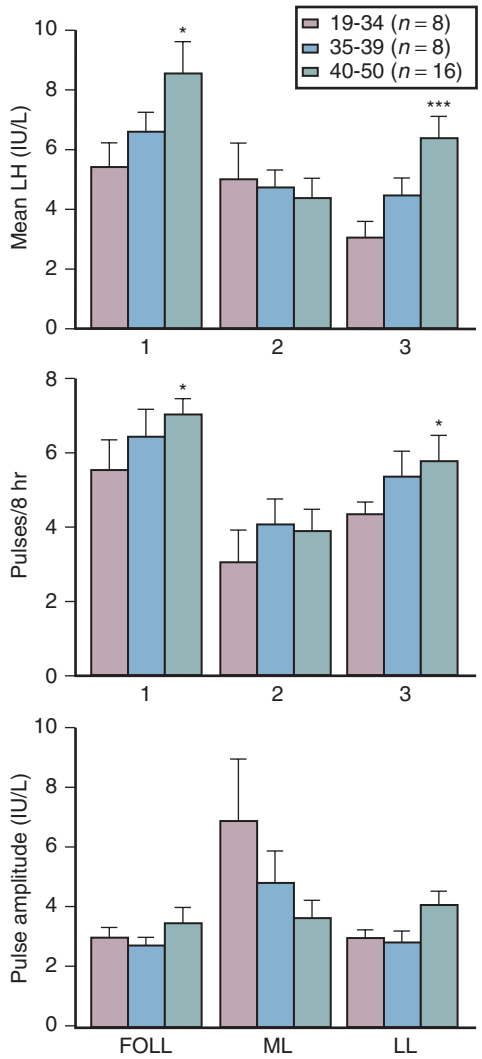


FIGURE 14.13 Effects of age on pulsatile luteinizing hormone *(LH)* secretory characteristics (age groups are in years). All subjects were studied across the same menstrual cycle. *FOLL*, Early follicular phase; *ML*, midluteal phase; *LL*, late luteal phase. *, $P < .05$; ***, $P < .001$. *(Modified from Reame NE, Kelche RP, Beitins IZ, et al: Age effects on follicle-stimulating hormone and pulsatile LH secretion across the menstrual cycle of pre-menopausal women.* J Clin Endocrinol Metab *81:1512–1518, 1996.)*

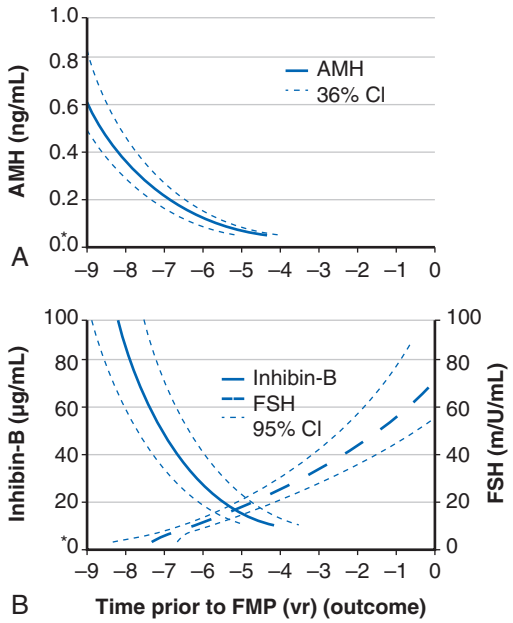


FIGURE 14.14 Anti-müllerian hormone *(AMH)*, Inhibin B, and follicle-stimulating hormone *(FSH)* measured longitudinally prior to menopause. (A) AMH decreases to undetectable levels (0.05 ng/mL) 5 years before the final menstrual period, and inhibin B (10 pg/mL) does so 4 years before the last menstrual period. (B) Rapid decline in levels of AMH/MIS with aging. Levels are undetectable prior to menopause. *FMP*, First menstrual period. *(Modified from Sowers MR, Eyvazzadeth AD, McConnell D, et al: Anti-müllerian hormone and inhibin in the definition of ovarian aging and the menopause transition.* J Clin Endocrinol Metab *93[9]:34768–34783, 2008.)*

Although some aging effects of the brain are likely to exist, there is abundant human evidence for an ovarian-induced menopause. While there is slowing of LH pulsatility with aging in rodents, LH pulse frequency and amplitude increase with age as menopause approaches in women (Fig. 14.13).[106] A sleep-entrained alteration in GnRH pulse dynamics has been observed in postmenopausal women, namely the inability to increase GnRH pulse amplitude at night.[107] There is some evidence that the high frequency and amplitude pulses of LH observed in the first few years in postmenopausal women slows down in late menopause[108]; this latter effect is clearly related to aging, per se.

Ovarian aging is a programmed event, and the return of atresia, accelerating at around age 37.5, until the natural age of menopause, has now been shown to occur in almost the exact way in the chimpanzee.[109] Ovarian aging from a hormonal standpoint is best characterized by small elevations in serum FSH occurring at the beginning of the menstrual cycle (days 2 to 3), reductions in inhibin B, as well as steep declines in serum müllerian inhibiting substance or AMH was introduced previously (Fig. 14.14).[110] It has been confirmed that once a level of inhibin B or AMH becomes undetectable, menopause will ensue in 4 to 5 years (see Fig. 14.14A). There have been several prediction models of the age of natural menopause based on levels of AMH. A recent meta-analysis showed that AMH has good predictability with a hazard ratio of 5.6 to 9.2.[21] Nevertheless, there is no absolute precision with this prediction and it is questionable whether this knowledge has any practical value.

AMH is a very useful and practical determinant in that it tends to undergo less cycle-to-cycle variation compared to FSH or inhibin B, and can be measured during any phase of the cycle.[111] However, it should be kept in mind that the use of oral contraceptive pills can reduce AMH levels by approximately 20%.[112]

Effects on Various Organ Systems

- *Estrogen has many powerful effects on brain anatomy and function, mediated through specific receptors.*
- *The hallmark feature of the drop in estrogen at the time of menopause is the hot flush or vasomotor instability.*
- *Recent data point to alterations in KNDy neurons in the hypothalamus at the time of menopause, which are linked to thermoregulatory centers in the brain.*

- *Collagen content decreases after menopause and is, at least in part, responsive to estrogen.*
- *Vulvovaginal complaints are common after menopause and increase with age, and are well defined.*
- *Treatment improves symptoms, including dyspareunia.*
- *Osteoporosis after menopause is occasioned by an increase in inflammatory factors that increase bone resorption in the face of estrogen decline.*
- *There are several biochemical and radiographic methods to assess bone turnover and bone density, but bone strength is most important in determining fracture risk.*
- *Many agents are now available for prevention and treatment.*
- *Degenerative arthritis correlates with aging, but it may also be related to estrogen insufficiency.*
- *CVD is the leading cause of death in women, and the risk increases from the onset of menopause.*
- *Estrogen protects against atherosclerosis prior to menopause and in younger women after menopause, before the development of established atherosclerosis.*
- *Estrogen treatment in younger healthy postmenopausal women decreases coronary disease and mortality but is ineffective in older women and may be harmful.*
- *Stroke risk in women increases with age and is compounded by obesity and hypertension.*
- *The risk in younger women is ischemic in nature and is mediated by thrombotic risk factors.*

Central Nervous System

Estrogen has powerful effects on the brain mediated by estradiol receptors α and β as well as membrane effects. Most data point to neuroprotective effects of estrogen and older observational data point to a benefit of postmenopausal estrogen of cognitive decline and Alzheimer disease (AD), but this has not been confirmed in prospective studies. There are well-defined physiological and hormonal changes that occur during the hot flush—the hallmark feature of menopausal symptoms. A narrowing of the thermoregulatory zone is a theory for the etiology of the hot flush, but new data also point to alterations in hypothalamic kisspeptin, neurotensin, and dynorphin (KNDy) neurons at menopause.

The brain is an active site for estrogen action and estrogen formation.[113] Estrogen activity in the brain is mediated via estrogen receptors (ER)α and ERβ receptors. Whether or not a novel membrane receptor (non-ERα/ERβ) exists is still being debated.[114] However, both genomic and nongenomic mechanisms of estrogen action clearly exist in the brain. Fig. 14.15 illustrates the predominance of ERβ in the cortex (frontal and parietal) and the cerebellum, based on work in the rat.[115,116] While 17β-E_2 is a specific ligand for both receptors, certain synthetic estrogens have a greater affinity for ERβ.

There are multiple actions of estrogen on the brain as reviewed by Henderson (Box 14.2)[117]; thus, there are important functions linked to estrogen that contribute to well-being in general and, more specifically, to cognition and mood. The hallmark feature of declining estrogen status in the brain is the hot flush, which is more generically referred to as a vasomotor episode.

The *hot flash* usually refers to the acute sensation of heat, while the *flush* or vasomotor episode includes changes in

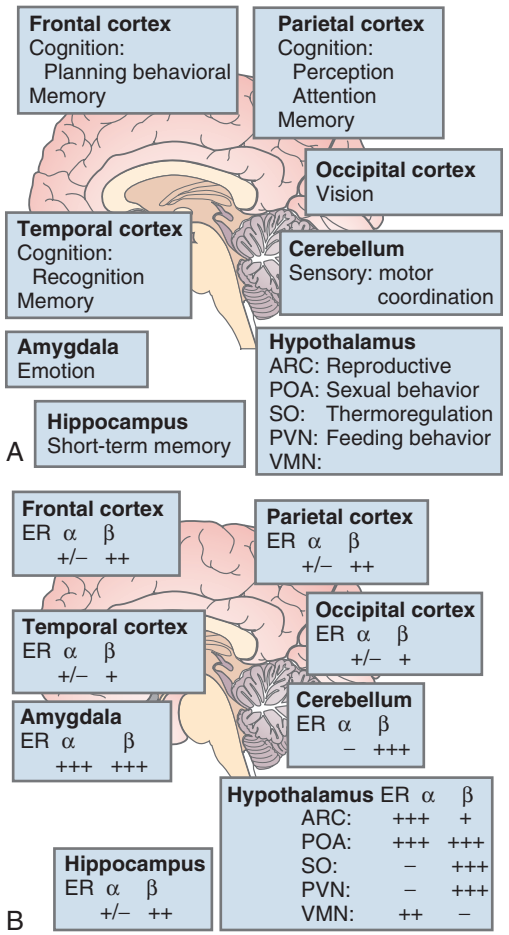


FIGURE 14.15 Brain functional areas and endowment of types of estrogen receptors in the rat brain. (A) Each region of the brain has an important role in specific brain functions. Optimal brain activity is maintained by means of the integration of different areas by neural tracts. (B) Distribution of estrogen receptors ERα and ERβ mRNA in the rat brain. *ARC*, Arcuate nucleus; *POA*, preoptic area; *PVN*, paraventricular nucleus; *SO*, supraoptic nucleus; *VMN*, ventromedial nucleus. ([B] Modified from Cela V, Naftolin F: Clinical effects of sex steroids on the brain. In Lobo RA, editor: *The treatment of postmenopausal woman: basic and clinical aspects*, ed 2, Philadelphia, 1999, Lippincott Williams & Wilkins, pp 247–262.)

the early perception of this event and other skin changes (including diaphoresis). Hot flushes usually occur for 2 years after the onset of estrogen deficiency, but can persist for 10 or more years.[118,119] A recent longitudinal study from SWAN showed that the median duration of significant vasomotor symptoms is 7.4 years.[120] In 10% to 15% of women, these symptoms are severe and disabling.[118,121] In the United States, the incidence of these episodes varies in different ethnic groups. Symptoms are greatest in Hispanic and African-American women, intermediate in white women, and lowest among Asian women (Fig. 14.16).[122]

The fall in estrogen levels precipitate the vasomotor symptoms. Although the proximate cause of the flush remains elusive, the episodes result from a hypothalamic response (probably mediated by catecholamines) to the change in estrogen status. The flush has been well characterized physiologically. It results in heat dissipation as witnessed by an increase in peripheral temperature (finger, toe); a decrease

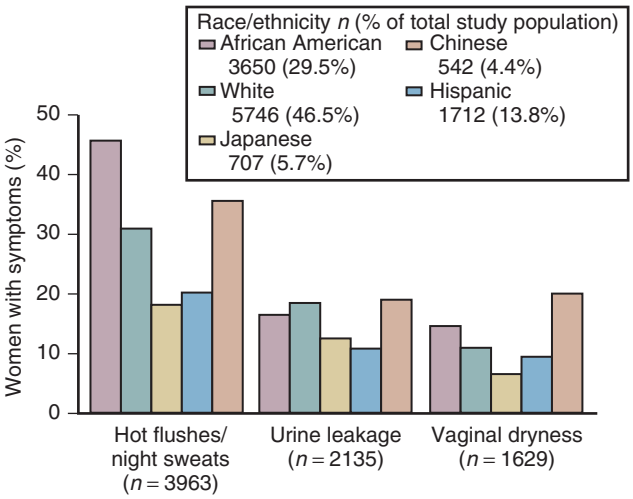


FIGURE 14.16 Study of Women's Health Across the Nation (SWAN): Symptom severity. *(Modified from Gold EB, Sternfeld B, Kelsey JL, et al: Relation of demographic and lifestyle factors to symptoms in a multi-racial/ethnic population of women 40–55 years of age.* Am J Epidemiol *152:463, 2000.)*

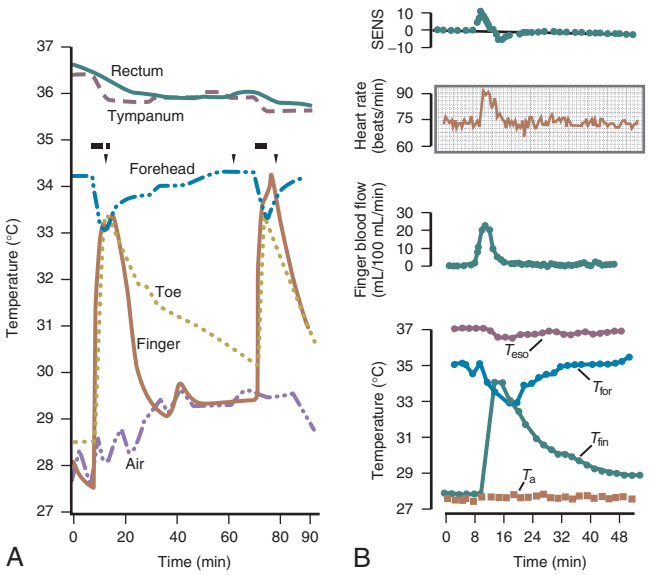


FIGURE 14.17 Temperature responses to two spontaneous flashes and evoked flash. *Down arrow* indicates finger stab for blood sample. *Black bars* indicate time of hot flush. *(Data from Molnar GW: Body temperature during menopausal hot flashes.* J Appl Physiol *38:499–503, 1975.)*

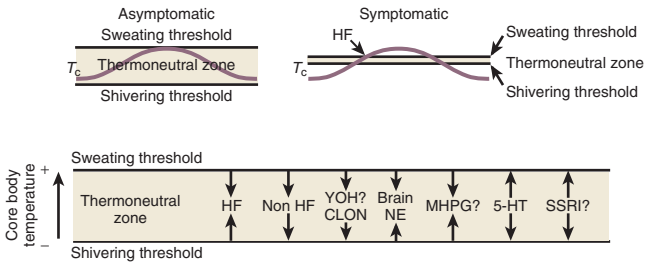


FIGURE 14.18 Narrowing of the thermoregulatory zone in symptomatic women. *HF,* Hot flush. *(Data from Freedman RR: Menopausal hot flashes. In Lobo RA, editor:* Treatment of the postmenopausal woman*, ed 3, New York, 2007, Academic Press, pp 187–198.)*

Box 14.2 Effects of Estrogen on Brain Function

1. Organizational actions
   Effects on neuronal number, morphology, and connections occurring during critical stage of development
2. Neurotrophic actions
   Neuronal differentiation
   Neurite extension
   Synapse formation
   Interactions with neurotrophins
3. Neuroprotective actions
   Protection against apoptosis
   Antioxidant properties
   Antiinflammatory properties
   Augmentation of cerebral blood flow
   Enhancement of glucose transport into the brain
   Blunting of corticosteroid response to behavioral stress
   Interactions with neurotrophins
4. Effects on neurotransmitters
   Acetylcholine
   Noradrenaline
   Serotonin
   Dopamine
   Glutamate
   γ-Aminobutyric acid
   Neuropeptides
5. Effects on glial cells
   a. Effects on proteins involved in Alzheimer disease
      Amyloid precursor protein
      Tau protein
      Apolipoprotein E

in skin resistance, associated with diaphoresis; and a reduction in core body temperature (Fig. 14.17).[123] There are hormonal correlates of flush activity, such as an increase in serum LH and in plasma levels of pro-opiomelanocortin peptides (ACTH, β-endorphin) at the time of the flush,[124] but these occurrences are thought to be epiphenomena and not the proximate cause of the flush. Nevertheless, as will be discussed below, there may be interplay in the hypothalamus between the thermoregulatory center and release of GnRH/LH.

Data from Freedman have suggested that the major physiological finding in postmenopausal women with and without hot flushes is a narrowing of the temperature threshold for sweating and shivering in symptomatic women (Fig. 14.18).[125] This has been the major theory expounded for hot flushes occurring in an estrogen deficient state; however, recent evidence points to brain neuromodulatory changes. The KNDy neurons in the hypothalamus activate kisspeptin and other receptors on GnRH neurons and activation releases GnRH. At the same time, KNDy neurons also impinge upon the thermoregulatory center in the hypothalamus. Estrogen loss has been shown to increase the size of KNDy neurons, and to activate the genes for neurokinin B and kisspeptin as suggested in Fig. 14.19.[126] Experimentally, neurokinin B, activating neurokinin 3 has been shown to induce hot flushes in postmenopausal women.[127] This activation of the KNDy neuronal system would also release GnRH/LH, which is what has been observed during a hot flush. The potential exists, therefore, that specific neurokinin (NK)

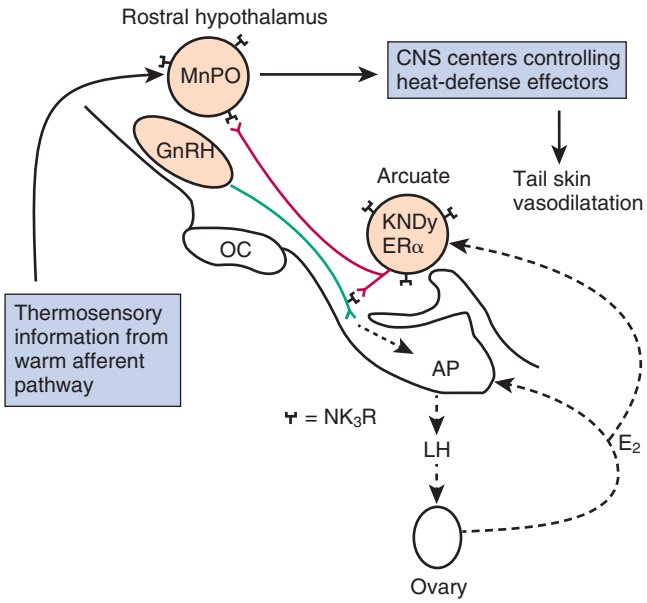


FIGURE 14.19 Diagramatic depiction (in a rat model) of KNDy neurons in the hypothalamus, not only influencing GnRH pulses and gonadotropin secretion but interacting with thermosensory and heat regulatory centers in the brain. Hypertrophy of the KNDy neurons occurs at the time of menopause. *AP,* Anterior pituitary; *CNS,* central nervous system; E_2, estradiol; *GnRH,* gonadotropin-releasing hormone; *KNDy,* kisspeptin, neurotensin, and dynorphin; *LH,* luteinizing hormone; *MnPO,* median preoptic nucleus. *(Modified from, Mittleman-Smith MA, Williams H, Krajewski-Hall SJ, McMullen NT, Rance NE: Role for kisspeptin/neurokinin B/dynorphin [KNDy] neurons in cutaneous vasodilatation and the estrogen modulation of body temperature.* Proc Natl Acad Sci USA *109:19846–19851, 2012.)*

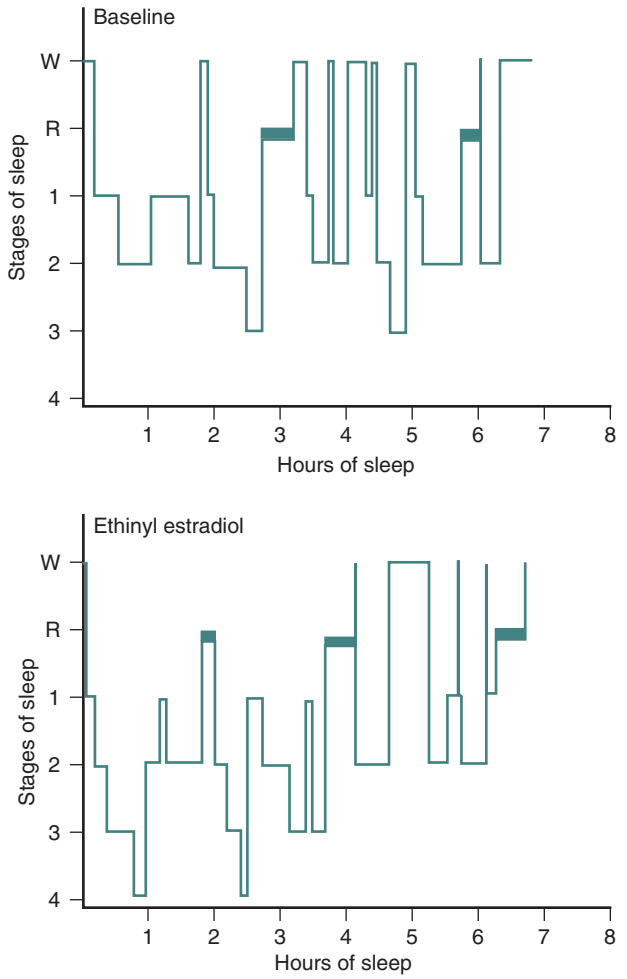


FIGURE 14.20 Sleepgrams measured in symptomatic patient before and after 30 days' administration of ethinyl estradiol, 50 μg 4 times daily. *(Modified from Erlik Y, Tataryn IV, Meldrum DR, et al: Association of waking episodes with menopausal hot flushes.* JAMA *245:1741–1744, 1981.)*

antagonists (which are available for oral use) may be able to inhibit hot flushes in women.

One of the primary complaints of women with hot flushes is sleep disruption. They may awaken several times during the night, and require a change of bedding and clothes because of diaphoresis. Nocturnal sleep disruption in postmenopausal women with hot flushes has been well documented by electroencephalographic (EEG) recordings.[128] Sleep efficiency is lower, and the latency to rapid eye movement sleep is longer in women with hot flushes compared with asymptomatic women.[118,129] This disturbed sleep often leads to fatigue and irritability during the day. The frequency of awakenings and of hot flushes are reduced appreciably with estrogen treatment (Fig. 14.20).[128,131,132] Sleep may be disrupted even if the woman is not conscious of being awakened from sleep. In this setting, EEG monitoring has indicated sleep disruption in concert with physiological measures of vasomotor episodes.

In postmenopausal women, estrogen has been found to improve depressed mood regardless of whether or not this is a specific complaint.[133-139] (Critics of some of this work point out that mood is affected by the symptomatology and by sleep deprivation.) Blinded studies carried out in asymptomatic women have also shown benefit.[138] In an estrogen-deficient state, such as occurs after the menopause, a higher incidence of depression (clinical or subclinical) is often manifest. However, menopause per se does *not* cause depression, and while estrogen does generally improve depressive mood, it should *not* be used for psychiatric disorders. Nevertheless, very high pharmacological doses of estrogen have been used to treat certain types of psychiatric depression in the past.[140-142] Progestogens as a class generally attenuate the beneficial effects of estrogen on mood, although this effect is highly variable.[143,144]

Cognitive decline in postmenopausal women is related to aging as well as to estrogen deficiency. The literature is somewhat mixed in showing whether there are benefits of estrogen in terms of cognition. In more recent studies, verbal memory appears to be enhanced with estrogen[145-148] and has been found to correlate with acute changes in brain imaging, signifying brain activation.[147-149]

Dementia increases as women age, and the most common form of dementia is AD. Listed in Box 14.2 are several neurotrophic and neuroprotective factors that relate to how estrogen deficiency may be expected to result in the loss of protection against the development of AD. In addition, estrogen has a positive role in enhancing neurotransmitter function, which is deficient in women with AD. This function of estrogen has particular importance and relevance for the cholinergic system that is affected in AD.[150,151]

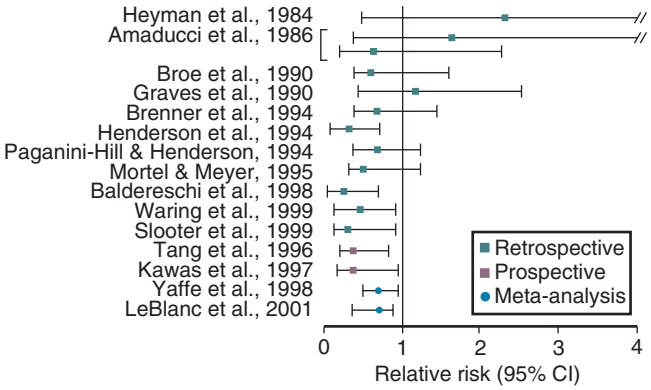


FIGURE 14.21 Estrogen and hormone replacement therapy use and Alzheimer disease risk. *(Modified from LeBlanc ES, Janoowsky J, Chan BK, Nelson HD: Hormone replacement therapy and cognition: systematic review and meta-analysis.* JAMA *285:1489–1499, 2001.)*

Estrogen use after menopause has been shown in observational studies to decrease the likelihood of developing or delay the onset of AD (Fig. 14.21).[152-163] However, there are no randomized prospective studies as yet on this issue. It is clear, however, that if estrogen has a beneficial role, it is only in those women who receive estrogen at the onset of menopause; in older women it may be detrimental.[164,165] A recent short-term study could not show a cognitive benefit in women who received estrogen within 6 years of menopause and those who received it 10 years later.[166] However, recent brain imaging studies have suggested that women treated early after menopause with estrogen may have less amyloid deposition, particularly if they have the Apo-E allele, a risk factor for AD.[167] Once a woman is affected by AD, estrogen is unlikely to provide any benefit.[168] In the Women's Health Initiative (WHI) study, women over the age of 65 years receiving estrogen and progestogen for the first time had a decrease in cognition,[169] which was not statistically significant for the group of women receiving estrogen alone.[170] Still, to date, there are no compelling prospective data in younger postmenopausal women to confirm earlier observational studies on the benefits of estrogen in preventing cognitive decline or AD risk.

Collagen

Estrogen has a positive effect on *collagen*, which is an important component of bone and skin and serves as a major support tissue for the structures of the pelvis and urinary system. Both estrogen and androgen receptors have been identified in skin fibroblasts. Nearly 30% of skin collagen is lost within the first 5 years after menopause, and collagen decreases approximately 2% per year for the first 10 years after menopause.[171] This statistic, which is similar to that of bone loss after menopause, strongly suggests a link between skin thickness, bone loss, and the risk of osteoporosis.[172]

Although the literature is not entirely consistent, estrogen therapy generally improves collagen content after menopause and improves skin thickness substantially after about 2 years of treatment.[171,173-177] There is a possible biomodal effect with high doses of estrogen causing a reduction in skin thickness.[171-178] The supportive effect of estrogen on collagen has important implications for bone homeostasis and for the pelvis after menopause. Here, reductions in collagen support and atrophy of the vaginal and urethral mucosa have been implicated in a variety of symptoms, including prolapse and urinary incontinence.[179,180]

Symptoms of urinary incontinence and irritative bladder symptoms occur in 20% to 40% of perimenopausal and postmenopausal women.[181-183] Uterine prolapse and other gynecological symptoms related to poor collagen support, as well as urinary complaints, may improve with estrogen therapy.[184-186] While estrogen generally improves symptoms, urodynamic changes have not been shown to be altered.[187,188] Estrogen has also been shown to decrease the incidence of recurrence of urinary tract infections.[189] These data relate to the use of vaginal estrogen, rather than the use of estrogen systemically. Somewhat paradoxically, systemic estrogen may increase stress urinary incontinence, while local vaginal therapy may improve urge incontinence.[190]

In Sweden, the restoration of bladder control in older women with estrogen has been shown to decrease the need for admission to nursing homes.[191] Estrogen may also have an important role in normal wound healing. In this setting, estrogen enhances the effects of growth factors, such as transforming growth factor β (TGFβ).[192,193]

Genital Atrophy

Vulvovaginal complaints are often associated with estrogen deficiency. In the perimenopause, symptoms of dryness and atrophic changes occur in 21% and 15% of women, respectively. However, these findings increase with time, and by 4 years these incidences are 47% and 55%, respectively.[194,195] With this change, an increase in sexual complaints also occurs, with an incidence of dyspareunia of 41% in sexually active 60-year-old women.[196] Estrogen deficiency results in a thin and more pale vaginal mucosa. The moisture content is low, the pH increases (usually greater than 5), and the mucosa may exhibit inflammation and small petechiae.

With estrogen treatment, vaginal cytology changes have been documented, transforming from a cellular pattern of predominantly parabasal cells to one with an increased number of superficial cells. Along with this change, the vaginal pH decreases, vaginal blood flow increases, and the electropotential difference across the vaginal mucosa increases to that found in premenopausal women.[197] Recent studies have suggested that intravaginal DHEA (0.25% to 1%) is efficacious for altering vaginal cytology and symptoms of atrophy, presumably by allowing for local conversion to other androgens and estrogen.[198] This product (prasterone) is now commercially available, having been approved by the US Food and Drug Administration (FDA) for symptoms of dyspareunia in postmenopausal women.

Bone Loss

Estrogen deficiency has been well established as a cause of bone loss. This loss can be noted for the first time when menstrual cycles become irregular in the perimenopause. From 1.5 years before the menopause to 1.5 years after menopause, spine bone mineral density (BMD) has been shown to decrease by 2.5% per year, compared with a premenopausal loss rate of 0.13% per year.[199,200] Loss of

trabecula bone (spine) is greater with estrogen deficiency than is loss of cortical bone.

Postmenopausal bone loss leading to osteoporosis is a substantial healthcare problem. In white women, 35% of all postmenopausal women have been estimated to have osteoporosis based on BMD.[201] Further, the lifetime fracture risk for these women is 40%.[202] The morbidity and economic burden of osteoporosis is well documented.[203] Interestingly, there are data to suggest that up to 19% of Caucasian men also have osteoporosis.

Bone mass is substantially affected by sex steroids through classic mechanisms to be described later in this chapter. Attainment of peak bone mass in the late second decade (Fig. 14.22)[204] is key to ensuring that the subsequent loss of bone mass with aging and estrogen deficiency does not lead to early osteoporosis. Estradiol, together with GH and insulin-like growth factor-1, acts to double bone mass at the time of puberty,[205] beginning the process of attaining peak bone mass. Postpubertal estrogen deficiency (amenorrhea from various causes) substantially jeopardizes peak bone mass. Adequate nutrition and calcium intake are also key determinants. While estrogen is of predominant importance for bone mass in both women and men, testosterone is important in stimulating periosteal apposition; as a result, cortical bone in men is larger and thicker.[206,207]

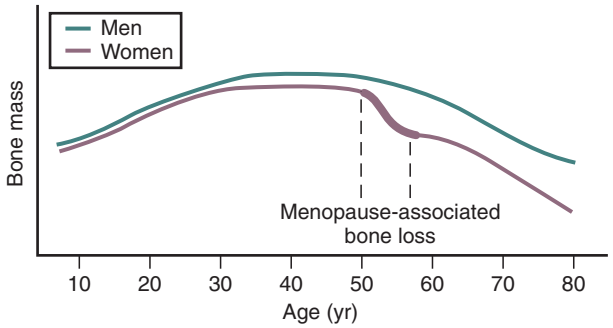


FIGURE 14.22 Bone mass by age and sex. *(Modified from Finkelstein JS. In Cecil RL, Goldman L, Bennett JC, editors:* Cecil textbook of medicine, *ed 21, Philadelphia, 1999, Saunders, pp 1366–1373; and Riggs BL, Melton LJ III: Involutional osteoporosis.* N Engl J Med *314:1676–1686, 1986.)*

ERs are present in osteoblasts,[208,209] osteoclasts,[210,211] and osteocystes.[212,213] Both ERα and ERβ are present in cortical bone, while ERβ predominates in cancellous or trabecular bone.[214] However, the more important actions of estradiol are believed to be mediated via ERα.

Estrogens suppress bone turnover and maintain a certain rate of bone formation.[215] Bone is remodeled in functional units, called *bone multicenter units* (BMUs), where resorption and formation should be in balance.[216] Multiple sites of bone go through this turnover process over time. Estrogen decreases osteoclasts by increasing apoptosis and thus reduces their lifespan.[217] The effect on the osteoblast is less consistent, but E_2 antagonizes glucocorticoid-induced osteoblast apoptosis.[215,218] Estrogen deficiency increases the activities of remodeling units, prolongs resorption, and shortens the phase of bone formation[215]; it also increases osteoclast recruitment in BMUs, thus resorption outstrips formation.

The molecular mechanisms of estrogen action on bone involve the inhibition of production of proinflammatory cytokines including interleukin-1, interleukin-6, and tumor necrosis factor, which inhibits bone resorption. Receptor-activation of nuclear factor kappa-B ligand (RANKL) is responsible for osteoclast differentiation and action.[219-221] A scheme for how all these factors interact has been proposed by Riggs (Fig. 14.23).[217]

In women, Riggs has suggested that bone loss occurs in two phases. In the first phase, with declining estrogen at the onset of menopause there is an accelerated phase of bone loss; this loss is predominantly of cancellous or trabecula bone. Here 20% to 30% of cancellous bone and 5% to 10% of cortical bone can be lost in a short span of 4 to 8 years.[222]

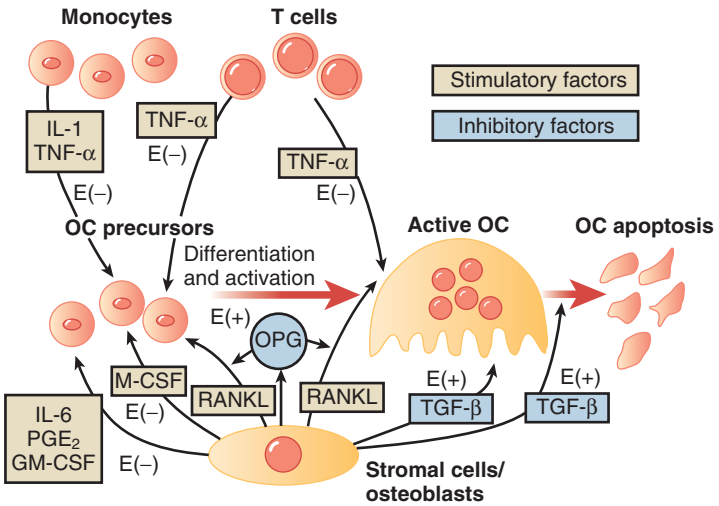


FIGURE 14.23 Model for mediation of effects of estrogen *(E)* on osteoclast formation and function by cytokines in bone marrow microenvironment. Stimulatory factors are shown in *orange* and inhibitory factors are shown in *blue*. Positive (+) and negative (–) effects of E on these regulatory factors are shown in *red*. The model assumes that regulation is accomplished by multiple cytokines working together in concert. *GM-CSF,* Granulocyte macrophage colony stimulating factor; *IL,* interleukin; *M-CSF,* monocyte colony stimulating factor; *OC,* osteocalcin; *OPG,* osteoprotegerin; *PGE2,* prostaglandin E2; *TGFβ,* transforming growth factor β; *TNF-α,* tumor necrosis factor-α. *(Modified from Riggs BL: The mechanisms of estrogen regulation of bone resorption.* J Clin Invest *106:1203–1204, 2000.)*

Thereafter, a slower phase of loss (1% to 2% per year) ensues where, proportionately, more cortical bone is lost. This phase is thought to be induced primarily by secondary hyperparathyroidism.[223] The first phase is also accentuated by the decreased influence of stretching or mechanical factors, which generally promote bone homeostasis, as a result of estrogen deficiency.[224-226]

Genetic influences on bone mass are more important for attainment of peak bone mass (heritable component, 50% to 70%) than for bone loss. Polymorphisms of the vitamin D receptor gene, TGFβ gene, and the Spl-binding site in the collagen type 1 AI gene have all been implicated[227] as being important for bone mass.

While testosterone is important for bone formation and stimulation of bone mass, even in men estrogen action is of paramount importance.[228-230] Bone mass was shown to increase in an aromatase-deficient man upon estrogen administration.[231]

Bone mass can be detected by a variety of radiographic methods (Table 14.2).[232] *Dual energy x-ray absorptiometry scans* have become the standard of care for detection of osteopenia and osteoporosis. By convention, the *T score* is used to reflect the number of standard deviations of bone loss from the peak bone mass of a young adult. Osteopenia is defined by a T score of –1 to –2.5 standard deviations; osteoporosis is defined as greater than 2.5 standard deviations. Since bone mass does not completely reflect bone strength, which is really what matters in terms of fracture risk, several approaches have been made to assess bone strength. An assessment of biochemical bone turnover (discussed later in the chapter), in addition to bone mass, is deemed important. One newer approach is to assess bone microarchitecture, a so-called virtual bone biopsy, by using a high-resolution (HR) peripheral (p) quantitative computed tomography (Fig. 14.24).[233] This technique has been used to assess bone strength and formation in boys and girls to assess sex differences in bone growth and strength, and the risk of fracture.[234] Various biochemical assays are also available to assess bone resorption and formation in both blood and urine (Table 14.3).[235] At present, serum markers appear to be most useful for assessing changes with antiresorptive therapy. Biochemical assays can provide some functional information, which may be helpful in assessing bone strength, and can reflect changes in bone resorption/formation more rapidly than imaging studies. However, these assays do not correlate well with bone density measurements.

Table 14.2 Techniques for the Detection of Osteopenia

Technique	Anatomical Site of Interest	Precision in vivo (%)	Examination and Analysis Time (min)	Estimated Effective Dose Equivalent (μSv)
Conventional radiography	Spine, hip	NA	<5	2000
Radiogrammetry	Hand	1–3	5–10	<1
Radiographic absorptiometry	Hand	1–2	5–10	<1
Single x-ray absorptiometry	Forearm, heel	1–2	5–10	<1
Dual x-ray absorptiometry	Spine, hip, forearm, total body	1–3	5–20	1–10
Quantitative computed tomography	Spine, forearm, hip	2–4	10–15	50–100
Quantitative ultrasound	Heel, hand, lower leg	1–3	5–10	None

NA, Not applicable.
Modified from van Kuijk C, Genant HK: Detection of osteopenia. In Lobo RA, editor. *Treatment of the postmenopausal woman: basic and clinical aspects*, ed 2, Philadelphia, 1999, Lippincott Williams & Wilkins, pp 287–292.

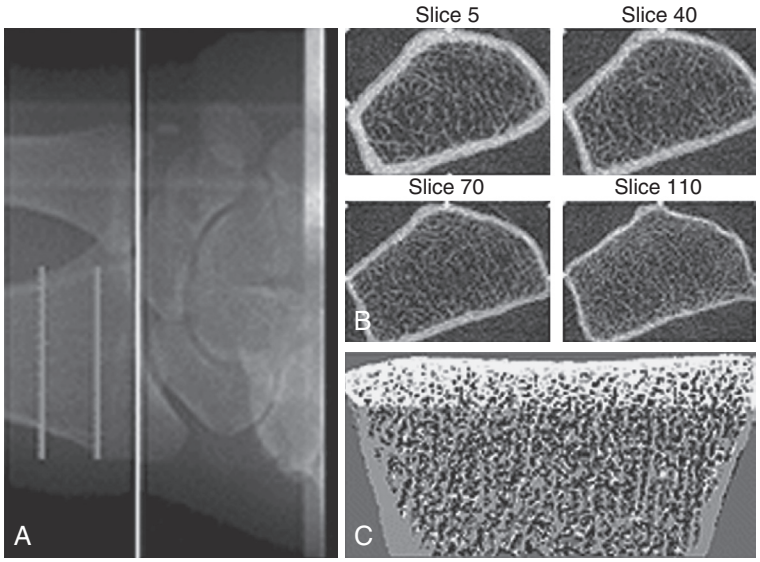


FIGURE 14.24 High-resolution peripheral quantitative computed tomography. (A) Radiograph of distal radius; *lines* indicate the section analyzed. (B) Representative cross-sectional images from computed tomography slices. (C) Representative three-dimensional image. *(Modified from Khosla S, Riggs BL, Atkinson EJ, et al: Effects of sex and age on bone microstructure at the ultradistal radius: a population-based noninvasive in vivo assessment.* J Bone Miner Res *21:124–131, 2006.)*

Table 14.3 Bone Turnover Markers

Marker	Specimen
Bone Resorption Markers	
Cross-linked N-telopeptide of type 1 collagen (NTX)	Urine, serum
Cross-linked C-telopeptide of type 1 collagen (CTX)	Urine (αα and ββ forms) Serum (ββ form)
MMP-generated telopeptide of type 1 collagen (ICTP or CTX-MMP)	Serum
Deoxypyridinoline, free and peptide bound (fDPD, DPD)	Urine, serum
Pyridinoline, free and peptide bound (fPYD, PYD)	Urine, serum
OHP	Urine
GylHyl	Urine, serum
HelP	Urine
Tartrate-resistant acid phospharase 5b Isoform specific for osteoclasts (TRACP 5b)	Serum, plasma
Cath K	Urine, serum
uOC	Urine
Bone Formation Markers	
OC	Serum
Procollagen type 1 C-terminal propeptide (PICP)	Serum
Procollagen type 1 N-terminal propeptide (PINP)	Serum
Bone-specific alkaline phosphatase (bone ALP)	Serum

Cath K, Cathepsin K; *GylHyl*, glycosyl hydroxylysine; *HelP*, helical peptide; *OC*, osteocalcin; *OHP*, hydroxyproline; *uOC*, osteocalcin fragments.

Data from Eastell R, Hannon RA: Biochemical markers of bone turnover. In Lobo RA, editor: *Treatment of the postmenopausal woman basic and clinical aspects*, 3 ed, St. Louis, 2007, Elsevier Academic Press, pp 337–350.

There are now many agents that can prevent osteoporosis. The use of estrogen will depend on whether or not there are other indications for estrogen treatment and whether there are contraindications. Estrogen has been shown to reduce the risk of osteoporosis as well as to reduce osteoporotic fractures. In the WHI study, hip fractures, as well as all fractures, were reduced with conjugated equine estrogens (CEE) and medroxyprogesterone acetate (MPA), and CEE alone, and this occurred in a nonosteoporotic population. Indeed, in a cohort of women who were followed after stopping hormones when the results of the WHI study were published, there was an increased risk of hip fracture and lower bone density compared to those women who continued therapy.[236,237]

A dose equivalent to 0.625 mg of CEE was once thought to prevent osteoporosis, but we now know that lower doses (0.3 mg of CEE or its equivalent) in combination with progestogens are able to prevent bone loss,[238,239] although there are no data on fractures. Whether or not the addition of progestogens, by stimulating bone formation, increases bone mass over that of estrogen alone is unclear. The androgenic activity of certain progestogens such as norethindrone acetate also has been suggested to play a role.[240]

Selective estrogen receptor modulators (SERMs), such as raloxifene, droloxifene, and tamoxifen, have all been shown to decrease bone resorption. Raloxifene has been shown to decrease vertebral fractures in a large prospective trial.[241] Tibolone has also been shown to be an effective treatment for osteoporosis. Tibolone (not marketed in the United States) has SERM-like properties, but it is not specifically a SERM because it has mixed estrogenic, antiestrogenic, androgenic, and progestogenic properties due to its metabolites. The drug does not cause uterine or breast cell proliferation and is beneficial for vasomotor symptoms. It prevents osteoporosis and has been shown to be beneficial in the treatment of established osteoporosis.[242,243]

Bisphosphonates have been shown to have a significant effect on the prevention and treatment of osteoporosis. With this class of agents (etidronate, alendronate, residronate, ibandronate, and zoledronic acid) there is incorporation of the bisphosphonate with hydroxyapetite in bone, which increases bone mass. The skeletal half-life of bisphosphonates in bone can be as long as 10 years.[244] Most data have been derived with alendronate, which, at a dosage of 5 mg daily (35 mg weekly) prevents bone loss; at 10 mg daily (70 mg weekly), alendronate is an effective treatment for osteoporosis, with evidence available that this treatment reduces vertebral and hip fractures.[245] Ibandronate is available as a monthly pill (150 mg) and by injection (3 mg) every 3 months. It has primary efficiency for vertebral fracture protection. Zoledronic acid, 5 mg, is available as an intravenous therapy, with infusion over 15 minutes.

There has been some concern over this class of very powerful bone resorption agents causing fractures of the long bones such as the femur because of "brittle" bone.[246] This only occurs with prolonged use of at least 7 years, and the incidence is in the range of 3.2 to 50 per 100,000 women.[246] Osteonecrosis of the jaw has also been cited as a concern, but this mainly occurs in the presence of poor dental health, and is rare with an incidence in the range of 1/10,000 women.[247] With long-term therapy, atrial fibrillation, as an adverse event also occurs, although this too is rare.[248] These adverse effects appear to be a "class" effect of bisphosphonates. Nevertheless, while all these findings are rare events, there are no good data for prolonged treatment of 10 or more years. For these and other reasons, bisphosphonates are not the drugs of choice in younger women prior to natural menopause and should not be used in women who wish to conceive.

Calcitonin, 50 IU subcutaneous injections daily or 200 IU intranasally, has been shown to inhibit bone resorption. Vertebral fractures have been shown to decrease[249,250] with calcitonin therapy. However, long-term effects have not been established.

Fluoride has been used for women with osteoporosis because it increases bone density.[251] Currently, a lower dose (50 μg daily) of slow-release sodium fluoride does not seem to cause adverse effects (gastritis) and has efficacy in preventing vertebral fractures.[252,253]

Denosumab is a monoclonal antibody targeting RANKL, which is secreted by osteoblasts and causes bone resorption (see Fig. 14.22). Thus it is an antiresorptive agent with significant potency. Denosumab 60 mg is administered subcutaneously every 6 months, and while it has a preventative role it is usually considered to be a second-line treatment for difficult-to-treat cases. Denosumab has efficacy both at the vertebrae and the hip,[254] but unlike the bisphosphonates, is shorter acting and wears off quickly rather than being bound to the bone with a long half-life in the case of bisphosphonates. Also it is devoid of the other side effects

of bisphosphonates (fractures, osteonecrosis, etc.) described above. Because of this profile and its benefit at the hip as well as the spine, denosumab has emerged as a popular therapy. Nevertheless, as a newer form of immune therapy, long-term potential consequences are not known.

An inhibitor of cathepsin K, odanacatib, also has a significant effect on decreasing bone resorption and has been successful in clinical trials at vertebral and nonvertebral bone sites.[255] However, odanacatib is not yet available for clinical use.

Intermittent parathyroid hormone (PTH 1-34, teriparatide) is an agent that increases bone mass in women with osteoporosis. In a randomized trial lasting 3 years, average bone density increased in the hip and spine with fewer fractures observed.[256] This therapy is available in the United States, at a standard dose of 20 μg/day injected subcutaneously for no longer than 18 months. It is expensive and is reserved for women who are difficult to treat and have a history of fractures.[257]

Another agent, which has the ability to increase bone formation, is a monoclonal antibody against sclerosin. Sclerosin is an inhibitor of normal bone formation, which activated the Wnt signaling system. While this monoclonal antibody, romosozumab, has shown great efficacy in increasing bone formation,[258] its cardiovascular risk profile has not been acceptable; and it is unlikely that this drug will be available for clinical use.

Adjunctive measures for the prevention of osteoporosis are calcium, vitamin D, and exercise. Calcium with vitamin D treatment has been shown to increase bone only in older individuals.[259] These modalities alone are not thought to be effective for the treatment of osteoporosis. A woman's total intake of elemental calcium should be 1200 to 1500 mg daily if no agents are being used to inhibit resorption, 400 to 800 IU of vitamin D should also be ingested. Levels of serum 25 hydroxy vitamin D have been found to be abnormally low (<20 ng/mL) in a large population of women, particularly in geographic regions of less sunlight exposure. Exercise has been shown to be beneficial for building muscle and bone mass and for reducing falls.[260,261] Guidelines regarding the management of osteoporosis were published by the National Osteoporosis Foundation, last updated in 2013 (www.nof.org). An update analysis has suggested that 37% of women are candidates for treatment to prevent fractures.[262] Also, the World Health Organization (WHO) has produced guidelines for assessing an individual's risk of osteoporosis based on history, anthropometry, and BMD. This new paradigm, called the Fracture Risk Assessment Tool, may be obtained at www.shef.ac.uk/FRAX.

Degenerative Arthritis

Chronic arthritis is a major source of disability in postmenopausal women, and while this is largely correlated with older age, there is some evidence that estrogen deficiency after menopause may contribute to its progression. Administration of estrogen after menopause has been shown to inhibit the damage to chondrocytes, which is a key activator of the problem of arthritis.[263,264] In the WHI study, the estrogen alone trial showed evidence for a significant decrease in osteoarthirits.[264,265] Nevertheless, much more work is needed in this area.

Cardiovascular Effects

Clearly after menopause, the risk of CVD in women is increased. Data from the Framingham study[266] have shown that the incidence is three times lower in women before menopause than in men (3.1 per 1000 per year in women aged 45 to 49). The incidence is approximately equal in men and women aged 75 to 79 (53 and 50.4 per 1000 per year, respectively). This trend also pertains to gender differences in mortality due to CVD. Coronary artery disease is the leading cause of death in women, and the lifetime risk of death is 31% in postmenopausal women versus a 3% risk of dying of breast cancer.[267]

Although CVD becomes more prevalent only in the later years following a natural menopause, premature cessation of ovarian function (before the average age of menopause) constitutes a significant risk. Premature menopause, occurring before age 35, has been shown to increase the risk of myocardial infarction twofold to threefold, and oophorectomy before age 35 increases the risk severalfold.[268]

An analysis of several studies on this issue has been conducted and reviewed,[269] as shown in the data depicted in Fig. 14.25, on the effect of early menopause on the prevalence and type of CVD. It has been suggested that total mortality is increased if bilateral oophorectomy occurs even after the natural menopause, until around age 60. This change in total mortality is due to an excess in coronary disease, suggesting a protective effect of the ovary even beyond the normal age of menopause.[270]

When the possible reasons for the increase in CVD are examined, the most prevalent finding is that of the accelerated rise in total cholesterol in postmenopausal women. The changes of weight, blood pressure, and blood glucose with aging, while important, are not thought to be as important as the rate of rise in total cholesterol, which is substantially different in women versus men. This increase in total cholesterol is explained by increases in levels of low-density lipoprotein cholesterol (LDL-C). The oxidation of LDL-C is also enhanced, as are levels of very-low-density lipoproteins and Lp(a) lipoprotein. HDL-C levels trend downward with time, but these changes are small and inconsistent relative to the increases in LDL-C.[271]

Coagulation balance is not substantially altered as a counterbalancing change occurs. Some procoagulation factors increase (Factor VII, fibrinogen, and plasminogen activator inhibitor-1 [PAI-1]), but so do counterbalancing factors like antithrombin III, plasminogen, protein C, and protein S.[272] Inflammation markers, such as C-reactive protein and cytokines, are increased; and blood flow in all vascular beds decreases after menopause. Prostacyclin production decreases, endothelin levels increase, and vasomotor responses to acetylcholine are constrictive, reflecting reduced nitric oxide synthetase activity. With estrogen, all these parameters (generally) improve and coronary arterial responses to acetylcholine are dilatory with a commensurate increase in blood flow.[273-280] Circulating plasma nitrites and nitrates have also been shown to increase with estrogen, and angiotensin-converting enzyme levels tend to decrease. Estrogen and progesterone receptors have been found in vascular tissues, including coronary arteries (predominantly ERβ). In addition, there are membrane effects mediated by estrogen—which may or may not relate to either ERα or ERβ.[281,282] The

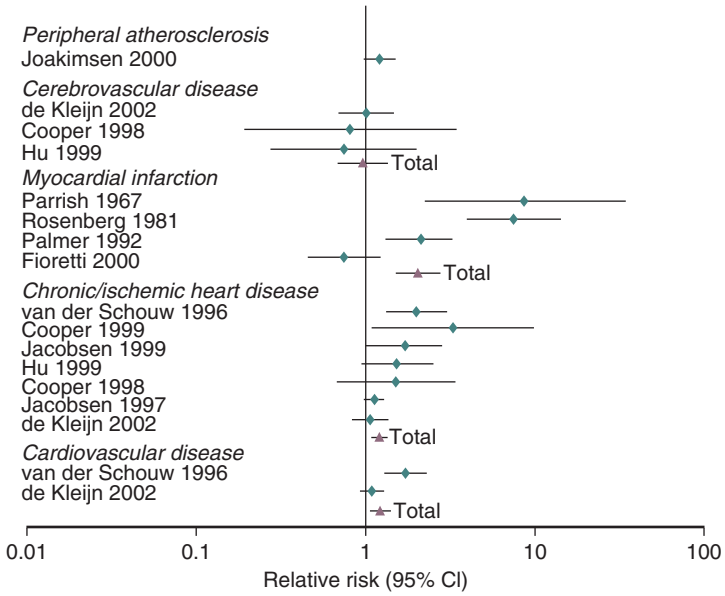


FIGURE 14.25 Effect of "early" menopause on types of cardiovascular disease. *(From Atsma F, Bartelink ML, Grobbee DE, et al: Postmenopausal status and early menopause as independent risk factors for cardiovascular disease: a meta-analysis.* Menopause *13[2]:265–279, 2006 [review]. See reference 68 for data sources.)*

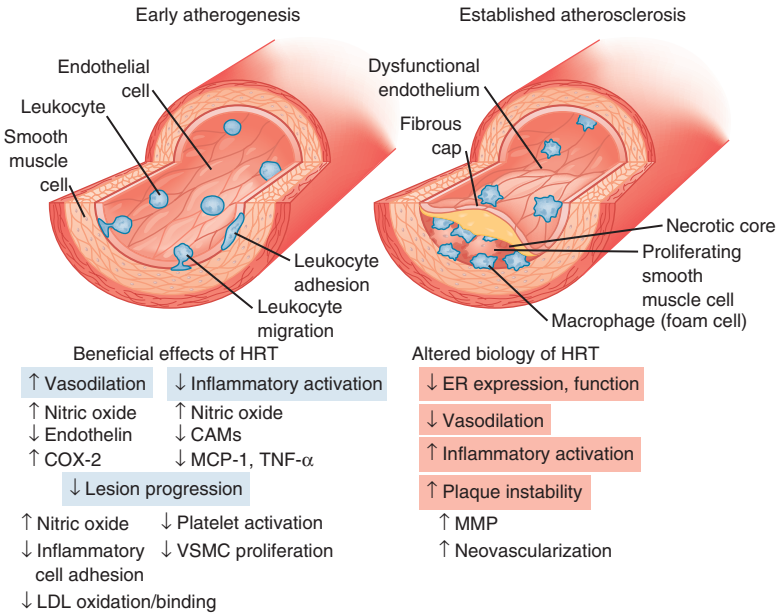


FIGURE 14.26 Early and esterified atherosclerosis with aging and the beneficial and negative effects of estrogen during these stages. *CAM,* Cell adhesion molecule; *COX-2,* cyclooxygenase-2; *ER,* estrogen receptor; *HRT,* hormone replacement therapy; *LDL,* low-density lipoprotein; *MCP,* monocyte chemoattractant protein; *MMP,* matrix metalloproteinase; *TNF-α,* tumor necrosis factor-α; *VSMC,* vascular smooth muscle cell. *(From Mendelsohn ME, Karas RH: Molecular and cellular basis of cardiovascular gender differences.* Science *308[5728]:1583–1587, 2005 [review].)*

statements above pertain to the effects of estrogen in a relatively normal coronary artery (devoid of significant atherosclerosis). Once there is significant atherosclerotic plaque, the normal actions of estrogen do not occur (Fig. 14.26).[283]

Overall, the direct vascular effects of estrogen are viewed to be as important, or more important, than the changes in lipid and lipoproteins after menopause. While replacing estrogen has been thought to be beneficial for the mechanisms previously cited, these beneficial arterial effects can only be seen in younger (stage +1) postmenopausal women. Women with significant atherosclerosis or risk factors, such as those studied in a secondary prevention trial, do not respond in a beneficial manner (see Fig. 14.26).[284-288] Some of this lack of effect may be accounted for by increased methylation of the promoter region of ERα, which occurs with atherosclerosis and aging.[289]

Another theory proposed to explain differences in the effects of estrogen when given earlier rather than later is the interfering effect of endogenous 27-hydroxy cholesterol. This endogenous metabolite of cholesterol increases with

advancing levels of cholesterol and competes for binding with E_2 at the ER in the endothelium. Thus, when cholesterol is elevated, high levels of 27-C may prevent estrogen action (Fig. 14.27).[290]

In normal, nonobese postmenopausal women, carbohydrate tolerance also decreases as a result of an increase in insulin resistance. This, too, may be partially reversed by estrogen.[291] In postmenopausal women, use of hormones decreases the risk of new onset diabetes.

Biophysical and neurohormonal responses to stress (stress reactivity) are exaggerated in postmenopausal women compared with premenopausal women, and this heightened reactivity is blunted by estrogen.[292] Whether or not these changes influence cardiovascular risk with estrogen deficiency is not known, but clearly estrogen treatment returns many parameters into the range of premenopausal women in early postmenopausal women.

These consistently strong basic science and clinical data for the protective effects of estrogen on the cardiovascular system, together with strong epidemiological evidence for a protective effect of estrogen (Fig. 14.28),[293] led to the belief that estrogen should be prescribed to prevent CVD in women. However, randomized clinical trials (RCTs) in women with established disease did not find benefit, and there was a trend towards more harm. Results from several "secondary prevention" randomized trials in women who had coronary disease,[294-296] found a lack of benefit, and in some studies, there were more coronary events in older women given estrogen at a standard dose for the first time.[296]

This trend toward increased cardiovascular events in women who are older and/or who have documented diseased coronary arteries ("early harm")[284,296-296] occurs within the first 1 to 2 years. This is thought to result from oral estrogen increasing circulating levels of matrix metalloproteinases, which dissolve part of the gelatinous plaque in the mural portion of an atherosclerotic coronary vessel, causing plaque instability and rupture resulting in a coronary thrombosis.[297] The WHI trial, which compared CEE/MPA with placebo, showed this effect in older women.[298] This trial was considered to be a primary prevention trial, but with a mean age of 63 years and a range up to 79 years, there were many fewer younger women in their 50s recruited, and the higher frequency of cardiovascular events reported for the entire study was predominantly explained by the findings in the older cohort of women.

The protective effect of estrogen demonstrated in the Nurse's Health Study (see Fig. 14.28)[293] as well as other observational cohorts, evaluated by meta-analyses, was because

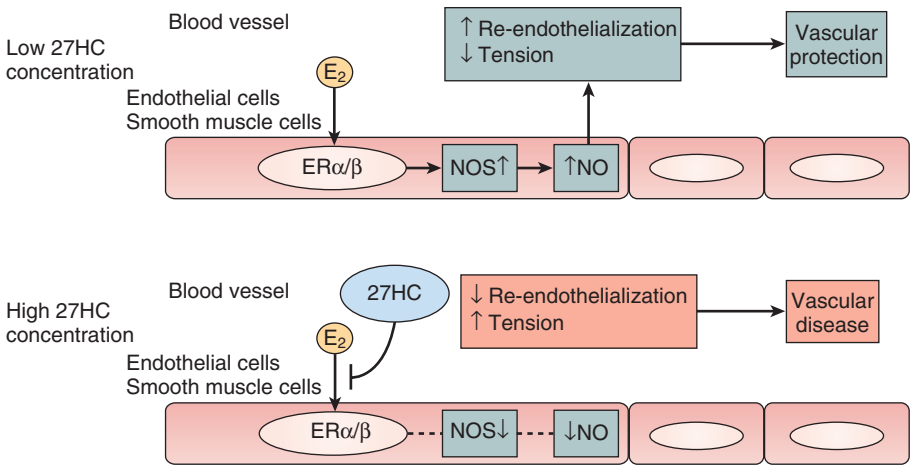


FIGURE 14.27 Hypothesis of how elevated cholesterol (27-hydroxycholesterol *[27HC]*) can influence the effect of estradiol (E_2). *ER*, Estrogen receptor; *NO*, nitric oxide; *NOS*, nitric oxide synthase. *(From Umetani M, Domoto H, Gormley AK, et al: 27-Hydroxycholesterol as an endogenous SERM that inhibits the cardiovascular effects of estrogen.* Nat Med *13[10]:1185–1192, 2007.)*

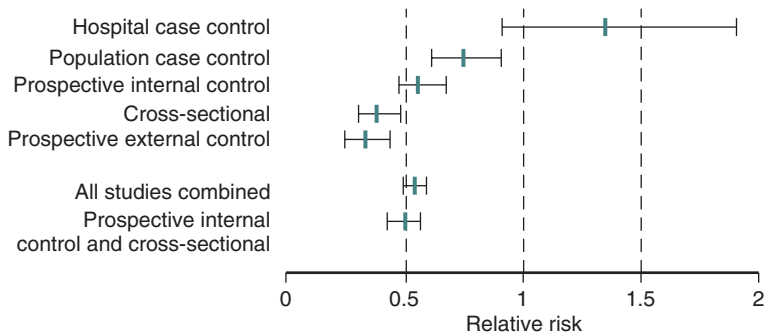


FIGURE 14.28 Estrogen replacement therapy and coronary heart disease. Relationship between relative risk and study type. *(Modified from Stampfer MJ, Colditz GA: Estrogen replacement therapy and coronary heart disease: a quantitative assessment of the epidemiologic evidence.* Prev Med *20:47–63, 1991.)*

treatment was carried out in predominantly young healthy women who were symptomatic, and were receiving estrogen for menopausal symptoms.

Table 14.4 compares the demographics of the participants of WHI and the Nurse's study. Trials carried out in the monkey model have shown that there is a 50% to 70% protective effect against coronary atherosclerosis when estrogen is begun at the time of oophorectomy, with or without an atherogenic diet; delaying the initiation of hormonal therapy for even 2 years (in the monkey) prevents this protective effect (Fig. 14.29).[299-303] This early intervention is thought to relate to the first 6 years after menopause in women.

It is now well established that the late treatment of postmenopausal women with standard doses of estrogen may be harmful and affords no coronary protection. This finding pertains to various trials with end points of coronary events, or angiographically determined disease, as noted above, and does not appear to be modified by the hormonal regimen or route of administration. This is also true whether or not the woman has sustained a known coronary event. Since atherosclerosis is highly age dependent, even women who have not had a coronary event have diseased arteries (Fig. 14.30).[303] Also, as shown in Fig. 14.30, well over 70% of the women studied in the WHI would have been expected to have atherosclerotic vessels.

As noted previously, the "early harm" observed when older women are exposed to estrogen for the first time is likely due to plaque instability and rupture. It has been reported that these effects in older women were not observed in those women receiving statins concurrently.[304] Statins are known to stabilize plaque. In women who had been receiving estrogen for a prolonged time, mortality was decreased in those who sustained a myocardial infarction.[305] Young women initiating hormones within the first few years of menopause do not appear to have the risk described in previous text. No increase in cardiovascular events was found in young healthy symptomatic women during the first 2 years of various hormonal regimens in clinical trials.[306]

In concert with the view that estrogen given to early (and younger) postmenopausal women may have different effects, data have been analyzed in the 50- to 59-year-old age group in WHI, and in those less than 10 years from menopause. The definitions of menopause in WHI were not precise, and more women in the 50- to 59-year-old age group were older than 55 years old. The data are in strong contrast to the results of the entire group (two-thirds over 60 years old). In the estrogen only arm of WHI (hysterectomized women) receiving CEE 0.625 mg, the 50- to 59-year-old age group had reduced coronary event scores of borderline significance and a composite coronary score of statistical significance.[307] An analysis of 20 RCTs in younger women (which included WHI) showed a statistically significant benefit in the reduction of coronary events[308] and mortality.[309,310] Younger women in WHI using estrogen only also had significantly reduced coronary calcium.[308] Ten-year follow up data of the estrogen alone arm published in 2011 confirmed that the 50- to

Table 14.4 Baseline Characteristics: Nurses' Health Study Compared with Women's Health Initiative

Characteristic	NHS	WHI
Mean age or age range at enrollment (years)	30–55	63
Smokers (past and current)	55%	49.9%
BMI (mean)	25.1 kg/m^2	28.5 kg/m^2*
Aspirin users	43.9%	19.1%
HT regimen	Unopposed or sequential	Continuous-combined
Menopausal symptoms (flushing)	Predominant	Uncommon

*34.1% had BMI ≥ 30 kg/m^2.
BMI, Body mass index; *HT*, hormone therapy; *NHS*, Nurses' Health Study; *WHI*, Women's Health Initiative study.
Data from Colditz GA, Stampher MJ, Willet WC, et al: A prospective study of parental history of myocardial infarction and coronary heart disease in women. *Am J Epidemiol* 123:48–58, 1986; Grodstein F, Manson JE, Colditz GA, et al: A prospective, observational study of postmenopausal hormone therapy and primary prevention of cardiovascular disease. *Ann Intern Med* 133:933–941, 2001; Grodstein F, Stampfer MJ, Manson JE, et al: Postmenopausal estrogen and progestin use and the risk of cardiovascular disease. *N Engl J Med* 335:453–461, 1996; and Writing Group for the WHI Investigators. Risks and benefits of estrogen plus progestin in healthy postmenopausal women. *JAMA* 288:321–333, 2002.

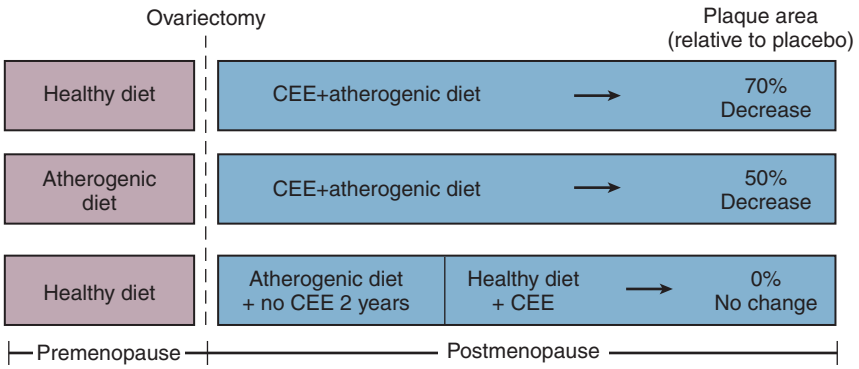
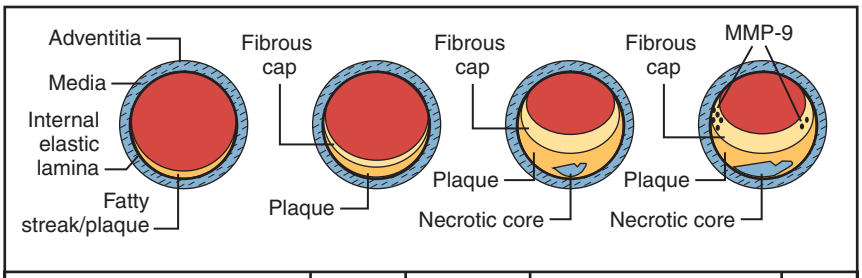
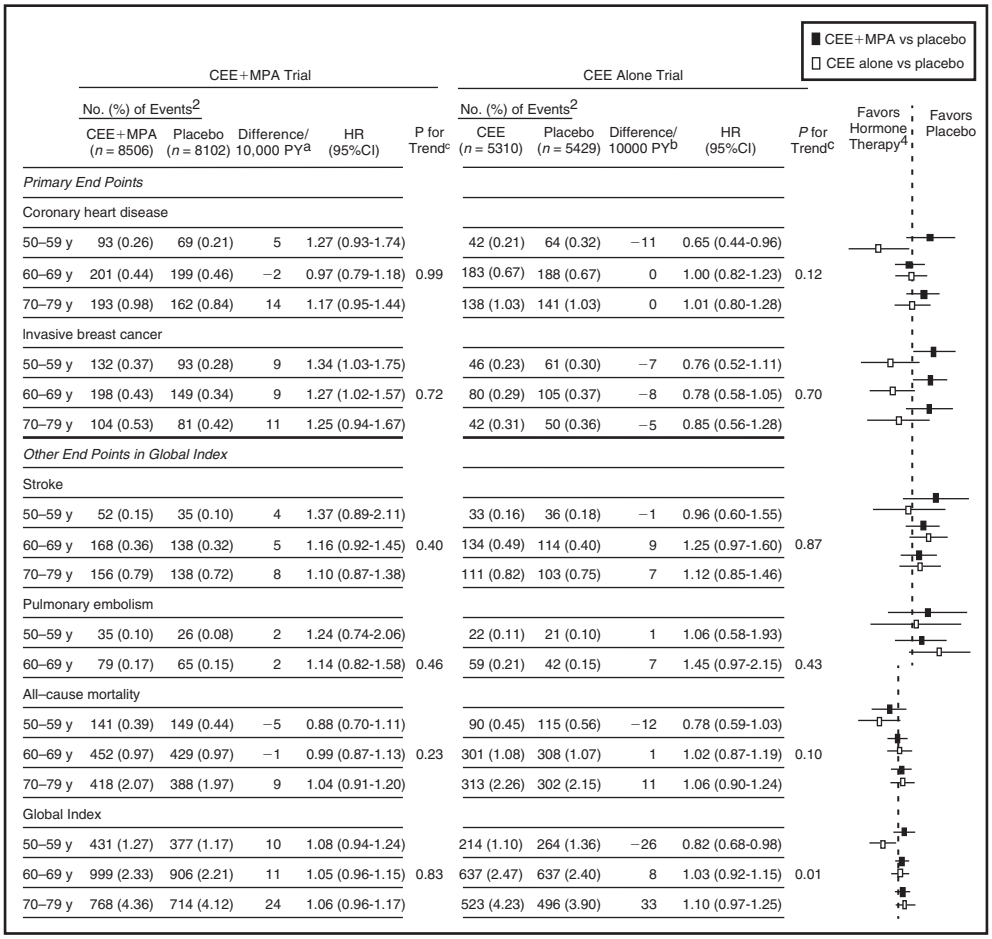


FIGURE 14.29 Importance of timing of intervention on the effect of estrogens on atherogenesis in nonhuman primates. *CEE*, Conjugated equine estrogens. *(Modified from Clarkson TB, Anthony MS, Jerome CP: Lack of effect of raloxifene on coronary artery atherosclerosis of postmenopausal monkeys.* J Clin Endocrinol Metab *83:721–726, 1998; Adams MR, Register TC, Golden DL, et al: Medroxyprogesterone acetate antagonizes inhibitory effects of conjugated equine estrogens on coronary artery atherosclerosis.* Arterioscler Thromb Vasc Biol *17:217–221, 1997; Clarkson TB, Anthony MS, Morgan TM: Inhibition of postmenopausal atherosclerosis progression: a comparison of the effects of conjugated equine estrogens and soy phytoestrogens.* J Clin Endocrinol Metab *86:41–47, 2001; and Williams JK, Anthony MS, Honore EK, et al: Regression of atherosclerosis in female monkeys.* Arterioscler Thromb Vasc Biol *15:827–836, 1995.)*



Years postmenopause	<5	5 to <10	10 to <15	≥15
% of WHI enrollees	17%	19%	21%	43%

FIGURE 14.30 Relationship between number of years since menopause to progression of atherosclerosis in Women's Health Initiative *(WHI)* enrollees. *MMP-9*, Matrix metalloproteinase-9. *(Modified from Clarkson TB: The new conundrum: do estrogens have any cardiovascular benefits?* Int J Fertil *47:61–68, 2002.)*



	CEE+MPA Trial					CEE Alone Trial				
	No. (%) of Events[2]					No. (%) of Events[2]				
	CEE+MPA (n = 8506)	Placebo (n = 8102)	Difference/ 10,000 PY[a]	HR (95%CI)	P for Trend[c]	CEE (n = 5310)	Placebo (n = 5429)	Difference/ 10000 PY[b]	HR (95%CI)	P for Trend[c]
Primary End Points										
Coronary heart disease										
50–59 y	93 (0.26)	69 (0.21)	5	1.27 (0.93-1.74)		42 (0.21)	64 (0.32)	−11	0.65 (0.44-0.96)	
60–69 y	201 (0.44)	199 (0.46)	−2	0.97 (0.79-1.18)	0.99	183 (0.67)	188 (0.67)	0	1.00 (0.82-1.23)	0.12
70–79 y	193 (0.98)	162 (0.84)	14	1.17 (0.95-1.44)		138 (1.03)	141 (1.03)	0	1.01 (0.80-1.28)	
Invasive breast cancer										
50–59 y	132 (0.37)	93 (0.28)	9	1.34 (1.03-1.75)		46 (0.23)	61 (0.30)	−7	0.76 (0.52-1.11)	
60–69 y	198 (0.43)	149 (0.34)	9	1.27 (1.02-1.57)	0.72	80 (0.29)	105 (0.37)	−8	0.78 (0.58-1.05)	0.70
70–79 y	104 (0.53)	81 (0.42)	11	1.25 (0.94-1.67)		42 (0.31)	50 (0.36)	−5	0.85 (0.56-1.28)	
Other End Points in Global Index										
Stroke										
50–59 y	52 (0.15)	35 (0.10)	4	1.37 (0.89-2.11)		33 (0.16)	36 (0.18)	−1	0.96 (0.60-1.55)	
60–69 y	168 (0.36)	138 (0.32)	5	1.16 (0.92-1.45)	0.40	134 (0.49)	114 (0.40)	9	1.25 (0.97-1.60)	0.87
70–79 y	156 (0.79)	138 (0.72)	8	1.10 (0.87-1.38)		111 (0.82)	103 (0.75)	7	1.12 (0.85-1.46)	
Pulmonary embolism										
50–59 y	35 (0.10)	26 (0.08)	2	1.24 (0.74-2.06)		22 (0.11)	21 (0.10)	1	1.06 (0.58-1.93)	
60–69 y	79 (0.17)	65 (0.15)	2	1.14 (0.82-1.58)	0.46	59 (0.21)	42 (0.15)	7	1.45 (0.97-2.15)	0.43
All–cause mortality										
50–59 y	141 (0.39)	149 (0.44)	−5	0.88 (0.70-1.11)		90 (0.45)	115 (0.56)	−12	0.78 (0.59-1.03)	
60–69 y	452 (0.97)	429 (0.97)	−1	0.99 (0.87-1.13)	0.23	301 (1.08)	308 (1.07)	1	1.02 (0.87-1.19)	0.10
70–79 y	418 (2.07)	388 (1.97)	9	1.04 (0.91-1.20)		313 (2.26)	302 (2.15)	11	1.06 (0.90-1.24)	
Global Index										
50–59 y	431 (1.27)	377 (1.17)	10	1.08 (0.94-1.24)		214 (1.10)	264 (1.36)	−26	0.82 (0.68-0.98)	
60–69 y	999 (2.33)	906 (2.21)	11	1.05 (0.96-1.15)	0.83	637 (2.47)	637 (2.40)	8	1.03 (0.92-1.15)	0.01
70–79 y	768 (4.36)	714 (4.12)	24	1.06 (0.96-1.17)		523 (4.23)	496 (3.90)	33	1.10 (0.97-1.25)	

FIGURE 14.31 Cumulative outcomes with 13 years of follow-up for women receiving conjugated equine estrogens *(CEE)* with medroxyprogesterone acetate *(MPA)* or CEE alone in various age groups in the Women's Health Initiative *(WHI)*. Results are more favorable in younger women and in those receiving CEE alone. *(Data from Manson JE: Menopausal hormone therapy and health outcomes during the intervention and extended poststopping phases of the Women's Health Initiative randomized trials.* JAMA *310:1353–1368, 2013.)*

59-year-old group had a significant reduction in coronary heart disease events and total mortality.[311] The latest long-term follow-up of both the estrogen alone and the estrogen/progestogen arms of the hormone trials, was published in 2013 (Fig. 14.31).[312] Clearly younger women, aged 50 to 59 or less than 10 years from menopause, had a much better risk-benefit profile compared to older women. The effects of estrogen alone may be summarized in Table 14.5. However, it should be noted that even with CEE/MPA, with 13 years of follow-up data, the coronary events witnessed were not increased for the entire group or even in any specific age group, when considered separately. This is in vast contrast

Table 14.5 Cumulative Data From the Estrogen Alone Arm of Women's Health Initiative Study After 13 Years in the 50- to 59-Year-Old Group of Women (Relative Risks and Absolute Risks)

Coronary heart disease	0.65 (0.44–0.96)	–11/10,000 woman years
Myocardial infarction	0.60 (0.39–0.91)	–11/10,000 woman years
Breast cancer	0.76 (0.52–1.11)	–7/10,000 woman years
All cancers	0.80 (0.64–0.99)	–18/10,000 woman years
Global index	0.82 (0.82–0.98)	–26/10,000 woman years
Mortality	0.78 (0.59–1.03)	–12/10,000 woman years

Data from Manson JE, Chlebowski RT, Stefanick ML, et al: Menopausal hormone therapy and health outcomes during the intervention and extended poststopping phases of the Women's Health Initiative randomized trials. *JAMA* 310:1353–1368, 2013.

to the original publication in 2002, which suggested a significantly increased coronary risk in all groups.[312]

While it is plausible to conclude that there is some attenuation of the coronary benefit with the continuous addition of MPA, the trials in WHI were different, and studied different populations of women. Also providing some evidence that certain progestogens and regimens may not attenuate the coronary benefit are trials from Denmark and Finland, which show a coronary benefit and decreased mortality with estradiol alone and estradiol combined with norethindrone (NET) acetate.[313-315] The WHI conducted an observational trial in parallel with the RCTs. The results of the observational trials are more in keeping with the older observational data suggesting coronary protection and with no adverse effects on stroke.[316,317] These data and reports from WHI reinforce the notion that early initiation of therapy and length of treatment influences these findings.[307,318]

A Bayesian meta-analysis looking at randomized trials and observational data in younger women confirmed an approximate 30% reduction in mortality (Fig. 14.32),[319] which is

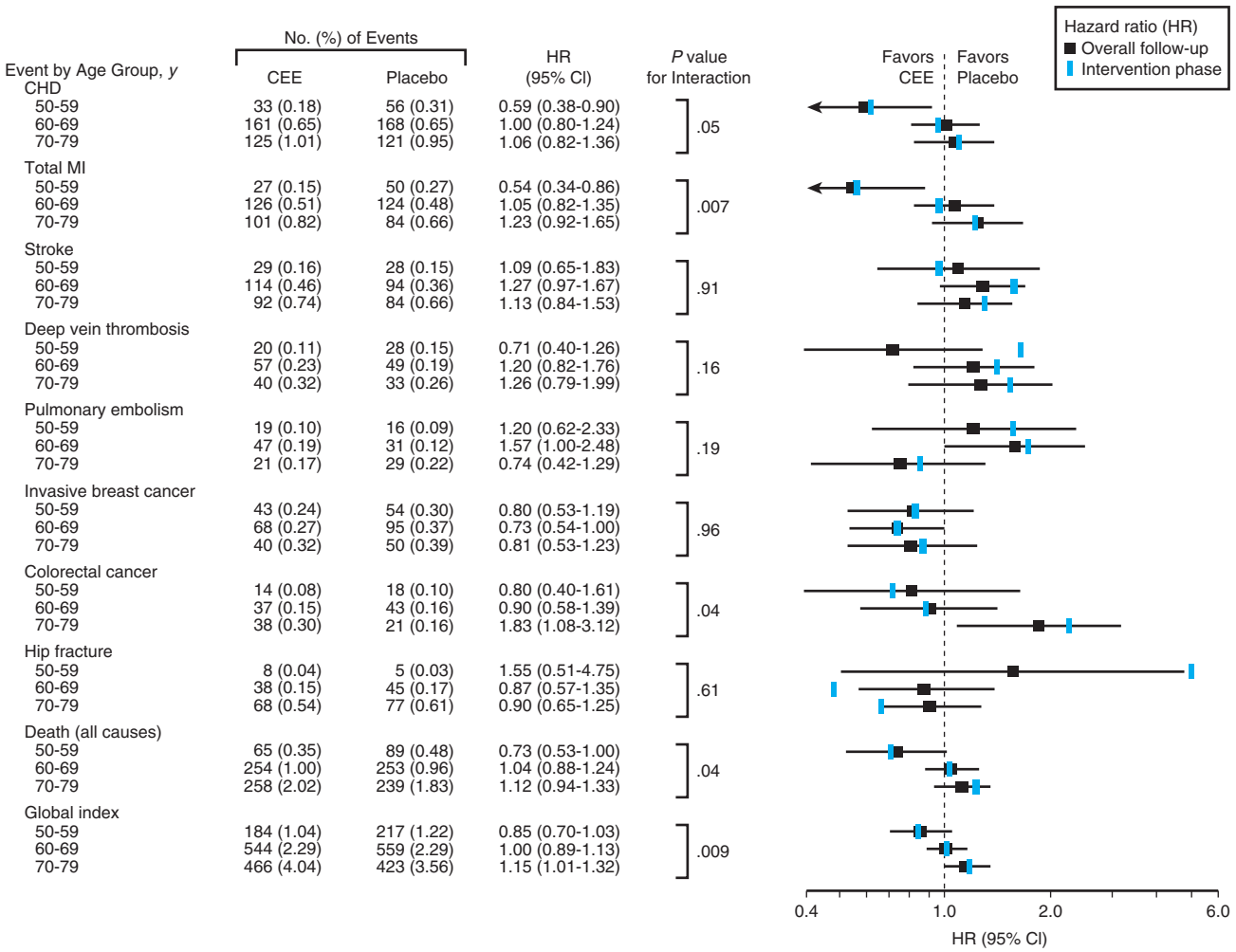


FIGURE 14.32 Ten-year follow-up of the estrogen alone arm in Women's Health Initiative showing in the 50- to 59-year-old age group a significant reduction in coronary heart disease *(CHD)* events and total mortality. *CEE*, Conjugated equine estrogens; *HR*, high resolution; *MI*, myocardial infarction.

completely consistent with older data. A Cochrane meta-analysis also concluded that in younger women there was coronary benefit and a reduction in total mortality.[320] Table 14.6 compiles these findings on the reduction in all-cause and coronary mortality for younger and older women.

Although the "timing" hypothesis suggests that younger women receiving hormone therapy at the onset of menopause may have a reduction in CVD while older women may be subjected to harm, this has not been subjected to the rigors of RCTs until recently. Because cardiovascular events are rare in younger women, a very long trial would be required to demonstrate an effect. Therefore, in trials of approximately 4 to 5 years duration, only intermediate cardiovascular endpoints can be studied, such as carotid intima-media thickness and coronary calcium, which may or may not relate to hard endpoints, such as myocardial infarction and cardiovascular mortality. The Kronos Early Estrogen Prevention Study (KEEPS) and the Early versus Late Intervention Trial with Estradiol (ELITE) are two recently conducted trials on this point. However, KEEPS did not truly test the "timing" hypothesis as only younger postmenopausal women participated, and there were no women treated who were distant from the onset of menopause.[321] In the 4-year KEEPS trial, which compared CEE 0.45 mg to transdermal E_2, 50 μg and placebo, statistical benefit between the three arms in Carotid-Intima-Media Thickness (CIMT) was not seen, although there were other beneficial effects of estrogen.[321] There was a trend for a reduction in coronary calcium with estrogen (Fig. 14.33). It may be hypothesized that these younger healthy women at the onset of menopause did not have sufficient atherosclerosis progression over 4 years to differentiate the placebo effect from estrogen. ELITE was a true test of the "timing" hypothesis and was published in 2016.[322] This was a 5-year prospective study of women receiving estradiol 1 mg who were either within 6 years of menopause onset or treated more than 10 years after menopause. Carotid IMT was the primary endpoint, and showed a benefit in terms of progression of IMT thickness, compared to placebo in the younger women, but not in the women more than 10 years from menopause (Fig. 14.34).[322] Coronary calcium changes, however, were similar in the two groups suggesting a longer duration of observation may be required. In keeping with the timing hypothesis, Danish women treated for 10 years from the onset of menopause had a significant reduction in mortality and a composite coronary outcomes index in a 16-year follow-up study (Fig. 14.35).[313]

Putting all these studies and meta-analyses together, it seems quite compelling that younger women benefit in terms of coronary disease prevention and reductions in total mortality. The data are similar to older observational data described above. This has led to the suggestion that we may consider using estrogen-based therapy as a general preventative therapy for early postmenopausal women.[323] Indeed the suggestion is that we may have come full circle in our thinking about the use of hormones after menopause(Fig. 14.36).[323] It is important to note that this supposition is bolstered by the lack of efficacy of other prevention strategies used in men, such as aspirin and statins, which in women have not been shown to reduced mortality.[324-331] Only lifestyle improvements have been shown to have any significant effect in women and the magnitude of this effect, 10% to 16% reduction in risk,[332] is half of the findings in benefit shown for estrogen, as discussed above.

Table 14.6 Changes in Mortality: Analysis of Prospective Trials of Hormone Therapy Meta-Analysis by the Cochrane Collaboration

Cardiovascular mortality in all women* versus placebo: 0.96 (0.78–1.18)
CHD mortality in women >10 years since menopause: 1.07 (0.96–1.20)
All-cause mortality in women† <10 years since menopause: 0.70 (0.52–0.95)
CHD mortality in women <10 years since menopause: 0.52 (0.29–0.96)

*All primary and secondary prevention trials.
†Versus placebo.
CHD, Coronary heart disease.
Data from Boardman HM, Hartley L, Eisinga A, et al: Hormone therapy for preventing cardiovascular disease in postmenopausal women. *Cochrane Databse Syst Rev* (3):CD002229, 2015.

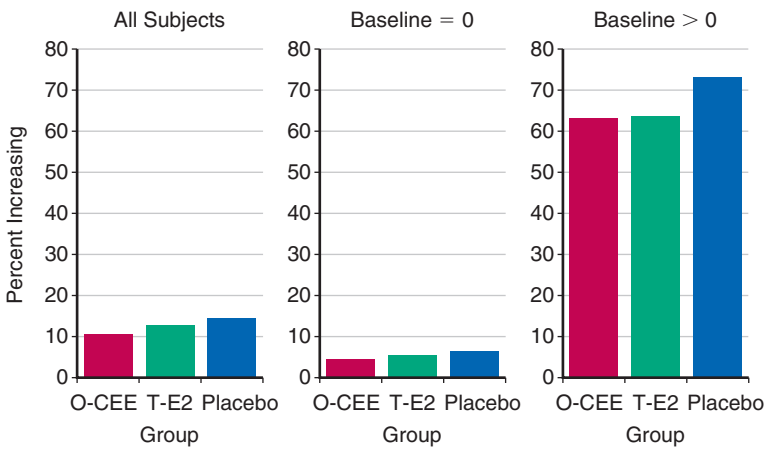
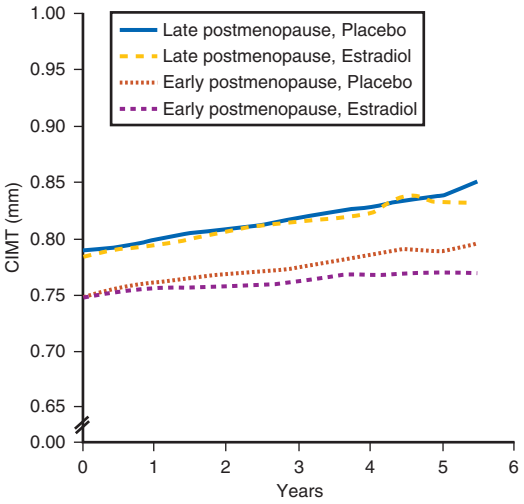
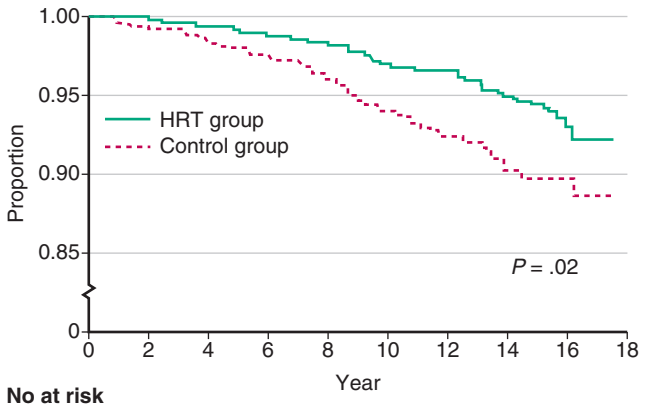


FIGURE 14.33 Data from the Kronos Early Estrogen Prevention Study *(KEEPS)* suggesting that there was less coronary calcium in women on hormone therapy (not statistically significant) and coronary calcium seen was very low. *CEE*, Conjugated equine estrogens. *(From Harman M: Primary findings of the KEEPS. 23rd annual meeting of the North American Menopause Society, Oct. 3, 2011 [submitted]).*



No. of Participants							
With CIMT data	643	533	522	515	424	295	56
Who completed or discontinued study	0	106	119	128	215	345	582
Without CIMT data	0	4	2	0	4	3	5

FIGURE 14. 34 Carotid intima media thickness *(CIMT)* progression according to study group and postmenopause stratum. Early postmenopause receiving oral estradiol 1 mg compared to placebo had a significant reduction in the increase in CIMT over 6 years; while in late menopause there was no effect. *(Data from Hodis HN, Mack WJ, Henderson VW, et al: Vascular effects of early versus late postmenopausal treatment with estradiol.* N Eng J Med *374:1221–1231, 2016.)*



No at risk									
HRT	502	502	498	496	483	487	484	477	155
Control	504	502	497	492	484	475	466	455	90

FIGURE 14.35 Sixteen-year follow-up of women randomized to hormone therapy showing a reduction in death, heart failure, and myocardial infarction. *HRT,* hormone replacement therapy. *(Modified from Schierbeck L: Effect of hormone replacement on cardiovascular events in recently postmenopausal women: randomized trial.* BMJ *345:e6409, 2012.)*

Stroke

Stroke is the third leading cause of death in women, and the interaction between hormones and stroke risk in women has been studied for some time.

In the original papers of the WHI study, overall stroke was significantly increased in women receiving CEE-MPA or CEE. However, the findings of increased stroke risk

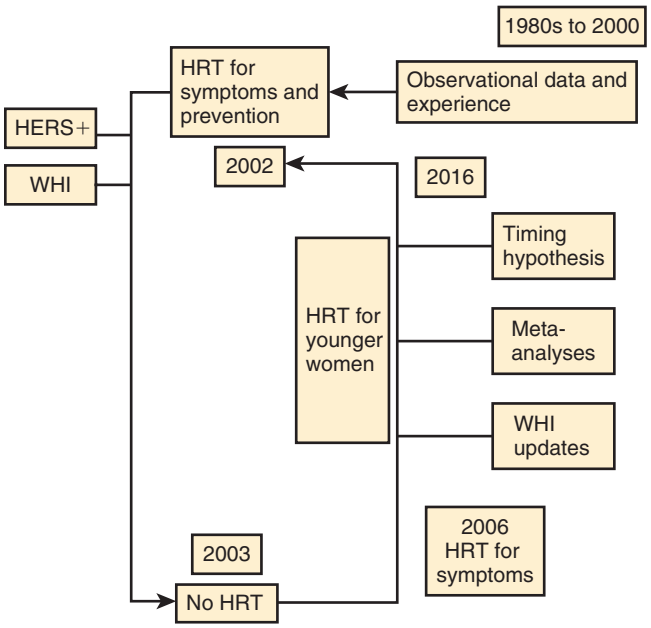


FIGURE 14.36 Diagrammatic depiction asking the question as to whether we have come full circle in the prescribing of hormone therapy. Hormone therapy use prior to 2002, based on strong epidemiological data and meta-analyses, was for symptom control and prevention. Hormone therapy use essentially stopped soon after various randomized trials were reported at that time. Some limited use for symptoms began again around 2006. The suggestion in this figure is that the use of hormone therapy may be or should be coming around full circle based on new data as depicted by the arrows. *HERS,* Heart and estrogen/progestin replacement study; *HRT,* hormone replacement therapy; *WHI,* Women's Health Initiative study. *(Lobo RA, Pickar JH, Stevenson JC, Mack WJ, Hodis HN: Back to the future: hormone replacement therapy as part of a prevention strategy for women at the onset of menopause.* Atherosclerosis *254:282–290, 2016.)*

in younger women are more of a borderline nature and constitute very few events. Age, obviously, and particularly hypertension, influences the risk of stroke in postmenopausal women; and this is significantly influenced by the dose and route of administration of estrogen.[333] It is ischemic stroke, and not hemorrhagic stroke, which is influenced by the use of HT.

When large numbers of women are studied, both meta-analyses[334] and observational studies[335] have shown a small but significant increased risk of ischemic stroke with standard doses of hormone therapy. This is in the range of a 30% increase (RR, ~1 to 3), because in younger postmenopausal women the risk of stroke is 6 to 8/10,000 women-years, the absolute risk is no more than 1 to 2 cases/10,000 women/year, a truly rare event. Our recent analysis suggests that those rare events in younger, postmenopausal women[336] are related to thrombosis, such as occurs rarely in women on oral contraceptives[337] and is not due to atherosclerosis, which occurs in older women. In concert with this is the observation that less prothrombotic forms of hormone therapy (transdermal)[334] and lower doses[335] have not been found to increase the risk of ischemic stroke.

It has been acknowledged for some time that oral estrogen increases the risk of venous thrombosis and thromboembolism (VTE) in postmenopausal women. This risk tends to occur

early (within the first 1 to 2 years of therapy) and is markedly increased if there is an underlying thrombophilia (about a 15-fold increased risk).[338] However, in the absence of a family history or a prior thrombotic event, it is not standard practice to screen for factor V Leiden mutation or other abnormalities. Although the RR of thrombosis with oral estrogen is in the range of 2 to 3, the prevalence of this is low, particularly in a younger population. For example, the risk of pulmonary embolism may increase from 20 to 40 cases per 100,000 women years with HT, but this is less than the general risk of VTE observed in pregnancy (60/100,000 women/year). The overall RR of VTE reported in the WHI study was in the range of 2 to 3 as noted above, but did not achieve statistical significance in the hysterectomized group using estrogen alone. Although this was a more obese group who could have been considered at higher risk, two other possibilities exist. The first is that approximately 50% of women had used estrogen in the past, and it is possible that this population of exposed women had received therapy beyond the first year or two when VTE usually occurs in susceptible women, and were not susceptible. Second, there is a possibility that the progestogen addition (MPA) with CEE increases the risk further. In a larger French observational study, the type of progestogen was considered to confer an additional risk of VTE, with natural progesterone not enhancing the risk.[339]

Further data from this cohort of women in the ESTHER study showed no increase in VTE risk with transdermal estrogen.[340,341] Several other recent studies have suggested the relative safety of transdermal over oral estrogen, even in high-risk patients, unless higher doses (≥50 μg/day) are used (Fig. 14.37).[340-343]

As noted earlier, blood pressure increases after menopause, which increases CV risk. Apart from an idiosyncratic hypertensive response to oral estrogen in some women, the overall effect of estrogen on blood pressure is neutral, including women who are already hypertensive. There are studies showing some small increase, others showing no changes and others showing a decrease, even in hypertensive women.[344] Uncontrolled hypertension in postmenopausal women constitutes a major concern for stroke, and this may be aggravated in some women with the use of HT.

Breast Cancer

- *Breast cancer risk increases with aging after menopause, and most cancers are estrogen responsive tumors.*
- *Estrogen-alone therapy does not increase the risk through a promotional effect, except with prolonged use at high doses.*
- *There is evidence that breast cancer mortality is reduced in users of estrogen.*

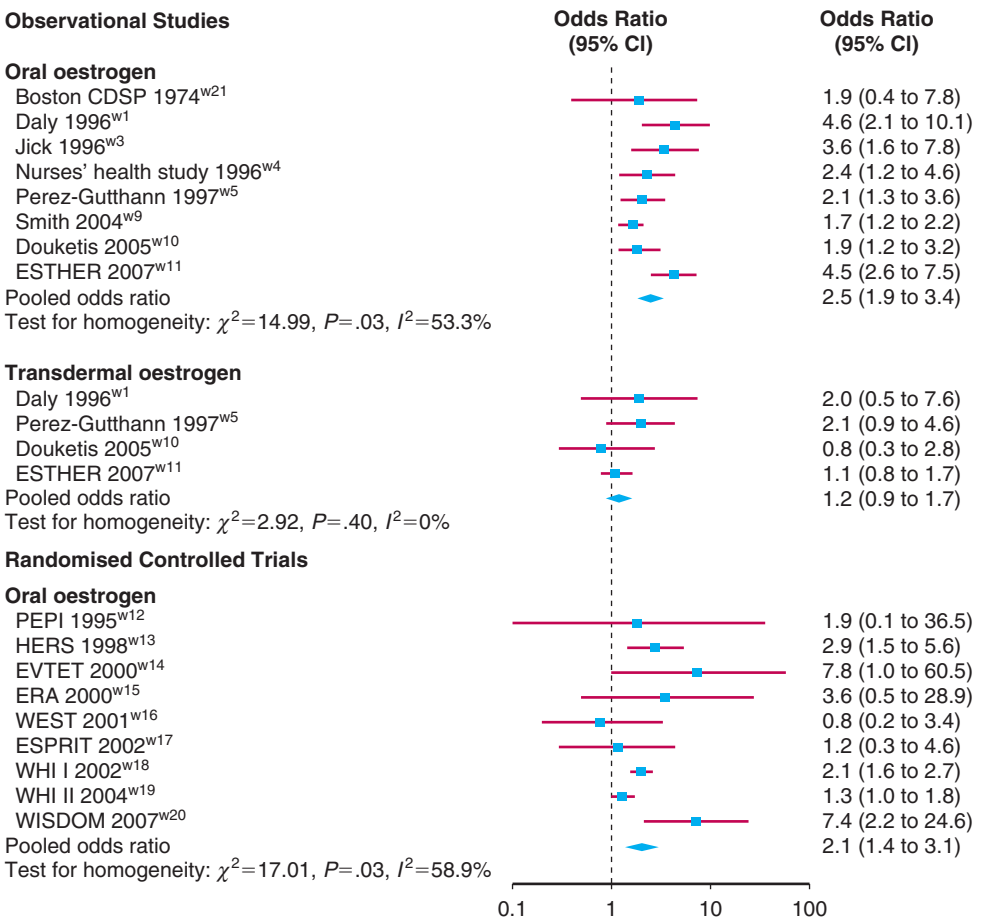


FIGURE 14.37 Meta-analysis of various studies showing no increased risk of thrombosis with transdermal therapy. *(Modified from Canonico M, Plu-Bureau G, Lowe GD, Scarabin PY: Hormone replacement therapy and risk of venous thromboembolism in postmenopausal women: systemic review and meta-analysis.* BMJ *336:1227–1231, 2008.)*

Table 14.7 Women Who Will Develop Breast Cancer: Risk According to Age

Decade of Life	Incidence
Third	1 of 250
Fourth	1 of 77
Fifth	1 of 42
Sixth	1 of 36
Seventh	1 of 34
Eighth	1 of 45

Modified from Lobo RA: Treatment of the postmenopausal woman: where we are today. In Lobo RA, editor. *Treatment of the postmenopausal woman: basic and clinical aspects*, ed 2, Philadelphia, 1999, Lippincott Williams & Wilkins, pp 655–659.

- *Estrogen in combination with synthetic progestogen does cause a promotional increase in risk, which is related to dose and duration.*
- *Many endogenous risk factors pose a greater risk for breast cancer than HT.*

Because of the enormous importance of this topic, breast cancer and its relationship to HT use will be reviewed separately and in the context of the risk-benefit assessment discussed later (see also Chapter 29).

Listed in Table 14.7 are the approximate rates of breast cancer by decade of life; clearly age is a major determinant of risk. More baseline risk information may be found in Chapters 11 and 29. However, postmenopausal breast cancer, fortunately, is not as lethal as lung cancer or CVD. In Fig. 14.38, the age-specific mortality rate is depicted, and shows that breast cancer mortality decreases after the initial age of menopause, while deaths from lung cancer are higher after menopause, and the rates of CVD mortality increase dramatically from this time onward. The effect of HT on breast cancer risk has been studied for at least 30 years, and only recently has there been a little more clarity on the issue.[345] Most of the data on breast cancer risk have been derived from case control and cohort observational studies. There have been several larger RCTs, such as data from the WHI study (at least for the use of two specific regimens)[346,347] and these will be presented separately.

In summary, RCTs show lower point estimates than observational data and little increased risk of estrogen alone.[345-347] With estrogen alone, the WHI and observational data showed reduced risk[347,348] and others, including the Million Women's Study that showed some increased risk.[349] This latter study, although large, has been widely criticized on methodological grounds. An update of the Nurses' Health Study showed no increasing risk for up to 20 years in hysterectomied women using CEE 0.625 mg.[348] As shown in Table 14.8, the overall risk going out 15 to 20 years is principally in lean women. Since obesity itself is associated with an increased risk of breast cancer, an additional risk with HT has not been demonstrated.

It has been known for some time, based on autopsy studies, that there is an "occult" or undiagnosed breast cancer rate of approximately 15.6%. These tumors have a doubling of time of 70 to 350 days, leading to possible detection by mammography when they reach 0.88 to 1.66 cm in diameter. It has been estimated, based on iterative analysis and modeling, that of the tumors that emerged in the E + P arm of the WHI study, 93.3% were occult lesions that grew and 6.7% arose de novo. Therefore, the promotional effect of E + P shortened the doubling time from an average of 200 days to 150 days, allowing for early detection by mammography towards the end of the trial.[350] With estrogen-alone therapy in the WHI study, the reverse was suggested with apoptosis occurring in some of the tumors, arresting the doubling time with estrogen causing a lower number of tumors to be detected compared to placebo.[350]

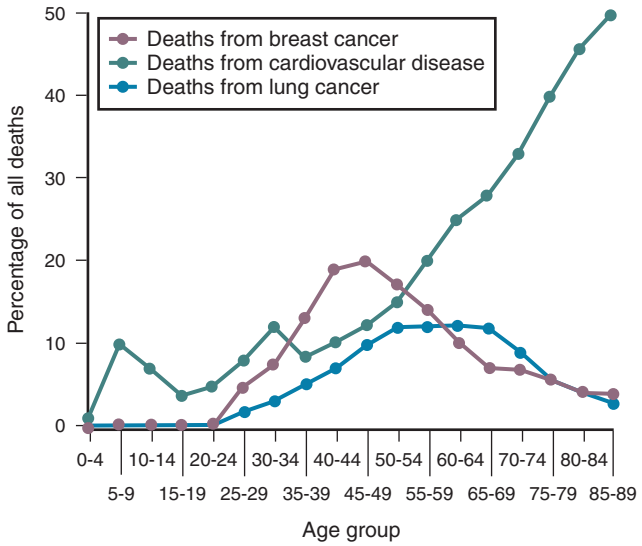


FIGURE 14.38 Risks of breast cancer and lung cancer versus cardiovascular disease in various age categories. *(Modified from Phillips KA, Glendon G, Knight JA: Putting the risk of breast cancer in perspective.* N Engl J Med *340:141–144, 1999.)*

In the CEE-alone trial of the WHI, there was a borderline significant reduction in breast cancer risk, which was statistically significant for adherent women and for ductal cancers.[347] These data are reassuring for a negligible effect of estrogen alone on breast cancer risk, but should not be interpreted as estrogen being protective for breast cancer.

There seems to be consistent findings of increased risk with estrogen and progestogen regimens after 5 years of use. This risk estimate ranges from 1.2 to 1.7 and is related to dose, possibly the type of progestogen,[351] and duration of use. However, there are no clear data showing a difference between continuous combined and sequential regimens of progestogen therapy. In a less well-known publication from the WHI study, when adjustments were made for breast cancer risk factors, the overall risk for the 5 to 6 years of CEE and MPA use was not significant at 1.20 (0.94 to 1.53).[346] Of great importance was the finding that in women who had never received HT (70% of the WHI population), the RR was 1.02 (0.77 to 1.36)[346]; that is, the trend for an increased risk was accounted for by prior use and a longer cumulative exposure to estrogen and progestogen.[346] There also has been a suggestion that estrogen and progestogen therapy increases the relative frequency of lobular cancers, which are normally rarer, but generally better differentiated and less aggressive. However, this has not been proven.

In a follow-up of women in the WHI estrogen-only arm, over 10 years, the significant reduction in breast cancer incidence was confirmed.[352] Moreover, in terms of breast cancer mortality, this was significantly lower among the users

Table 14.8 Risk of Invasive Breast Cancer by Duration of Estrogen Therapy Use Among All Postmenopausal Women Who Had Undergone Hysterectomy and Those With ER+/PR+ Cancers Only*

	All Postmenopausal Women Who Had Undergone Hysterectomy				ER+/PR+ Cancers Only			
	All		Screened Cohort†		All		Screened Cohort†	
ET Use and Duration (yr)	*Cases*	*Risk*	*Cases*	*Risk*	*Cases*	*Risk*	*Cases*	*Risk*
Never current	226	1.00	104	—	87	—	48	—
<5	99	0.96 (0.75–1.22)	59	1.06 (0.76–1.47)	38	1.00 (0.67–1.49)	26	1.04 (0.64–1.70)
5–9.9	145	0.90 (0.73–1.12)	95	0.91 (0.68–1.21)	70	1.19 (0.86–1.66)	50	1.08 (0.72–1.62)
10–14.9	190	1.06 (0.87–1.30)	141	1.11 (0.85–1.44)	85	1.27 (0.93–1.73)	77	1.29 (0.89–1.86)
15–19.9	129	1.18 (0.95–1.48)	95	1.19 (0.89–1.58)	61	1.48 (1.05–2.07)	58	1.50 (1.02–2.21)
≥20	145	1.42 (1.13–1.77)	127	1.58 (1.20–2.07)	69	1.73 (1.24–2.43)	74	1.83 (1.25–2.68)
P for trend for current use	—	<.001	—	<.001	—	<.001	—	<.001

*All cases are reported as number of cases; risks are reported as multivariate relative risk (95% CI), controlled for age (continuous), age at menopause (continuous), age at menarche (continuous), BMI (quintiles), history of benign breast disease (yes or no), family history of breast cancer in first-degree relative (yes or no), average daily alcohol consumption (0, 0.5–5, 5–10, 10–20, or ≥20 g/day), parity/age at first birth (nulliparous; 1–2 children and age at first birth ≤22 years; ≥3 children and age at first birth 23–25 years; ≥3 children and age at first birth >25 years).

†Screened cohort defined as those women starting in 1988 who reported either a screening mammogram or clinical breast examination in the previous 2 years. All cases before 1988 are excluded.

BMI, Body mass index; *CI*, confidence interval; *ER+/PR+*, positive for both estrogen and progesterone receptors; *ET*, estrogen therapy, unopposed. From Chen WY, Manson JE, Hankinson SE, et al: Unopposed estrogen therapy and the risk of invasive breast cancer. *Arch Intern Med* 166:1027–1032, 2006.

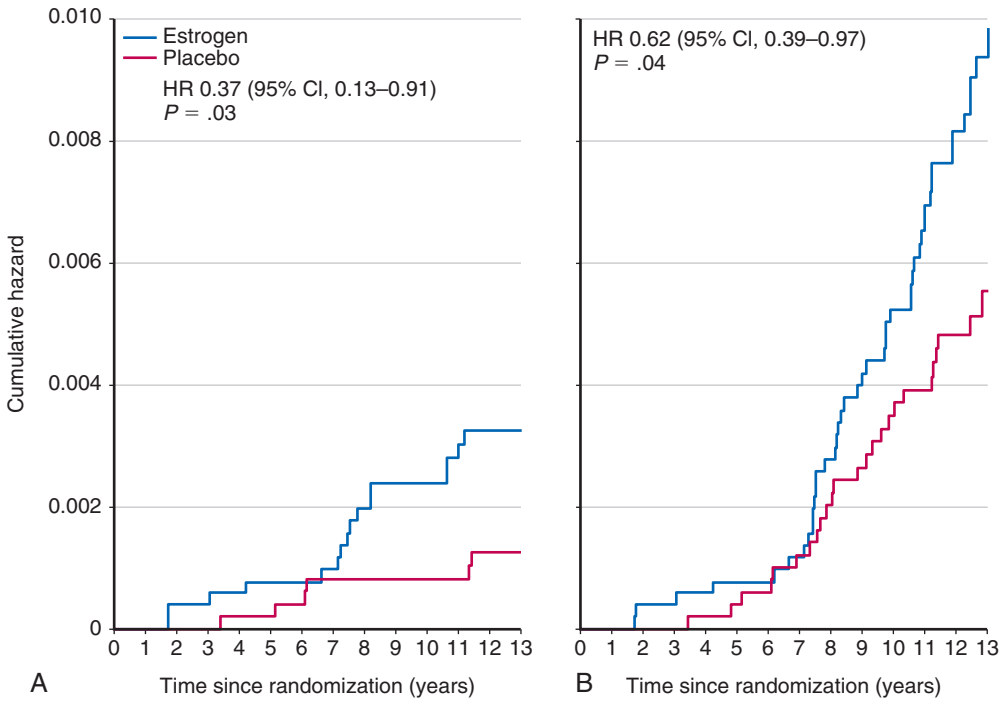
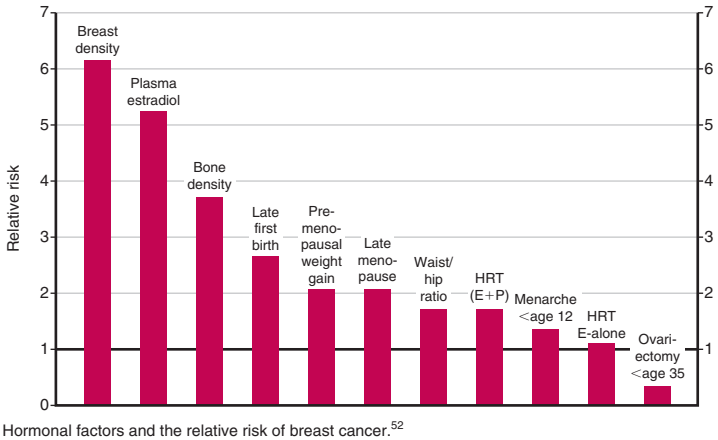


FIGURE 14.39 In women with breast cancer, women taking estradiol had significantly reduced mortality: breast cancer (A) and total (B). *(Modified from Anderson G, Chlebowski RT, Aragaki A, et al: Conjugated equine oestrogen and breast cancer incidence and mortality in postmenopausal women with hysterectomy: extended follow-up of the Women's Health Initiative randomized placebo-controlled trial.* Lancet Oncol *13:476–486, 2012.)*

of estrogen as has been suggested before. This study also confirmed a statistically significant reduction in total mortality in estrogen users (Fig. 14.39).[352] More recent observational data out of Finland have also suggested lower mortality for breast cancer when women have received HT.[353] If we assume as correct what was originally reported by the WHI study for combination standard dose estrogen and progestogen therapy over 5 years, that there is an increase in the risk of breast cancer of 24% (RR, 1.24), what does this translate into in absolute terms? If the background risk between the ages of 50 and 60 is 2.8% (2.8 women out of 100 will be expected to get breast cancer over this 10-year time span), then the rate would increase to 3.4% (less than 1% increase). Clearly, there is probably no increased risk in women who have never had therapy for up to 5 years and, particularly, if lower than the standard dose is used. Also, observational



Hormonal factors and the relative risk of breast cancer.[52]

FIGURE 14.40 Risks of breast cancer with various exposures and endogenous traits, particularly increased breast density. *E,* Estrogen; *HRT,* hormone replacement therapy; *P,* progestogen. *(Modified from Gompel A, Santen RJ: Hormone therapy and breast cancer risk 10 years after the WHI. Climacteric 15:241–249, 2012.)*

data from France have suggested that progesterone and dydrogesterone are not associated with an increased risk, as opposed to synthetic progestogens.[351] However, these data remain to be confirmed.

This RR of 1.2 to 1.6 for 5 years of estrogen and progestogen use as discussed above should also be compared to other experiences, such as having a waist-to-hip ratio greater than 0.8:3.3 (1.1 to 10.4) or being an airline flight attendant 1.87 (1.15 to 2.23). There are many more everyday experiences such as these for breast cancer risk.[354]

Compared to the small increase in breast cancer observed with standard dose E + P in the WHI study, other exposures and endogenous risks are much higher (Fig. 14.40).[355] The highest RR is seen in women with increased breast density, which also makes mammographic detection of small tumors challenging. While E + P treatment increases breast density, it is unclear if this imparts an additional risk for cancer; clearly these induced changes in breast density are reversible.

A report showing a downward trend in breast cancer rates in the United States suggested that this might be related to a reduction in hormone use after the WHI study and other reports.[356] However, there are several other possible explanations as well, including a reduction in mammography use and other variables reviewed elsewhere. Of interest is that the reduction in breast cancer in the United States also occurred in older women in their seventh decade as well (not users of hormones) and has not been reported in many other countries[355] where HT use has dropped as well. A 3-year follow-up of the WHI study showed that the breast cancer risk also persisted (not significantly) over this follow-up period.[357]

Decision to Use Estrogen

- *This is an individual decision, which needs to take into account many factors that are discussed.*
- *The risk-benefit equation is highly favorable in younger women <60 years of age or within 10 years of menopause.*

Most chronic diseases in women occur 10 or more years after the onset of menopause. These include CVD, osteoporosis, cognitive decline, metabolic disease, and cancer. Therefore, an important perspective is to institute preventative therapies at the onset of menopause to prevent or delay these events from occurring. Menopause heralds an opportunity to assess all women for risks of chronic disease and to institute preventative therapies. This perspective and strategy have been outlined in a review commissioned by the International Menopause Society for World Menopause Day in 2014.[358] As noted above, because compelling evidence suggests that estrogen decreases coronary disease and all-cause mortality in young women, initiating therapy at the onset of menopause,[323] a consideration may be given for the role of estrogen in prevention even in the absence of symptoms,[323,358] although this is not universally accepted.

Hormonal therapy should be considered as a very individual decision. The woman must take into account symptoms, risk factors, and individual preferences and needs. The predominant indication for estrogen is for symptoms (vasomotor and other symptoms and vulvovaginal complaints).

Alternatives should also be considered. If hormonal therapy is chosen, there should be flexibility in prescribing because there is no ideal regimen for every woman, and each woman has individual risks and needs.

Because hormone therapy is clearly the most efficacious treatment for symptoms, it should be considered a first-line therapy. Since the results of the WHI study, which were misinterpreted and generalized to all women, caused most women and many providers to move away from hormone therapy, it was deemed important for several prominent medical societies to come together and make a definitive statement 10 years after the WHI study was first published. This statement of agreement amongst "experts" caring for women clearly states that estrogen is appropriate for younger, healthy women at the onset of menopause[359]; in most cases, the benefits far outweigh the risks. This assessment will be explored further below, including a discussion of the possible expansion of the role of hormones for prevention of disease and to decrease all-cause mortality for some women.

Risk-Benefit Assessment

Recent guidelines have been formulated regarding HT and are updated periodically. These guidelines stress the relative

safety in symptomatic women, and that lower doses should be used with individualization regarding the length of treatment, with no preconceived time line.[360-362] Whether osteoporosis prevention alone is a sufficient indication for HT is controversial, but has been recommended in women at high risk for osteoporotic fracture.[363] Also, the use of estrogen as a prevention strategy in young healthy postmenopausal women, even if they do not have major symptoms, is also emerging as a possibility,[323] although this has not been universally accepted. Two of the guidelines state that HT may be considered for more than hot flushes per se[361,362]; there are more symptoms of menopause than just hot flushes.

The Endocrine Society statement[361] and an algorithm from North American Menopause Society (NAMS)[364] for treatment of moderate-to-severe hot flushes suggest screening women at the onset of menopause for CVD and the risk of breast cancer. The use of a risk calculator by the American College of Cardiology and the American Heart Association has been advocated to screen such women, with women at moderate risk (5% to 10% 10-year risk of cardiovascular events) receiving only transdermal estrogen, and women with greater risk (>10% 10-year risk) avoiding therapy altogether. The use of transdermal therapy in higher risk women, particularly those who are obese, has also been suggested by the National Institute for Care Excellence.[362]

Using a breast cancer risk assessment tool has also been suggested by the Endocrine Society and NAMS.[361,364] If the assessment according to the National Cancer Institute shows an intermediate risk (1.67% to 5% 5-year risk), they suggest HT should be used with caution, and if the risk is high (>5% 5-year risk), it is suggested that HT should be avoided.

The risk assessment tool for CVD has been controversial and has not been shown to have true predictive power. While high-risk women should be treated with caution, it is not clear that these risk assessment tools are the definitive answer in making a case-by-case determination. In some young women with risk factors, and who have significant symptomatology, it may be reasonable to treat, using lower doses of nonoral estrogen, particularly if other medications are already in use, such as statins, which are known to allow for coronary plaque stability. Similarly for breast cancer the various breast cancer risk-assessment models have been extrapolated from chemoprevention trials and may not be pertinent for the general population. Also, even in women with a higher risk of breast cancer, there is no evidence that using estrogen further increases their risk over their already increased risk. Here, individualization is important, and a low-dose estrogen-based therapy may be chosen.

In the NAMS algorithm[364] it is suggested that if there are no moderate to severe hot flushes and no vaginal symptoms, there is no indication for HT, and that HT should be "avoided." This statement is at odds with other indications for HT, including other symptoms of menopause, osteoporosis risk, and the emerging acceptance for using estrogen for prevention.[323]

The notion to consider using estrogen as part of a prevention therapy for younger women at the onset of menopause is heightened by the important opportunity to prevent diseases at the onset of menopause,[323,358] and because well-known primary prevention strategies used in men (statins, aspirin) do not decrease mortality in women as discussed above.[324-331] Only lifestyle factors, such as diet and exercise, are beneficial, but these effects are small and less than half the effects of estrogen.[332] Fig. 14.27 diagrammatically depicts the use of HT over time. Prior to various randomized trials in older women, it was thought that HT may have a role in prevention as suggested by observational studies and meta-analyses (see Fig. 14.27); it appears that now we may have come full circle, returning to the notion of possible prevention after the abrupt cessation of use after the WHI study.[323] The choice of estrogen and other therapies is critical and will be discussed in more detail in subsequent text.

What Are the Real Risks of Hormonal Treatment in Young Healthy Women?

If HT is to be considered more broadly for postmenopausal women, it is important to examine the real risks of such exposure. As noted above, the reported risks associated with HT in the WHI trials were not statistically significant, with the exception of venous thrombosis and ischemic stroke in older women. In women <60 years of age and/or <10 years-since-menopause the only statistically significant risk with estrogen and estrogen/progestogen in the WHI study was a rare risk of deep vein thrombosis seen with estrogen/progestogen (Fig. 14.41).[323]

Breast cancer risk with combined HT for the duration of the trial was not significant in women who had never been previously exposed. Even if we assume these risks were statistically significant, the absolute risks, which are in the range of 5 to 8 cases per 10,000 women per year, are considered "rare" according to the WHO. Note that the risks may vary depending on the dose and regimen prescribed, and the venous thrombosis risk would be eliminated with nonoral therapy, as discussed subsequently. It is clear that the risks associated with HT are of the same time and of similar or less magnitude than other medications routinely used for the prevention of CVD and other chronic conditions.

Even though there are risks in everyday life, the true risks of HT need to be compared to such exposures. According to the US National Safety Council, the annual risk of death in a motor vehicle is 1/6500; death from walking across the street 1/48,500; and getting murdered 1/10,000 to 1/16,500.[363] The risk of some dietary supplements also may carry risks; calcium supplementation has been shown to increase the risk of myocardial infarction twofold[365] and calcium channel blockers may also increase the risk of breast cancer twofold.[366] Aggressive control of diabetes mellitus has been shown to statistically significantly increase the risk of all-cause mortality in two National Institutes of Health (NIH)–funded randomized controlled trials.[367]

For breast cancer risk, the regimen of CEE combined with MPA in the WHI study only increased the risk of breast cancer with prolonged exposure estimated with this regimen after 6 to 7 years, and the risk was limited to women who used hormone replacement therapy (HRT) prior to randomization. For estrogen therapy alone, the risk of breast cancer was decreased as was total mortality and breast cancer mortality, as discussed previously.[347,348,352,353] Endogenous risk factors, such as increased breast density, increased waist/hip ratio, and late first birth, are all higher than the putative risk of breast cancer with combined estrogen/progestogen exposure.[355] Although not confirmed by randomized trial data, observational studies suggest that the addition of natural

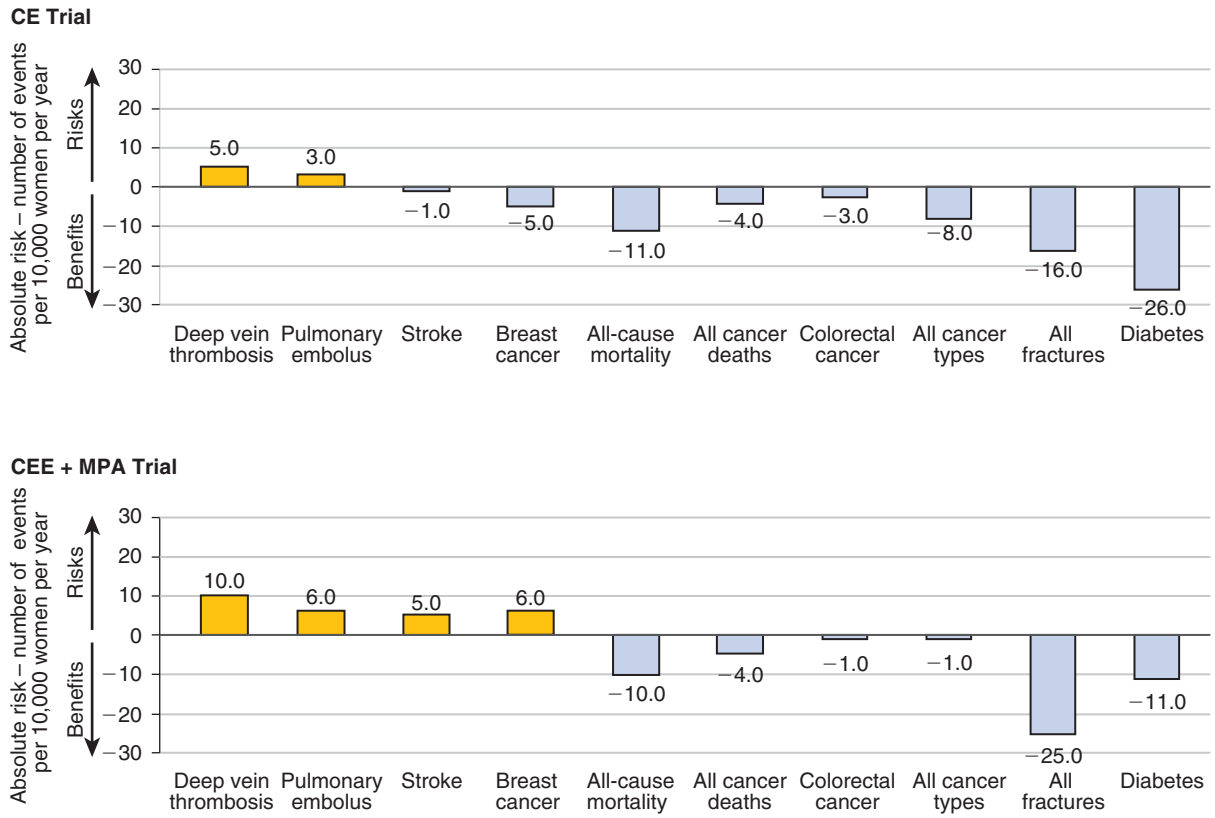


FIGURE 14.41 Absolute benefits and risks from the 13-year follow-up study from the hormone trials of Women's Health Initiative Study, conjugated equine estrogens *(CEE)* alone trial, and the trial with CEE combined with medroxyprogesterone acetate *(MPA)*. Data on the initiation of hormone therapy in women 50 to 59 years of age or less than 10 years from the onset of menopause: number of events per 10,000 women per year. *(Modified from Manson JE, Kaunitz AM:* Menopause management—getting clinical care back on track. N Engl J Med *374:803–806, 2016; appearing in Lobo R: Back to the future: hormone replacement therapy as part of a prevention strategy for women at the onset of menopause.* Atherosclerosis *254:282–290, 2016.)*

progesterone to estrogen therapy does not increase the risk of breast cancer,[351] while other data indicate no difference among varying progestational agents. In a very large nationwide population study (4 million women-years of follow-up), breast cancer mortality was statistically significantly reduced in HRT users versus nonusers, as was all cancers,[353] which has also been reported previously, although not all the literature is in agreement.

Apart from the risks of developing serious disease, there are practical concerns women have to consider regarding the use of HT, particularly if they are considering a therapy when they are asymptomatic. These include breast tenderness, abdominal or pelvic bloating, vaginal bleeding, and some mood disturbances. These are very individual potential complaints, which can usually be dealt with by changes in the HT regimen to be discussed in subsequent text. There is also the idiosyncratic reaction of increased blood pressure, which appears in a small percentage of women and is related only to certain doses of oral estrogen. Women may also report weight gain, which is not supported by randomized trial data, but may be a real concern on an individual basis.

Several analyses have shown HT to be a cost-effective therapy.[368,369] Risks of endometrial and ovarian cancer will be discussed separately. In the final analysis, even though risks are extremely rare and no greater than other commonly used medications and supplements, and somatic complaints may easily be dealt with by regimen changes, there is no escaping that for some women the overall "fear" of using hormones outweighs any potential benefits; the choice of using HT remains very much an individual one.

Endometrial Disease Risk and Other Cancers

- *Unopposed estrogen increases the risk of endometrial cancer, which is reduced with the addition of progestogen.*
- *Ovarian cancer risk is probably not related to hormonal use.*
- *Colon cancer risk is reduced with HT and lung cancer and mortality do not appear to be related to hormonal therapy.*

Endometrial disease occurs with unopposed estrogen therapy in women who have a uterus (see Chapter 29). Although a woman's risk for endometrial cancer with unopposed estrogen use is twofold to eightfold higher than that for the general population, precursor lesions (primarily endometrial hyperplasia) signal the presence of an abnormality in most patients. Thus, the risk is far less for endometrial cancer than it is for varying degrees of hyperplasia. This discussion relates to endometrioid, well-differentiated cancers, which are estrogen-receptor positive. Serous cancers, which are usually not estrogen responsive, are similar in nature to ovarian cancers, are rarer, occur sporadically, and are not related to estrogen exposure.

One study showed that the risk of endometrial hyperplasia was 20% after 1 year of use of 0.625 mg of oral CEE.[370] In another study, the 3-year postmenopausal Estrogen/Progestin Interventions Trial,[371] the risk was approximately 40% at the end of 3 years. No cancers were reported in either of these two studies, and the addition of a progestogen essentially eliminated the hyperplasia. Using a dose of 0.3 mg of CEE results in a risk in the range of 5% to 10% after 2 to 3 years.

The risk for endometrial cancer is the same for a woman taking estrogen and progestogen HT as for the general population. The addition of a progestogen merely eliminates the excess risk attributed to estrogen. However, there are a few studies published suggesting a reduced risk with continuous combined HT. Other endometrial cancers occurring in postmenopausal women are not thought to be hormonally related (see Chapter 29). Although the risk for endometrial cancer is increased substantially in estrogen users, the risk of death from this type of endometrial cancer does not increase proportionately.[372,373] Endometrial cancers associated with estrogen use are thought to be less aggressive than spontaneously occurring cancers, in part because tumors in women taking estrogen are more likely to be discovered and treated at an earlier stage—thus improving survival rates.

Several studies have also suggested an increased risk of ovarian cancer with a long duration of use of estrogen therapy (ET) and HT. However, the data are inconsistent and the purported risk is in the range of less than a twofold RR.[374-377] An analysis found no association, and there was no increase reported in the WHI studies.[312,377,378] In the worst-case scenario, although the majority of studies have suggested there is no statistical increase in ovarian cancer with HT, if we assume a hypothetical 20% increase, this would translate to an increase from 5/10,000 cases per year to 6/10,000/year.

Observational studies and meta-analyses have reported a reduced risk of colorectal cancer in menopausal women who are current and past users of HT.[379,380] This was confirmed in the WHI trial using HT (HR, 0.65).[312] This protective effect is believed to increase with duration of use and may be related to action via ERβ inducing apoptosis in polyps.[381]

Lung cancer has not been shown to be increased with HT; the number of cases and mortality were not affected in a long-term follow-up study.[382]

With aging, there is a decline in macular function. In observational studies, estrogen therapy has been reported to reduce macular degeneration and maintain visual acuity in menopausal women.[383,384] There are also several studies showing that estrogen is associated with a reduction in tooth loss.[385,386]

Hormone Regimens

- *Various hormonal and non-HTs are available, which requires an individualized approach, and a philosophy of being flexible in prescribing.*

There are many hormonal preparations available for treatment, and the most comprehensive listing can be downloaded from the NAMS: www.menopause.org. Also, medications for osteoporosis may be found, including the SERMS, bisphosphonates, denosumab, and tibo.[1-34] For the clinician and patient, the decision to start estrogen therapy need not involve a long-term commitment. For short-term treatment of symptoms, estrogen can be used at a low dose sufficient to control hot flushes or can be administered via the vaginal route for symptoms of dryness or dyspareunia. However, we do not know what the threshold dose should be to provide a coronary benefit in younger women at the onset of menopause—it is likely to be somewhat higher than the "lowest" available dose. However, we do know that very low doses of estrogen are beneficial for preventing bone resorption. There are even data suggesting improved bone mass with vaginal therapy, which only minimally enters the systemic circulation.[387]

Oral ET results in higher levels of E_1 than E_2; this is true for oral estradiol as well as estrone products. CEE is a mixture of at least 10 conjugated estrogens derived from equine pregnant urine. E_1S is the major component, but the biological activities of equilin, 17β-dihydroequilin, and several other B-ring unsaturated estrogens, including Δ dihydroestrone, have been documented. Table 14.9 compares the standard doses of the most frequently prescribed oral estrogens and the levels of E_1 and E_2 achieved.[388,389] Much of the clinical information contained below may be found in systematic reviews.[390]

Synthetic estrogens, given orally, are more potent than natural estradiol. Ethinyl estradiol is used in oral contraceptives, with a dose of 5 μg being equivalent to the standard ERT doses used (0.625 mg CEE or 1 mg micronized estradiol). Standard ERT doses are five or six times less than the amount of estrogen used in oral contraceptives.[391] For hepatic markers, CEE 0.625 mg is generally more potent than E_2 and is closer to 1.5 mg E_2.

Oral estrogens have a potent hepatic "first pass" effect that results in the loss of approximately 30% of their activity with a single passage after oral administration. However, this results in stimulation of hepatic proteins and enzymes. Some of these changes are not particularly beneficial (an increase in procoagulation factors), whereas other changes are beneficial (an increase in HDL-C and a decrease in fibrinogen and PAI-1).

E_2 can be administered in patches, gels, and subcutaneously. These routes of administration are not subject to major hepatic effects as with oral therapy. In the United States, standard doses of alcohol-based or matrix patches are 0.05 or 0.1 mg. Lower-dose patches of 0.025 mg are also available for administration once or twice weekly. Matrix patches are preferable because there is less skin reaction, and estrogen

Table 14.9 Mean Serum Estradiol (E_2) and Estrone (E_1)

	Level (pg/mL)	
Estrogen Dose (mg)	*E_2*	*E_1*
CEE (0.3)*	18	76
CEE (0.625)	39	153
CEE (1.25)	60	220
Micronized E_2 (1)	35	190
Micronized E_2 (2)	63	300
E_1 sulfate (0.625)	34	125
E_1 sulfate (1.25)	42	220

*Conjugated equine estrogen (CEE) contains biologically active estrogens other than E_2 and E_1.

delivery is more reliable. Whereas levels of E_2 vary widely among women, levels with transdermal therapy are more constant in individual women than with oral ET. With the 0.05 mg patch, OK E_2 levels are in the 40 to 50 pg/mL range; with the 0.1 mg patch, levels are typically 70 to 100 pg/mL. Levels in excess of 200 pg/mL are not unusual for some women.[392] An ultralow dose patch, 0.014 mg, has been approved for osteoporosis protection in older women.

In women with vulvo-vaginal or urinary complaints, vaginal therapy is most appropriate. Creams of estradiol or CEE are available, as well as tablets and an estrogen ring. With creams, systemic absorption occurs but with levels that are one-fourth of that achieved after similar doses administered orally. Absorption decreases as the mucosa becomes more estrogenized. For CEE, only 0.5 g (0.3 mg) or less is necessary; for micronized E_2, doses as low as 0.25 mg are sufficient. Other products (tablets and rings) are available that have been designed to limit systemic absorption.[393,394] A silastic ring of E_2 is available that delivers E_2 to the vagina for 3 months with only minimal systemic absorption.[395]

Estrogen may be administered continuously (daily) or for 21 to 26 days each month. If the woman has a uterus, a progestogen should be added to the regimen.[396] For women who are totally intolerant of progestogens (regardless of the dose and route of administration) and take unopposed estrogen, annual endometrial sampling is necessary. Alternatively, different progestogens may be tried; micronized progesterone can be used vaginally, or an intrauterine system (IUS) can be used. The current IUS, releasing 20 µg levonorgestrel, is too large a dose for routine HRT, and the 10 µg IUS, although well studied, will not be marketed as such.[397]

Androgen Therapy

In a very subtle way, some women are relatively androgen deficient.[398] Clinicians have proposed adding androgen to ET or EPT for complaints or problems relating to libido and energy that are not relieved by adequate estrogen[399]; though well-controlled trials using parenteral testosterone have shown benefit in younger oophorectomized women, there have been few data showing benefit using more physiological therapy, until recently. Recent data using a testosterone patch (with near physiological levels) have shown improvement in several scales of well-being and sexual function.[400-404] An oral preparation (esterified estrogens 0.625 mg with 1.25 mg of methyl testosterone) was shown to improve sexual motivation and enjoyment in women with hypoactive sexual desire who were unresponsive to estrogen alone.[405] The latter findings correlated with an increase in circulating unbound testosterone levels. As newer forms and doses of androgen become available, perhaps more women may benefit from this approach. At present, androgen therapy should be individualized and considered for those women who have symptoms that are not adequately relieved with traditional HT.[399] At lower doses, androgenizing side effects are very infrequent but should be discussed before prescribing testosterone. At present, small doses of methyltestosterone (1.25 and 2.5 mg) added to esterified estrogens are available in tablets, as are testosterone patches that are available for men (and therefore require dose reductions) and testosterone subcutaneous pellets. The testosterone patch (300 µg) has not been approved for use in women in the United States, but it is available in Europe. Administration of DHEA at 25 to 50 mg/day may also be an option,[406] although there are few clinical data on efficacy supporting this.

Another SERM-like compound that is used worldwide but is not approved in the United States is tibolone. This progestin-like compound exhibits estrogenic, antiestrogenic, and androgenic effects by virtue of its structure and metabolites. At 2.5 mg, tibolone suppresses hot flushes, prevents osteoporosis, and has a positive effect on mood and sexual function.[407] There is also very limited (or no) uterine stimulation. However, there is a suppression of HDL-C, but at the same time a decrease in triglycerides. In the monkey, there was no deleterious effect of tibolone on coronary arteries.[408] In older women it may increase the risk of stroke.

Phytoestrogens

Phytoestrogens are a class of plant-derived estrogen-like compounds conjugated to glycoside moieties. Phytoestrogens are not biologically active in their native forms unless taken orally. After oral ingestion, colonic bacteria cleave the glycosides, producing active compounds that are subject to the enterohepatic circulation. These compounds can produce estrogen-agonistic effects in some tissues, whereas in other tissues, they can produce antagonistic effects.

Few randomized trials have examined the efficacy of phytoestrogens. For large daily doses (60 mg isoflavone) there appears to be some limited efficacy in relieving hot flushes.[409] With doses of 30 to 40 mg, cholesterol levels are reduced, but it is no longer recommended as a strategy.[410] It should be noted that there is an important reduction in hot flushes with *any* placebo treatment. Phytoestrogens do not appear to have much of an effect on bone loss or on vaginal atrophy. A trial of longer duration has shown no benefit of red clover and soy (Fig. 14.42).[411]

Estimates are that between 30% and 60% of women use so-called alternative interventions for the symptoms of menopause, including "natural" estrogens, plant estrogens, herbal medicines, and acupuncture. Botanicals, herbals, and many steroid products are sold over the counter, and some do, in fact, exert significant hormonal activity. The use of botanicals to alleviate the symptoms of menopause is extremely popular. This popularity is fostered by the notion that plant sterols might provide all the benefits of estrogen replacement therapy without the risks. However, most plant products recommended for menopause have performed poorly in clinical trials. The Dietary Supplement Health and Education Act of 1994 classifies most botanical medicines as food supplements and removes them from regulatory oversight and scrutiny by the FDA. Adulteration, contamination, and poor quality control in their harvesting, manufacture, and formulation yield products of questionable efficacy and safety.

The FDA has determined that more than 25% of Chinese patent medicines are adulterated with hidden pharmaceutical drugs. These kinds of deficiencies make it difficult for consumers and practitioners to employ botanicals with confidence and security. Furthermore, clinical trial data obtained using one brand of herbal product cannot necessarily be extrapolated to other brands using the same plant. DHEA is marketed as a dietary supplement for a variety of purported benefits. There are no data in women to support its role in well-being or immune function. As an androgen, DHEA is converted

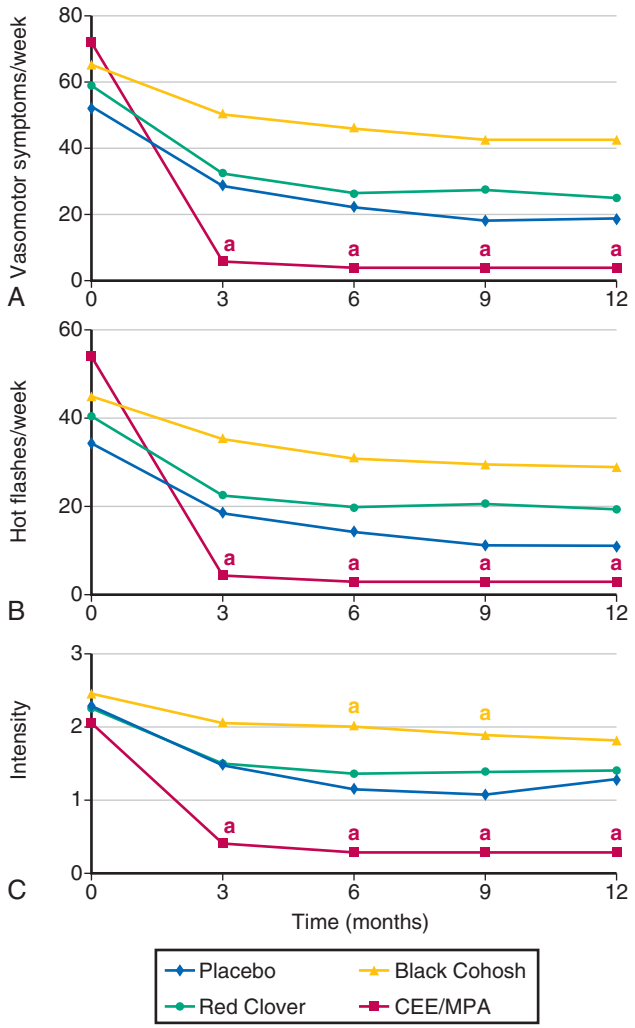


FIGURE 14.42 Black cohosh and red clover are not different from placebo. *CEE,* Conjugated equine estrogens; *MPA,* medroxyprogesterone acetate; *a,* statistically significant difference. *(Modified from Geller SE: Safety and efficacy of black cohosh and red clover for the management of vasomotor symptoms: a randomized controlled trial.* Menopause *16:1156–1166, 2009.)*

to androstenedione and testosterone. Doses of 25 to 50 mg raised testosterone and have been mentioned as an option for androgen therapy.[403]

In recent years, more women have turned to "bioidentical" hormones. In essence, estradiol and progesterone, which are available as FDA-approved products, are "bioidentical"; that is, identical to the steroids produced by the body. However, an industry has arisen where compounding pharmacies add various combinations of steroids to be administered in cream form. These products are not FDA approved and quality control cannot be guaranteed. There is no evidence that these preparations are safer than standard products. The use of saliva to quantify levels is extremely inaccurate. The major societies (e.g., NAMS, Endocrine Society, American Society for Reproductive Medicine [ASRM], American Congress of Obstetricians and Gynecologists [ACOG]) do not endorse this use. A joint statement has been issued by ASRM and ACOG.[412]

Use of a Progestogen

There are many ways to administer progestogens. The most commonly used oral progestins are MPA in doses of 5 to 10 mg, NET in doses of 0.3 to 1 mg, and micronized progesterone in doses of 100 to 300 mg. Equivalent doses to prevent hyperplasia when administered for at least 10 days in a woman receiving ET (equivalent to 0.625 mg CEE) are as follows: MPA, 5 mg; NET, 0.35 mg; and micronized progesterone, 200 mg.[413] Larger doses of estrogen may require larger doses and more prolonged regimens of progestins. In sequential administration of progestins, the number of days (length of exposure) is more important than the dose. Thus, if a woman is receiving oral ERT continuously, a regimen of at least 10 to 12 days of exposure is preferable to a 7-day regimen.

When progestogens are administered sequentially (10 to 14 days each month), withdrawal bleeding occurs in about 80% of women. Continuous administration of both estrogen and progestogen (continuous combined therapy) was developed to achieve amenorrhea. In the first 3 to 6 months, breakthrough bleeding and spotting is common. In some women on this regimen, amenorrhea is never completely achieved. The most common combinations in the United States are single tablets containing 0.625 mg CEE and 2.5 mg (or 5 mg) MPA, and the lower dose combination with 0.45 mg and 0.3 mg (CEE) 5 μg of EE with 1 mg NET; 1 mg micronized E_2 with 0.5 mg NET, and 1 mg of E_2, with 0.5 mg of drosperinone. Patches with E_2 NET of levonorgesterone are also available. Currently, the only marketed sequential regimen is one that contains 0.625 mg CEE and 5 mg MPA, which is added for 14 days each cycle.

Equal efficacy to standard doses has been demonstrated for several low-dose combinations in terms of reduction of hot flushes, maintenance of bone mass, metabolic profiles, and a reduction in the incidence of bleeding in the first year of treatment has been observed.

Progesterone administered vaginally (in low doses) avoids systemic effects and results in high concentrations of progesterone in the uterus. Intrauterine delivery of progestogens is ideal for targeting the uterus but is not approved in the United States.

Progestogens, particularly when taken orally, may lead to problems of continuance or compliance because of adverse effects, including mood alterations and bleeding. These have to be dealt with effectively, and they usually require more flexibility in prescribing habits. Most short-term clinical trials have demonstrated an attenuating effect of progestogens on cardiovascular end-points that are improved with estrogen; these effects include lipoprotein changes (an attenuation of the rise in HDL-C) and arterial and metabolic effects. A reduction in blood flow and some brain effects also may be found.

How progestogens influence cardiovascular risk is not clear at present. The observational studies, which showed a benefit for ET, did not find any diminution of this effect with EPT. Although there were differences in the effects of CEE with MPA and CEE alone in the WHI study, there were separate trials, which are difficult to compare. The addition of progestogens is probably responsible for the observed increase in the risk of breast cancer in susceptible women. Progestogens should not be prescribed in women who have undergone hysterectomy.

Tissue Selective Estrogen Complex

The concept of a tissue selective estrogen complex is to pair estrogen (CEE) with a SERM (bazedoxifene), which has certain estrogen-antagonistic effects in certain organ systems (breast, uterus). Not all SERMS are successful in this pairing. The effects of bazedoxifene are less marked in the brain (affecting hot flush susceptibility) and are also agonistic in bone. Thus, a combination of CEE and bazedoxifene could be used to prevent hot flushes without the need for a progestogen while also having beneficial effects for bone and neutral effects on the breast. While not approved for use in the United States as yet, CEE 0.625 and 0.45 paired with bazedoxifene 40 mg have gone through successful phase 3 clinical trials demonstrating efficacy and safety.[414,415]

Aging

- *Aging, per se, causes many of the changes that occur after menopause.*
- *Important considerations are GH changes, metabolic changes, the accumulation of body fat, and alterations in the adrenal axis.*

It is extremely difficult to separate the effects of menopause from that of natural aging. Some of these problems have been reviewed in detail elsewhere, and the much needed research in this area has been outlined.[416]

Telomere length is a key component of aging, with shortening of telomeres occurring. Shortening of telomeres with increasing age results in a terminal activity known as replicative senescence. This process is not only associated with aging but has implications for cancer initiation as well (Fig. 14.43).[417]

The key areas where it is important to dissect out aging effects from the effects of estrogen deficiency are in bone loss and osteoporosis, CVD, cognitive decline, decline in sexual function, and depression. While premenopausal estrogen therapy may play a role in protecting against these entities, aging also has significant effects.

From a reproductive endocrine perspective, the hormonal systems that are most notably affected by aging are declines in the somatotrophic axis, declines in adrenal steroids, and changes in cortisol secretion. Table 14.10 outlines the endocrine metabolic changes with aging.

Somatotrophic Axis

In men and women, GH decreases with aging,[418] beginning around age 40.[419,420] This decrease may be responsible for some of the changes in body composition. A redifferentiated proportion of body fat increases by 100%. Concomitantly there is a 20% to 50% decrease in muscle mass and a 20% decrease in body fat. In women, declines in GH-releasing hormone secretion and a loss of the priming effect of estrogen explain the decline in GH.[421-424]

The anabolic effects of replacing GH can result in stimulated muscle development and strength, a loss of fat, and an increase in bone mass.[425] Accordingly, GH releasing peptides have been studied for this purpose.[426,427]

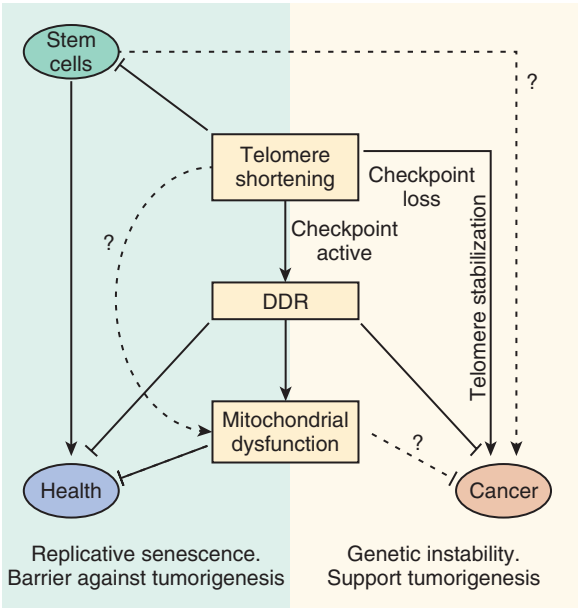


FIGURE 14.43 Short telomeres in aging and cancer. Major pathways affected by short telomeres and their impact on aging or cancer. DNA damage and tumor suppressor activity have been shown to affect tissue decline and aging. When DNA damage checkpoints are bypassed, cells with short telomeres could potentially progress to cancer. The role of stem cells with short telomeres in cancer and whether short telomeres could modulate other pathways independently of p53 (e.g., mitochondrial dysfunction) remains unknown. *DDR,* DNA damage response. *(From Bernardes de Jesus B, Blasco MA: Telomerase at the intersection of cancer and aging.* Trends Genet *29:513–529, 2013.)*

Table 14.10 Endocrine-Metabolic Changes With Aging

Substance	Change
Luteinizing hormone	↑
Follicle-stimulating hormone	↑
Growth hormone	↓
Adrenocorticotropic hormone	→*
Prolactin	↓
Thyroid-stimulating hormone	→*
Estradiol	↓
Estrone	↓
Progesterone	↓
Triiodothyronine	→
Thyroxine	→*
Cortisol	↑
Dehydroepiandrosterone	↓
Dehydroepiandrosterone sulfate	↓
Testosterone	↓
Androstenedione	↓
Inhibin	↓
Melatonin	↓
Insulin-like growth factor-1	↓
Dopamine	↓
Norepinephrine	↑

*May be slightly increased or decreased in response to specific secretagogue (e.g., corticotropin-releasing hormone, thyrotropin-releasing hormone, somatostatin, growth hormone-releasing hormone, adrenocorticotropin) with age.

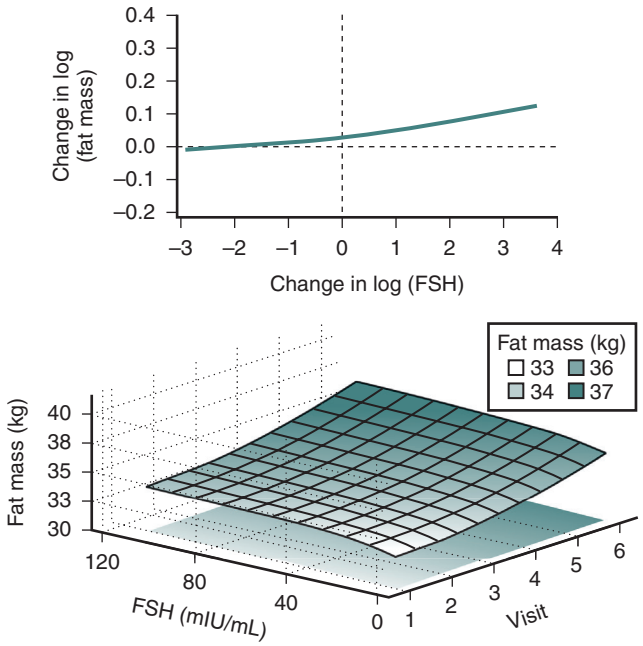


FIGURE 14.44 Changes in fat mass during the perimenopause and relationship to follicle-stimulating hormone *(FSH).* *FMP,* Final menstrual period.

Metabolic Changes

With aging, weight gain and fat accumulation occurs, as stated previously. These changes begin a few years before menopause and parallel increases in FSH (Fig. 14.44).[428] It has been confirmed in longitudinal studies that weight changes generally precede the hormonal changes, such as the decrease in SHBG.[428] These changes are associated with increases in leptin. In early menopause, associated with normal body mass index, adiponectin increases.[429] However, in late menopause, as with obesity, adiponectin is reduced, increasing CVD risk.[430] With aging, there is a reduction in pancreatic β cell secretion, increasing the risk of diabetes mellitus. Adding to this risk, insulin resistance increases with age but is accelerated with weight gain and obesity.

The major concern with increasing adiposity and reduction in muscle mass (sarcopenic obesity) is the evolution of chronic diseases. Increasing immobility compounds the transition to metabolic syndrome, overt diabetes, and CVD. In 18 randomized trials it was shown that the best way to combat sarcopenic obesity is by the combination of aerobic and strengthening exercise 2 to 3 days per week, combined with caloric restriction leading to a daily deficit of 750 Kcalories.[431] Diet and exercise should be a mainstay for combating the aging process.[431]

The increase in fat mass and the decrease in lean muscle mass in postmenopausal women may be enhanced by estrogen deficiency. Indeed, hormone therapy does not increase fat mass and tends to decrease abdominal obesity.[432,433] It appears that oral estrogen tends to slightly increase fat mass (not visceral fat mass) while transdermal estrogen does not affect fat mass.[434] The effect of oral estrogen may be mediated by a decrease in insulin-like growth factor 1.[423]

Adrenal Steroids

The age-related decline in adrenal androgens has been noted previously, as well as the possibility of administering DHEA for androgen support in postmenopausal women. While higher DHEAS levels in men are associated with a better cardiovascular survival, this correlation has not been found in women. Similarly, the data on enhancing insulin sensitivity and immune function, as well as quality of life assessments in postmenopausal women, are inconsistent[436] and require more study.

Because DHEA and DHEAS may be produced locally in the brain[437,438] and bind to the γ-aminobutyric (GABA) receptors,[439] there may be an important role for DHEA in remedying the mood and cognition declines that come with aging. Positive effects of DHEA on mood and cognition in the elderly have been reported.[440,441] Unfortunately, most clinical trials and DHEA in postmenopausal women have not shown benefit.

Cortisol levels are higher in older postmenopausal women.[442] This relates to a higher nocturnal rhythmicity, which has been related to loss of resiliency and could explain sleep disturbances in the elderly.

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