14 Menopause and Care of the Mature Woman

Endocrinology, Consequences of Estrogen Deficiency, Effects of Hormone Therapy, and Other Treatment Options

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KEY POINTS

- The average age of menopause in the United States is 51.3 years; it is younger in certain ethnic groups, and is genetically predetermined and is not related to the number of ovulations, race, socioeconomic conditions, education, height, weight, age at menarche, or age at last pregnancy.
- Because most diseases in women occur after menopause, the onset of menopause heralds an important opportunity to institute prevention strategies for prolonging and improving the quality of life for women.
- Vasomotor symptoms or hot flushes may persist for 10 or more years, with bothersome flushes occurring for about 7 years. Estrogen is the best therapy for the hot flush; other effective therapies are progestogens, selective serotonin reuptake inhibitors (SSRIs), gabapentin, clonidine, some phytoestrogens, acupuncture, and stellate ganglion blockade.
- Dual-energy x-ray absorptiometry (DEXA) is the most accurate method to measure bone density. A country-specific algorithm (FRAX) using DEXA has been developed to calculate the 10-year risk of fracture. In addition to estrogen (with and without progestogen), alendronate, risedronate, ibandronate, zoledronic acid, raloxifene, calcitonin, denosumab, romosozumab and teriparatide will reduce postmenopausal bone loss, and some agents will stimulate bone formation as well.
- The primary indication for estrogen therapy is symptoms of menopause (hot flushes as well as quality-of-life issues); bone health may also be an indication in some women. In younger postmenopausal women who are receiving hormonal therapy for symptoms, the benefits outweigh risks. There are consistent data for a reduction in all-cause mortality of 20% to 30% in younger women who initiate estrogen therapy at the onset of menopause. These findings suggest a potential role of estrogen as a prevention therapy after menopause

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 before 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. Although 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 51 years, more than a 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 older than 50, medical care specifically directed at postmenopausal women becomes an important aspect of modem medicine. **Indeed an opportunity exists at the onset of menopause for providers to address the long-term needs of women after menopause and to have an impact on longevity and quality of life** (Lobo, 2016). In the United States, the number of women entering menopause is projected to have doubled in the 30 years between 1990 and 2020, and the total number of postmenopausal women is expected to be in range of 60 million (Table 14.1).

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**) is thought to correlate with general health status; socioeconomic status is associated with an earlier age of menopause. Higher parity, on the other hand, has been found to be associated with a later menopause. Smoking has consistently been found to be associated with menopause onset taking place 1 to 2 years earlier. Hysterectomy has also been cited as resulting in an earlier menopause, presumably because of a diminution in the blood supply to the ovary; however, the data have not been consistent. Although body mass has been thought to be related to age of menopause (with greater body mass index [BMI] associated with later menopause), the data have not been consistent. However, physical or athletic activity has not been found to influence the age of menopause. There also appear to be ethnic differences in the onset of menopause. In the United States black and Hispanic women have been found to have menopause approximately 2 years earlier than white women. Although parity is generally greater around the world than in the United States, the age of menopause appears to be somewhat earlier outside the United States. Malay women have menopause at approximately age 45, Thai women at age 49.5, and Filipina women between ages 47 and 48. Menopause has also been reported to occur at an average age of 46.2 years in women from India (Ajuja, 2016). Women in countries at higher altitude (Himalayas or Andes) have been shown to have menopause 1 to 1.5 years earlier. Because the average age of menopause in the United States is 51 to 53 years, menopause before age 40 is considered premature and before age 45 is considered early. 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, de Bruin and colleagues (de Bruin, 2001) showed that heritability for age of menopause averaged 0.87, suggesting that

TABLE 14.1 U.S. Population Entering the Postmenopausal Years, Ages 55 through 64

Year	Population (in Millions)
1990	10.8
2000	12.1
2010	17.1
2020	19.3

Modified from U.S. Bureau of the Census. *Current Population Reports: Projections of the Population of the United States 1977 to 2050.* Washington, DC: U.S. Government Printing Office; 1993.

genetics explains up to 87% of the variance in menopausal age. The maternal contribution is around 50%.

Other than specific gene mutations that have been shown to cause **premature ovarian failure or insufficiency** (explained later in this chapter), no specific genes have been implicated to account for this genetic influence. However, several genes are likely to be involved in determining the age of menopause; they include genes regulating immune function and DNA repair (Stolk, 2012) and may also include genes coding telomerase activity, which affects aging in general.

PREMATURE OVARIAN INSUFFICIENCY

Premature ovarian failure (POF) or premature ovarian insufficiency (POI), which is a newer term, is defined as **hypergonadotropic ovarian failure occurring before age 40**. **POI occurs in 5% to 10% of women who are evaluated for amenorrhea**; thus the incidence varies according to the prevalence of amenorrhea in various populations. Estimates of the overall prevalence of POI in the general population range between 0.3% and 0.9% of women. Throughout life, there is an ongoing rate of atresia of oocytes. Because this process is accelerated with various forms of gonadal dysgenesis because of defective X chromosomes, one possible cause of POI 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 POI. Nevertheless, about 1000 (of the original 2 million) primarily follicles may remain. Although most of these oocytes are likely to be functionally deficient, **spontaneous pregnancies occur occasionally in young women in the first few years after the diagnosis of POI.** There are several possible causes of POI (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 as a result of genetic mosaicism. **Very small defects in the X chromosome may be sufficient to cause POI**. Familial forms of POI may be related to either autosomal dominant or sex-linked modes of inheritance. 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, but these are extremely rare outside of the Finnish population, in whom 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 men.

The permutation in fragile X syndrome has been shown to be associated with POI. Type 1 blepharophimosis/ptosis/epicanthus inversus (BPES) syndrome, an autosomal dominant disorder caused by mutations in the forkhead transcription factor FOXL2, includes POI. Triple X syndrome has also been associated with POI. It has been suggested that functional mutations of antimüllerian hormone (AMH) may also be associated with POI.

Dystrophic myotonia has also been linked to POI, although the mechanism underlying this relationship is unclear. Under the category of enzymatic defects, galactosemia is a major cause of POI 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, POI tends to occur. Another enzymatic defect linked to POI 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.

The degree to which **autoimmunity may be responsible for POI** is unclear, but it has been suggested to be associated in 17.5% of cases. Virtually all autoimmune disorders have been found to be associated with POI, including autoimmune polyendocrinopathies such as autoimmune polyendocrinopathy/candidiasis/ectodermal dystrophy (APECED), which is caused by mutations in the autoimmune *(AIRE)* gene on band 21 q22. The presence of the thymus gland appears to be required for normal ovarian function because POI has been associated with hypoplasia of the thymus. In patients who have undergone ovarian biopsy as part of their evaluation, lymphocytic infiltration surrounding follicles has been described, as well as resumption of menses after immunosuppression. Immunoassays using antibodies directed at ovarian antigens have been developed and have demonstrated positive findings in some patients with POI, 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-hydroxysteroid dehydrogenase (3βHSD) may also be the target of ovarian autoimmunity. Approximately 2% to 4% of women with autoimmunity for POI will have antiadrenal antibodies as well (Chen, 1996). This can be screened for by an assay for 21-hydroxlase antibodies. Adrenal function, more practically, can be assessed by measuring dehydroepiandrosterone sulfate (DHEA-S) levels, which are higher in younger women than in menopausal women, unless the adrenal gland is affected. It may also be helpful to assess ovarian volume and follicular presence by vaginal ultrasound in these women as well. The ovaries in younger women with POI are more normal in size and have follicles present compared with the smaller atrophic ovary in menopause.

From a practical standpoint, **screening for the common autoimmune disorders is appropriate in women found to have POI.** Not practical to measure, however, are abnormalities in the structure of gonadotropins, in their receptors, or in receptor binding, which could be associated with POI; these measurements are difficult. Although abnormal urinary forms of gonadotropins have been reported in women with POI, these data have not been replicated. Abnormalities of FSH receptor binding, as mediated by a serum inhibitor, have been described. A genetic defect that may lead to alterations in FSH receptor structure was mentioned previously.

BOX 14.1 Possible Causes of Premature Ovarian Failure

Genetic
Enzymatic
Immune
Gonadotropin defects
Ovarian insults
Idiopathic

Under the category of ovarian insults, POI 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. **A dose of 400 to 500 rads is known to cause ovarian failure 50% of the time**, and older women are more vulnerable to experiencing permanent failure. A dose of approximately 800 rads is associated with failure in all women. Ovarian failure (transient or permanent) may be induced by chemotherapeutic agents, although younger women receiving this insult have a better prognosis. **Alkalizing agents**, particularly cyclophosphamide, appear to be most toxic. By exclusion, the majority of women are considered to have idiopathic POI 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 Premature Ovarian Insufficiency

Evaluation of POI in women younger than 30 should include screening for autoimmune disorders and a karyotype; detailed recommendations for screening of such women are available (Rebar, 2000). 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 immunologic defect. **Women with POI caused by immunologic defects should be screened carefully for thyroid, adrenal, and other autoimmune disorders.**

Treatment of all cases usually consists of **estrogen replacement**. Although in menopausal therapy clinicians have steered away from the term *replacement* therapy, in this specific instance of POI, estrogen treatment is truly *replacement* therapy. If fertility is a concern, the most efficacious treatment is oocyte donation. Various attempts at ovarian stimulation are usually unsuccessful; sporadic pregnancies that may occur (~5%) are just as likely to occur spontaneously as with any intervention, and often while on physiologic estradiol (E_2) replacement. In this setting it has been our preference not to use oral contraceptive pills for replacement in women wishing to conceive. In a long-term follow-up of a large number of women diagnosed with POI, within a year spontaneous ovarian function was observed in 24% of the women and over time **the rate of spontaneous pregnancies was 4.4%** (Bidet, 2011).

Estrogen replacement in these young women with POI is extremely important and is not analogous to hormone therapy (HT) after menopause because these young women are at substantial long-term risk for osteoporosis and cardiovascular disease (CVD). Coronary heart disease and death are specifically increased in approximately 70% of women with POI, but not stroke. Another review emphasized the increased risks in several organ systems, including brain, cardiovascular, and bone, and early mortality with untreated premature or early menopause (Faubion, 2015). A more extreme example of this phenomenon is with premature oophorectomy, with which the risk of CVD is many-fold increased (Fig. 14.1) (Atsma, 2006). Women with POI should be offered estrogen replacement, with some form of progestogen in women with a uterus, at least up to the natural age of menopause.

MENOPAUSAL TRANSITION (PERIMENOPAUSE)

A workshop was convened in 2001 to build consensus on describing various stages of the menopausal transition. A follow-up conference, the **Study of Reproductive Aging Workshop (STRAW+10)**, had more streamlined bleeding criteria for the

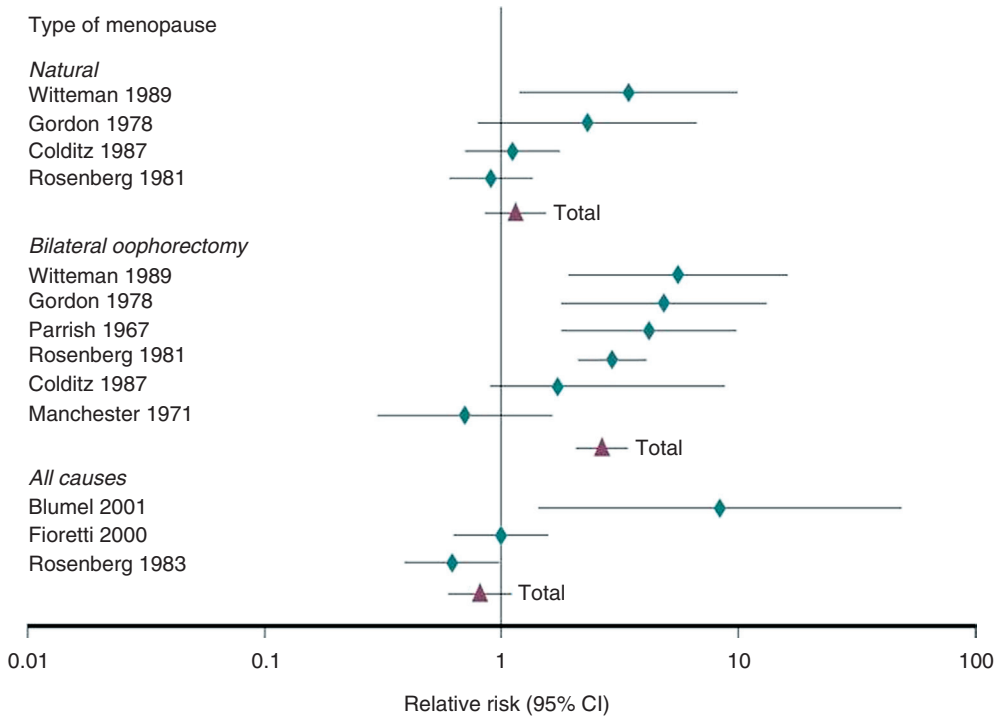


Fig. 14.1 Effect of type of "early" menopause on cardiovascular disease. Data taken from a meta-analysis. *CI,* Confidence interval. (From Atsma F, Bartelink ML, Grobbee DE, et al. Postmenopausal status and early menopause as independent risk factors for cardiovascular disease: a meta-analysis. *Menopause.* 2006;13(2):265-279.)

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			Low	Variable*	↑ Variable*	↑ >25 IU/L**	↑ Variable		Stabilizes	
AMH			Low	Low	Low	Low	Low		Very Low	
Inhibin B				Low	Low	Low	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

Fig. 14.2 The Stages of Reproductive Aging Workshop + 10 staging system for reproductive aging in women. *AMH,* Antimüllerian hormone; *FMP,* Final menstrual period; *FSH,* follicle-stimulating hormone. (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.* 2012;97(4):1159-1168.)

various stages and expanded the stages including the use of biochemical markers such as inhibin B and AMH, in addition to FSH (Harlow, 2012) (Fig. 14.2). This scheme is important from a descriptive standpoint for the physiology behind the normal menopausal transition and is useful for characterization of women in various stages in research studies. **The earliest sign of impending menopause during the menopause transition is a change in menstrual length.**

The ovary changes markedly from birth to the onset of menopause (Fig. 14.3). The greatest number of primordial follicles is present in utero at 20 weeks' gestation, and the follicles undergo 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 38 and menopause (Fig. 14.4), when no more than 1000 follicles remain. These remaining follicles are primarily atretic in nature.

These changes are reflected in circulating levels of AMH, which decline rapidly with ovarian aging. **When levels of serum AMH become undetectable, menopause is likely to occur in 4 to 5 years.**

Ovarian Changes During Perimenopause

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* and is reflected by decreased AMH, inhibin B levels, and antral follicle counts and a rising FSH. The concept of dissociation in ovarian function is appropriate. These changes may occur with normal menstrual function and no obvious endocrine deficiency; however, they may occur in some women as early as age 35 (10 or more years before endocrine deficiency ensues). Although subtle changes in endocrine and menstrual function can occur for up to 3 years before menopause, it has been shown that **the major reduction in ovarian estrogen production does not occur until approximately a year before menopause** (Fig. 14.5) (Randolph, 2011). There is also a slow decline in androgen status (i.e., androstenedione and testosterone), which cannot be adequately detected at the time of perimenopause. **The decline in androgen is largely a phenomenon of aging**. Products of the granulosa cell are most important for the feedback control of FSH. As the functional capacity of the follicular units decreases, the secretion of substances that suppress FSH also decreases. A marker of this is inhibin B, in which levels are lower in the early follicular phase in women in their late 30s (Fig. 14.6). Inhibin B is seldom measured clinically; rather AMH (which also reflects granulosa cell function) is most often assessed, as noted previously. Indeed, FSH levels are higher throughout the cycle in older ovulatory women than in younger

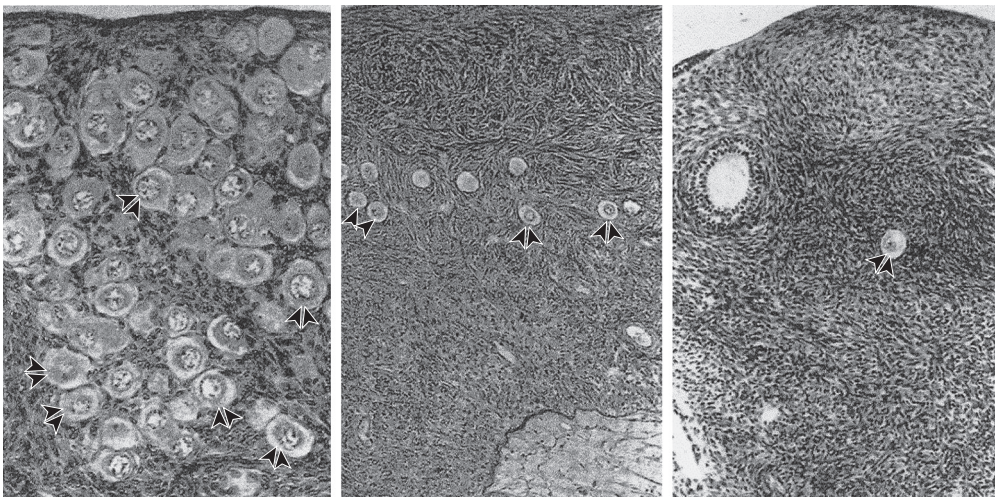


Fig. 14.3 Photomicrographs of the cortex of human ovaries from birth to age 50 years. Small nongrowing primordial follicles *(arrowheads)* have a single layer of squamous granulosa cells. (Modified from Erickson GF. An analysis of follicle development and ovum maturation. *Semin Reprod Endocrinol.* 1986;3:233.)

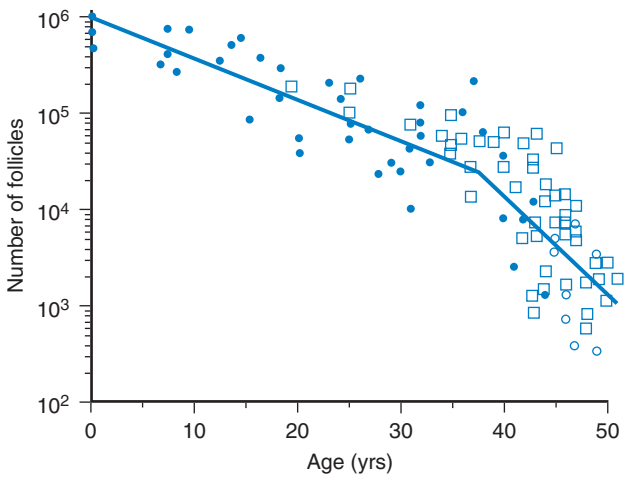


Fig. 14.4 The age-related decrease in the total number of primordial follicles (PFs) within both human ovaries from birth to menopause. As a result of recruitment (initiation of PF growth), the number of PFs decreases progressively from about 1 million at birth to 25,000 at 37 years. At 37 years, the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

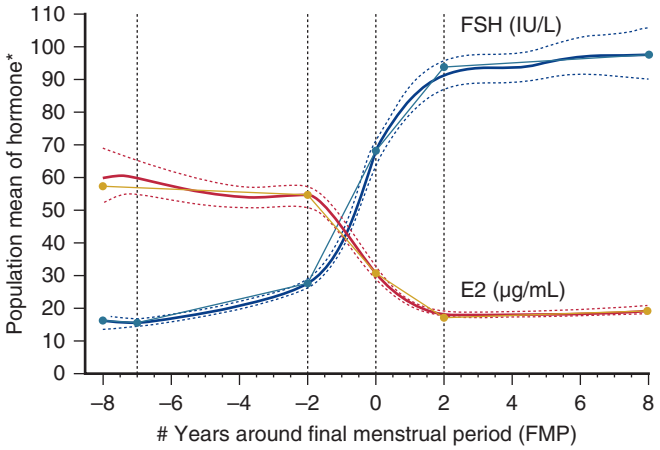


Fig. 14.5 Adjusted population means (95% confidence interval) for segmented mean profiles for follicle-stimulating hormone (FSH) and estradiol (E_2) across the final menstrual period in the Study of Women's Health Across the Nation (N = 1215). (From Randolph JF Jr, Zheng H, Sowers MR, et al. Change in follicle-stimulating hormone and estradiol across the menopausal transition: effect of age at the final menstrual period. *J Clin Endocrinol Metab.* 2011;96(3):746-754.)

women (Fig. 14.7). The functional capacity of the ovary is also diminished as women enter into perimenopause. With gonadotropin stimulation, although E_2 levels are not very different between younger and older women, total inhibin production by granulosa cells is decreased in women older than 35. 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. AMH serves as the most practical marker of reproductive aging. Levels decrease throughout life, being undetectable at menopause, and show less variability during the menstrual cycle compared with other markers such as FSH. However, values are lower by up to 20% in women on oral contraceptives, and this should be taken into account when assessing levels in younger women. When values reach an undetectable range (<0.05 ng/mL), menopause has been found to occur within 5 years, as stated previously (Fig. 14.8).

Although there is a general decline in oocyte number with age, an accelerated atresia occurs around age 37 or 38 (see Fig. 14.4). The reason for this acceleration is not clear, but one possible theory relates to activin secretion. Because granulosa cell–derived activin is important for stimulating FSH receptor expression, 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

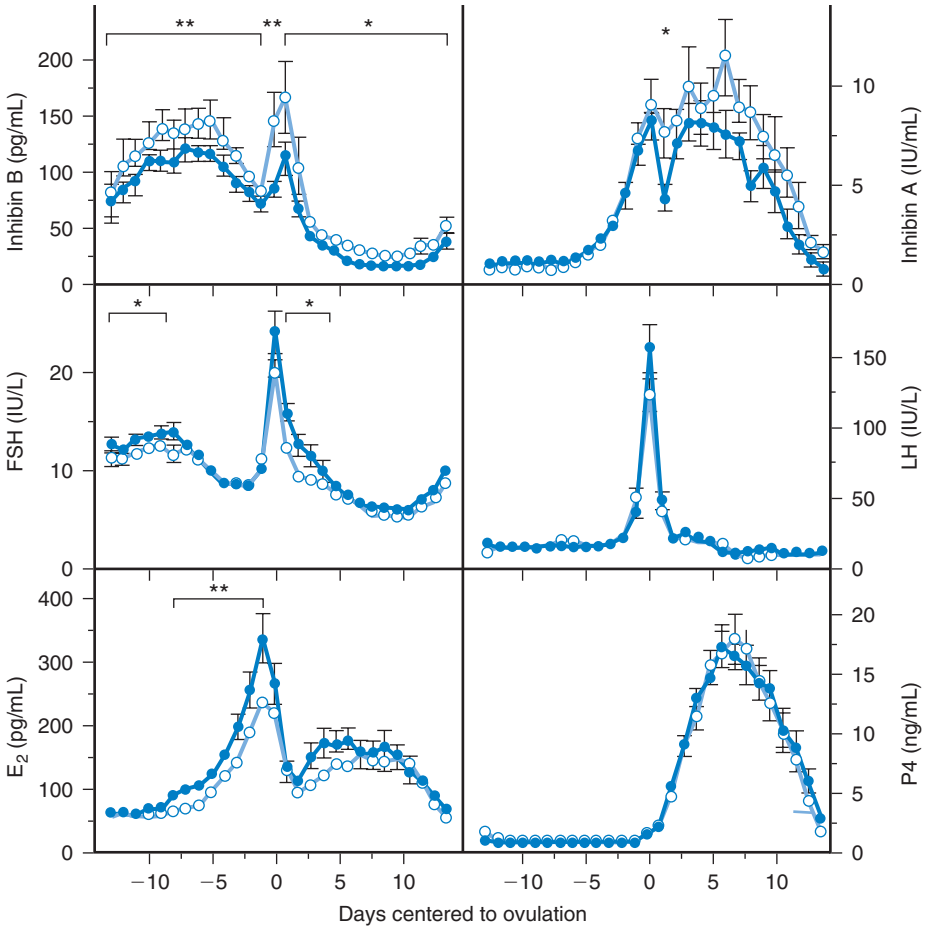


Fig. 14.6 An inhibin B, follicle-stimulating hormone (FSH), estradiol (E_2), inhibin A, and progesterone (P_4) levels in cycling women 20 to 34 years old (^) and 35 to 46 years old (•). Hormone levels are depicted as centered to the day of ovulation (* $P < .04$; ** $P < .02$) when comparing the two age groups. (From Welt CK, McNicholl DJ, Taylor AE, et al. Female reproductive aging is marked by decreased secretion of dimeric inhibin. *J Clin Endocrinol Metab.* 1999;84(1):105.)

women (Fig. 14.9). This autocrine action of activin, involving enhanced FSH action, might be expected to lead to accelerated growth and differentiation of granulosa cells. Furthermore, 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. Clinical treatment of perimenopausal women should address three general areas of concern: (1) irregular bleeding; (2) symptoms of early 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 and progesterone secretion may be normal or slightly decreased, 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 may be an option if symptoms warrant therapy. Alternatively, lower doses of estrogen used alone may be another option.

Hormonal Changes With Established Menopause

Fig. 14.10 depicts the typical hormonal levels of postmenopausal women compared with those of ovulatory women in the early follicular phase. The most significant findings are the marked reductions in E_2 and estrone (E_1). **Serum E2 is reduced to a greater extent than E1**. Serum E_1, on the other hand, is produced primarily by peripheral aromatization from androgens, which decline principally as a function of age. Levels of E_2 average 15 pg/mL and range from 10 to 25 pg/mL but are closer to 10 pg/mL or less in women who have undergone oophorectomy. More sensitive assays for E_2 using mass spectroscopy give lower levels of E_2 with average levels around 3 to 5 pg/mL. Serum E_1 values average 30 pg/mL but may be higher in women with obesity because aromatization increases as a function of the mass of adipose tissue. Estrone sulfate (E_1 S) is an estrogen conjugate that serves as a stable circulating reservoir of estrogen, and levels of E_1 S are the highest among estrogens in postmenopausal women. In premenopausal women, values are usually more than 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 −2 as early as age 38 (see Fig. 14.2), fluctuates considerably until approximately 4 years after menopause (stage +1c), when values are consistently greater than 20 mIU/mL. Specifically, growth hormone (GH), thyroid-stimulating hormone (TSH), and adrenocorticotropic hormone (ACTH) levels are normal. Serum prolactin levels may be slightly decreased because prolactin levels are influenced by estrogen status. Both the

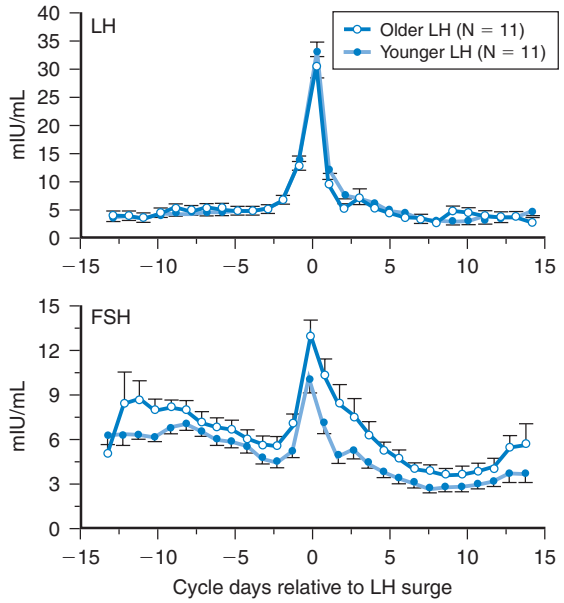


Fig. 14.7 The daily serum follicle-stimulating hormone (FSH) and luteinizing hormone (LH) levels throughout the menstrual cycle of 11 women in each group (mean ± standard error). The gonadotropin secretion pattern in normal women of advanced reproductive age in relation to the monotropic FSH rise. (Modified 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.* 1996;3:27.)

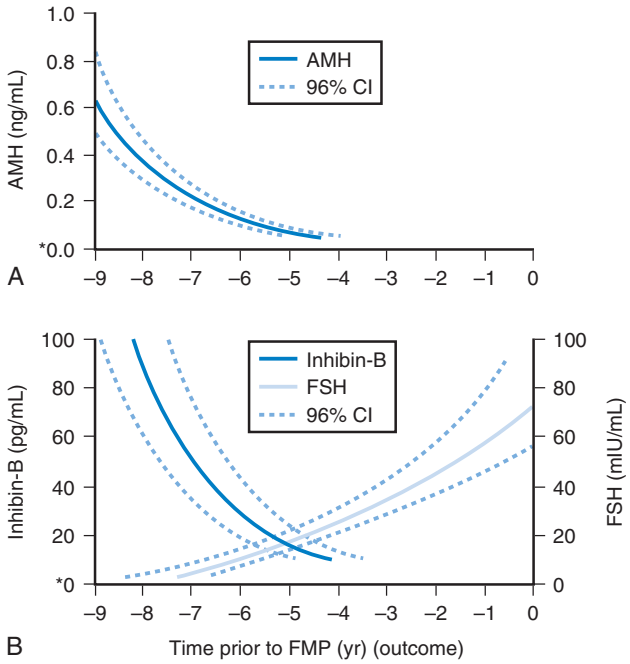


Fig. 14.8 A, Antimüllerian hormone (AMH) decreases to undetectable levels (0.05 ng/mL) 5 years before the final menstrual period. **B,** Inhibin B (10 pg/mL) does so 4 years before the last menstrual period. *CI,* Confidence interval; *FMP,* Final menstrual period; *FSH,* follicle-stimulating hormone. (From Sowers MR. Eyvazzadeth AD, McConnell D, et al. Antimüllerian hormone and inhibin in the definition of ovarian aging and the menopause transition. *J Clin Endocrinol Metab.* 2008;93(9):L34768-L34783.)

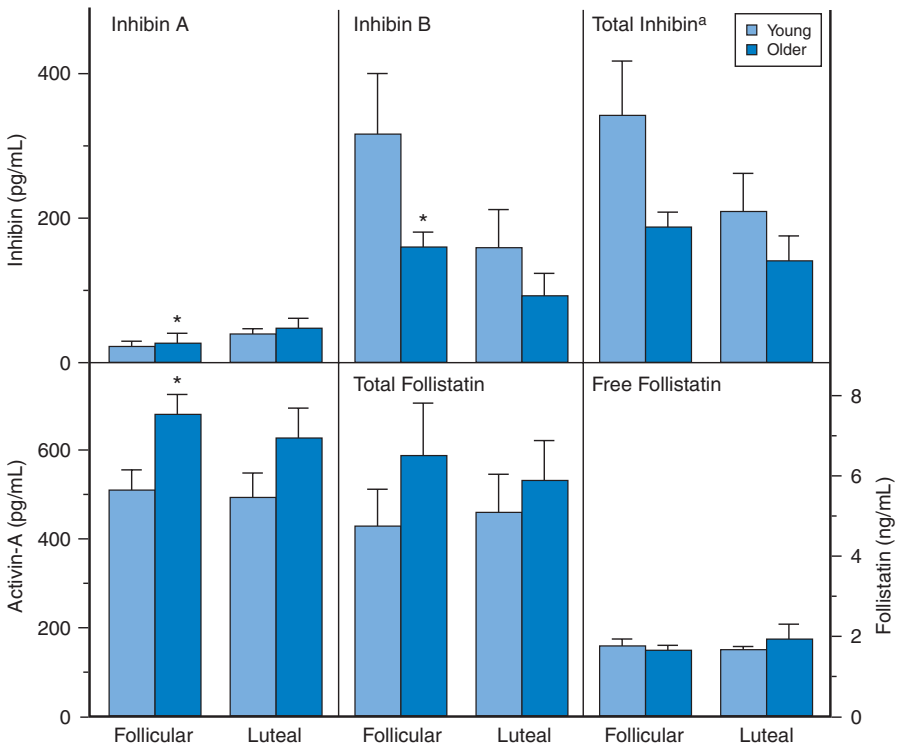


Fig. 14.9 Mean concentrations of gonadal proteins from the same subjects. Total inhibin is a derived number from the sum of inhibin A and inhibin B. *Group differences; $P < .05$. Net increase in stimulatory input resulting from a decrease in inhibin B and an increase in activin A may contribute in part to the rise in follicular phase follicle-stimulating hormone in 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 hormone of aging cyclic women. *J Clin Endocrinol Metab.* 1998;83:3302.)

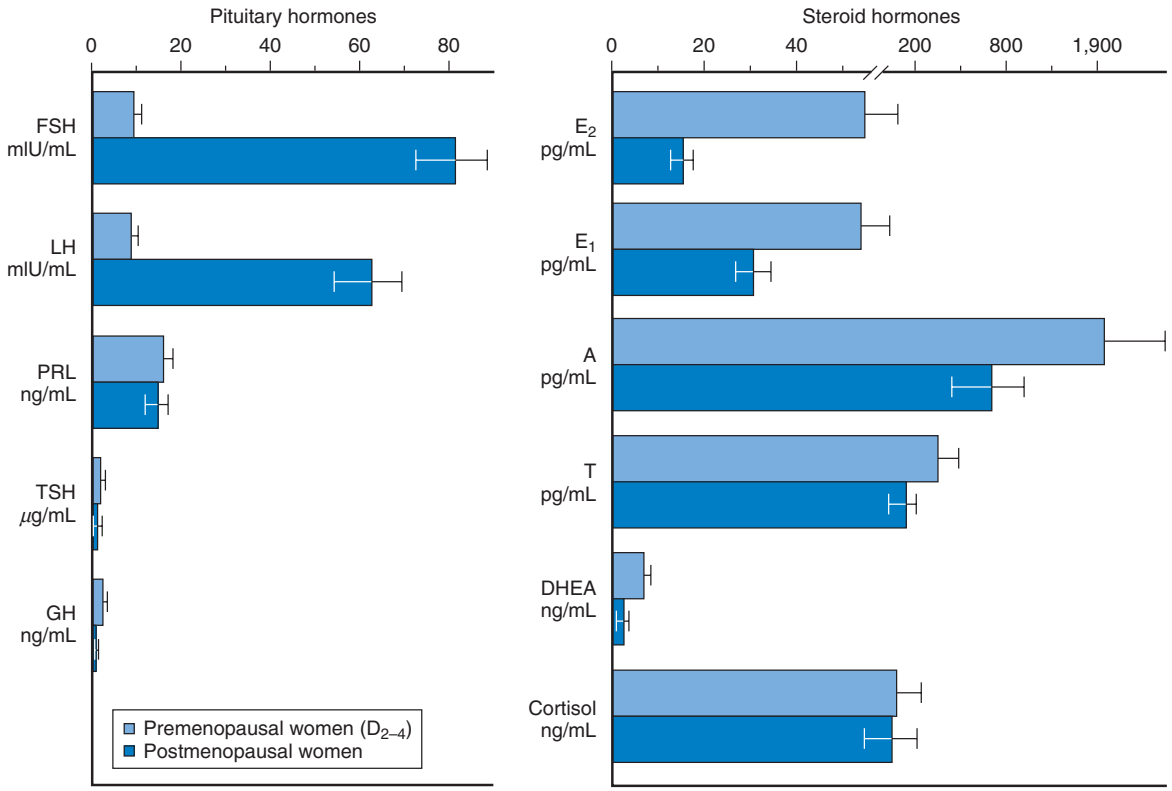


Fig. 14.10 Circulating levels of pituitary and steroid hormones in postmenopausal women compared with levels in premenopausal women studied during the first week (days 2 to 4 [D_{2-4}] of the menstrual cycle. *A,* Androstenedione; *DHEA,* dehydroepiandrosterone; E_1, estrogen; E_2, estradiol; *FSH,* 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.* 1977;18:287.)

postmenopausal ovary and the adrenal gland continue to produce androgen. The ovary continues to produce androstenedione and testosterone but not E_2, 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 values averaging 0.8 ng/mL and 0.1 ng/mL, respectively. The adrenal gland also continues to produce androstenedione, DHEA, and DHEA-S; primarily as a function of aging, these values decrease somewhat (adrenopause), although cortisol secretion remains unaffected. Most "ovarian" testosterone production may actually arise from the adrenal gland by way of precursors (Couzinet, 2001). Most likely, the adrenal gland supplies precursor substrates (DHEA and androstenedione) for ovarian testosterone production. More recent measurements of 11-oxygenated androgens, which are mainly adrenal derived, will be important to investigate, but there are few data on this at present. Although DHEA-S levels decrease with age (approximately 2% per year), data have suggested that levels transiently rise in perimenopause before the continuous decline thereafter (Fig. 14.11). This interesting finding from the Study of Women Across the Nation (SWAN) also suggested that DHEA-S levels are highest in Chinese women and lowest in African American women.

Testosterone levels also decline as a function of age, which is best demonstrated by the reduction in 24-hour means levels (Fig. 14.12). Because of the role of the adrenal gland in determining levels of testosterone after menopause, adrenalectomy or dexamethasone treatment results in undetectable levels of serum testosterone. Compared with total testosterone, the measurement

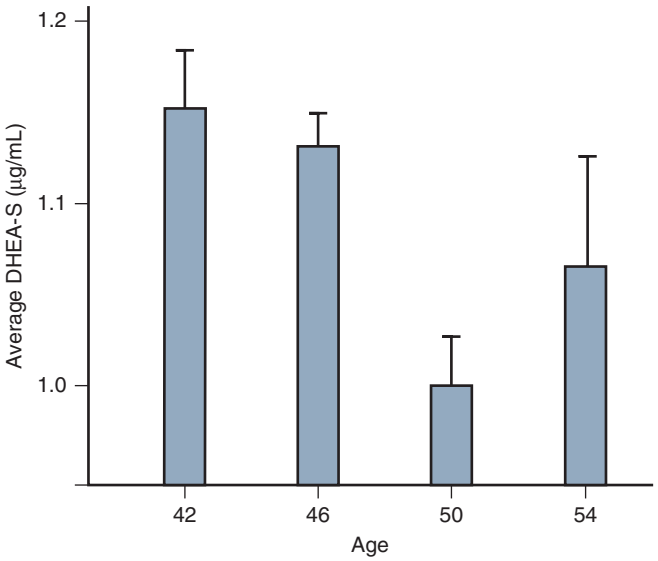


Fig. 14.11 Mean (± standard error) circulating dehydroepiandrosterone sulfate (DHEA-S) at each year of age of the entire study population before and after adjustment for age, current smoking, menopausal status, log body mass index (BMI), ethnicity, site, and the interaction between ethnicity and log BMI. (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.* 2002;87:3760-3767.)

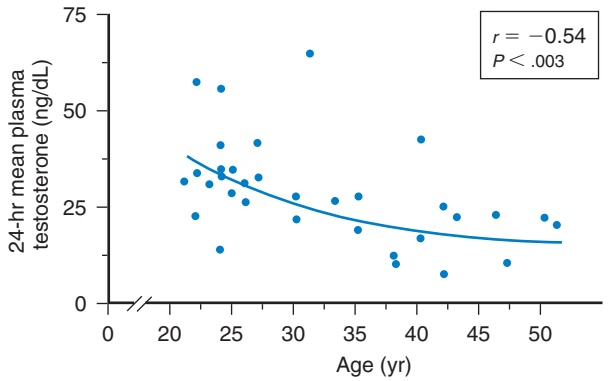


Fig. 14.12 The 24-hour mean plasma total testosterone (T) level compared with age in normal women. The regression equation was T (nmol/L) = 37.8 × age (years) − 1.12($r = -0.54$; $P < .003$). (Modified from Zumoff B, Strain GW, Miller LK, et al. Twenty-four hour mean plasma testosterone concentration declines with age in normal premenopausal women. *J Clin Endocrinol Metab.* 1995;80:1429.)

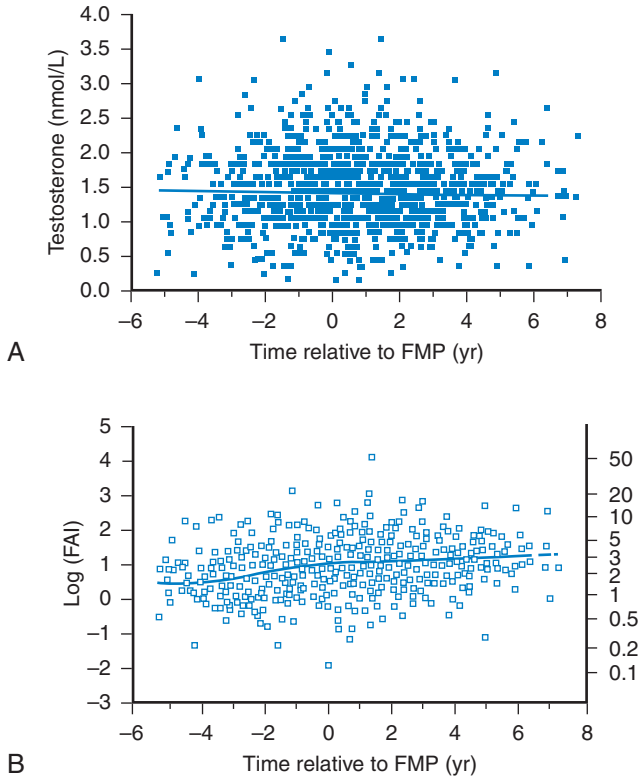


Fig. 14.13 A, Linear regression model: observed testosterone (T) and fitted levels of mean T across the menopausal transition. **B,** Double logistic model: observed free androgen index (FAI) and fitted levels of mean FAI across the menopausal transition. The left and right axes show FAI levels on the 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.* 2000;85:2832.)

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

Elevated gonadotropin (FSH/LH) levels arise from reduced secretion of E_2 and inhibin, as described earlier. Although some aging effects of the brain are likely to exist, there is abundant human evidence that menopause in women is an ovarian-induced event.

EFFECTS OF MENOPAUSE ON VARIOUS ORGAN SYSTEMS

Central Nervous System

The brain is an active site for estrogen action and estrogen formation. Estrogen activity in the brain is mediated via estrogen receptor (ER) α and ERβ. Whether or not a novel membrane receptor (non-ER α /ER β) exists is still being debated. However, both genomic and nongenomic mechanisms of estrogen action clearly exist in the brain. Fig. 14.14 illustrates the predominance of ER β in the cortex (frontal and parietal) and the cerebellum, based on work in rats. Although 17β E_2 is a specific ligand for both receptors, certain synthetic estrogens (e.g., diethylstilbestrol) have greater affinity for ERα, whereas phytoestrogens have a greater affinity for ERβ.

Estrogen has multiple actions on the brain, as reviewed by Henderson (Box 14.2); thus some important functions linked to estrogen 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*. *Hot flash* usually refers to the acute sensation of heat, and the flush or vasomotor episode includes changes in 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. **Prospective data suggest that the average time for persistence of bothersome hot flushes is 7.4 years** (Avis, 2015), and up to 42% of women aged 60 to 65 years have bothersome symptoms. In 10% to 15% of women, these symptoms are severe and disabling. In the United States the incidence of these episodes varies in different ethnic groups. Symptoms are greatest in Hispanic and black women, intermediate in white women, and lowest among Asian women (Fig. 14.15). The severity and persistence of hot flushes for 10 or more years may cause a series of "irregular" symptoms, such as irritability, which may affect quality of life (Oldervave, 1993) (Fig. 14.16). The fall in estrogen levels precipitate the vasomotor symptoms. It has been found that some women who experience hot flushes have a thermoregulatory disruption with a much narrower temperature range between sweating and shivering. Freedman has shown that the difference in temperature at which shivering occurs and when sweating occurs, termed the *thermoneutral zone*, is wide in asymptomatic women (Freedman, 2007). This zone is substantially more narrowed in symptomatic women, explaining their vulnerability to vasomotor symptoms (Fig. 14.17). Although these data have validity, our current **understanding of hot flush generation relates to the thermoregulatory region of the brain (**Fig. 14.18**),** which is innervated by afferent neurokinin-kisspeptin-dynorphin neurons. **With menopause these neurons swell and activate the thermoregulatory centers, triggering flush activity. This can be attenuated by estrogen, and more specifically by the use of NK3 receptor antagonists, which provide a therapeutic**

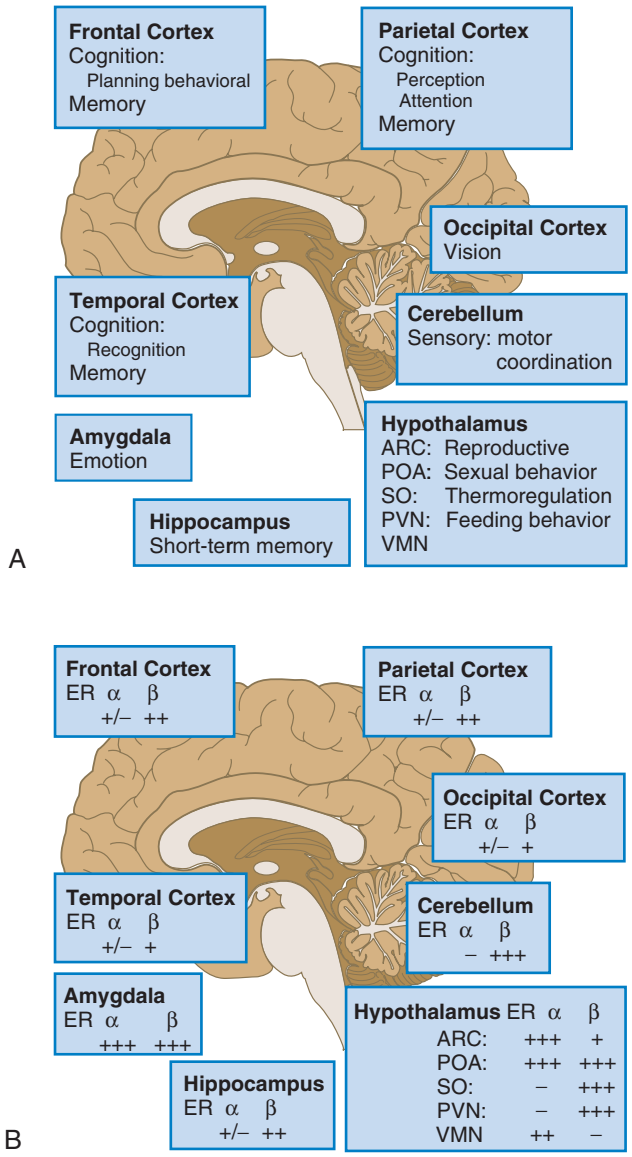


Fig. 14.14 A, Each region of the brain has an important role in specific brain functions. Optimal brain activity is maintained by means of the integration of different areas by neural tracts. **B,** Distribution of ERα and ERβ messenger RNA in the rat brain. *ARC,* Arcuate nucleus; *ER,* estrogen receptor; *POA,* preoptic area; *PVN,* paraventricular nucleus; *SO,* supraoptic nucleus; *VMN,* ventromedial nucleus. (**B,** Adapted from Cela V, Naftolin F. Clinical effects of sex steroids on the brain. From Lobo RA, ed. *The Treatment of the Post-menopausal Woman: Basic and Clinical Aspects.* 2nd ed. Philadelphia: Lippincott Williams & Wilkins; 1999:247-262.)

BOX 14.2 Effects of Estrogen on Brain Function

ORGANIZATIONAL ACTIONS

Effects on neuronal number, morphology, and connections occurring during critical stages of development

NEUROTROPHIC ACTIONS

Neuronal differentiation
Neurite extension
Synapse formation
Interactions with neurotrophins

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

NEUROTRANSMITTERS AFFECTED

Acetylcholine
Noradrenaline
Serotonin
Dopamine
Glutamate
Gamma-aminobutyric acid
Neuropeptides

EFFECTS ON GLIAL CELLS

PROTEINS INVOLVED IN ALZHEIMER DISEASE EFFECTED

Amyloid precursor protein
Tau protein
Apolipoprotein E

Modified from Henderson VW. Estrogen, cognition, and a woman's risk of Alzheimer's disease. *Am J Med.* 1997;103(Suppl 3A):11.

opportunity for nonhormonal treatment of hot flushes (Prague, 2017).

The flush has been well characterized physiologically. It results in heat dissipation, as witnessed by an increase in peripheral temperature (fingers, toes); a decrease in skin resistance, associated with diaphoresis; and a reduction in core body temperature (Fig. 14.19). **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,** but these occurrences are thought to be epiphenomena that result as a consequence of the flush and are not related to its cause. 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. Sleep efficiency is lower, and the latency to rapid eye movement (REM) sleep is longer in women with hot flushes compared with asymptomatic women. This disturbed sleep often leads to fatigue and irritability during the day, and 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 occurs in concert with physiologic measures of vasomotor episodes. The frequency of awakenings and hot flushes is reduced appreciably with estrogen treatment (Fig. 14.20).

In postmenopausal women, estrogen has been found to improve depressed mood regardless of whether or not this is a specific complaint (critics of some of this work point out that mood is affected by the symptomology and by sleep deprivation). Blinded studies carried out in asymptomatic women have also shown benefit. In an estrogen-deficient state such as occurs after menopause, a higher incidence of depression (clinical or subclinical) is often manifest. However, menopause per se does not cause depression, and although estrogen does generally improve depressive moods, it should not be used for psychiatric disorders. Nevertheless, very high pharmacologic doses of estrogen have been used to treat certain types of psychiatric depression.

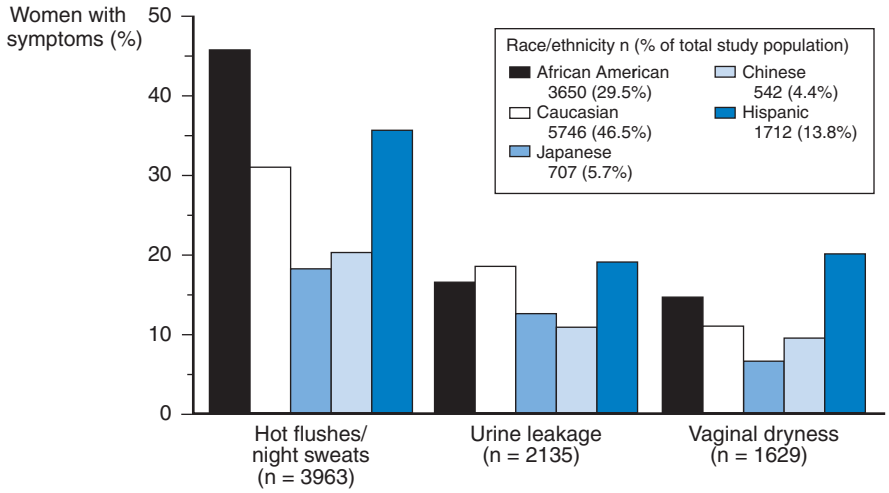


Fig. 14.15 The Study of Women's Health Across the Nation (SWAN). Symptom severity. (Modified from Gold EB, Sternfeld B, Kelsey JL, et al. Relation of demographic and lifestyle factors to symptoms in a multi-racial/ethnic population of women 40 to 55 years of age. *Am J Epidemiol.* 2000;152:463.)

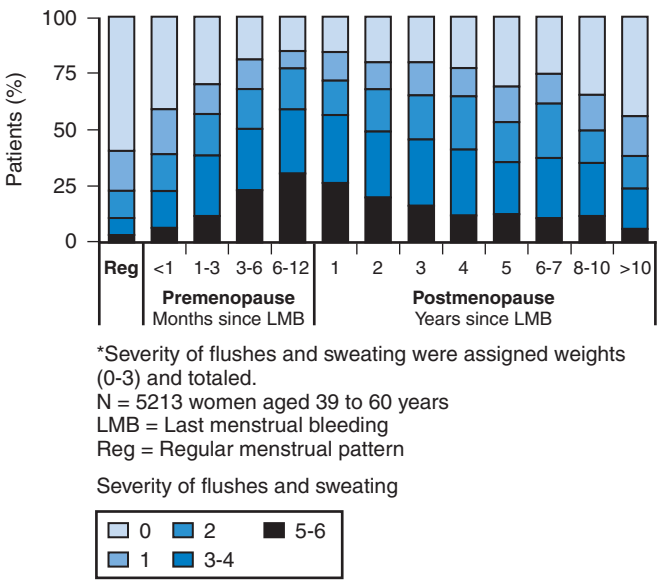


Fig. 14.16 Impact of menopause on well-being. (Modified from Oldenhave A, Jaszmann LJ, Haspels AA, et al. Impact of climacteric on well-being: a study based on 5213 women 39 to 60 years old. *Am J Obstet Gynecol.* 1993;168:772.)

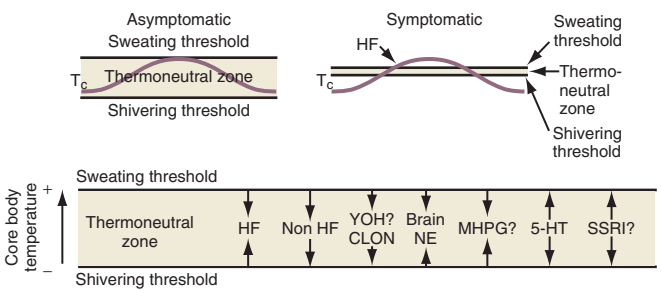


Fig. 14.17 Narrowing of the thermoregulatory zone in symptomatic women. *5-HT,* 5-Hydroxytryptamine; *HF,* Hot flush; *SSRI,* selective serotonin reuptake inhibitor. (Data from Freedman RR. Menopausal hot flashes. In: Lobo RA, ed. *Treatment of the Postmenopausal Woman.* 4th ed. New York: Academic Press; 2007:187-198.)

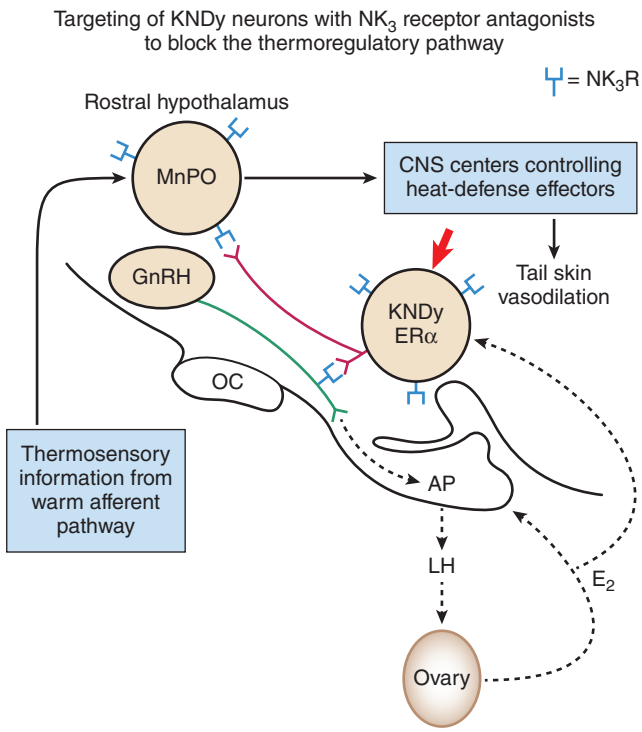


Fig. 14.18 Targeting the KNDy neuron with neurokinin 3 (NK3) receptor antagonists to block the thermoregulatory pathway, which has neuronal connections from the mid hypothalamus to the rostral hypothalamus where thermoregulatory control occurs (rat model). *CNS,* central nervous system; E_2, estradiol; *ER,* estrogen receptor; *GnRH,* gonadotropin-releasing hormone; *KNDy,* kisspeptin/neurokinin B/dynorphin; *LH,* luteinizing hormone. Modified from Mittelman-Smith MA, Williams H, Krajewski-Hall SJ, et al. Role for kisspeptin/neurokinin B/dynorphin (KNDy) neurons in cutaneous vasodilatation and the estrogen modulation of body temperature. *Proc Natl Acad Sci U S A.* 2012;109(48):19846-19851.

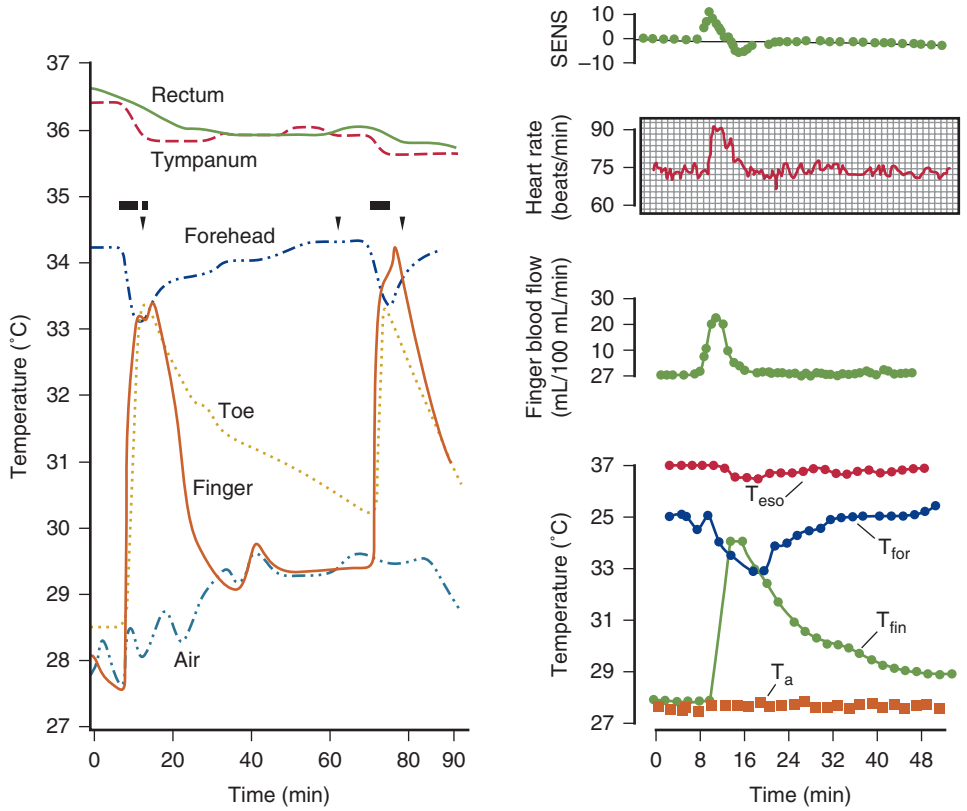


Fig. 14.19 Temperature responses to two spontaneous flashes and evoked flash. *Down arrow* indicates finger stab for blood sample. *Black bars* indicate time of flush. *SENS,* sensation; T_{fin}, temperature at various places on the body. (Data from Molnar GW: Body temperature during menopausal hot flushes. *J Appl Physiol.* 1975;38(3):499-303.)

Progestogens as a class generally attenuate the beneficial effects of estrogen on mood, although this effect is highly variable.

Cognitive decline in postmenopausal women is related to aging and to estrogen deficiency. The literature is somewhat mixed about whether there are benefits of estrogen in terms of cognition. **Studies have suggested that in natural menopause, there is an early decline in cognitive function at the onset of menopause, but this spontaneously improves over time,** (Greendale, 2009). **Verbal memory appears to be enhanced with estrogen** and has been found to correlate with acute changes in brain imaging, signifying brain activation. Dementia increases as women age, and the most common form of dementia is Alzheimer disease (AD). Box 14.2 lists several neurotropic and neuroprotective factors related 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, which is affected in AD. **Estrogen use after menopause appears to decrease the likelihood of developing or delaying the onset of AD according to several observational studies and meta-analyses.** However, once a woman is affected by AD, estrogen is unlikely to provide any benefit. Data from the Women's Health Initiative (WHI), however, suggested a lack of benefit of estrogen or estrogen/progestogen, or even a worsening of cognition, in women initiating hormonal therapy after age 65. This suggests that **timing of initiation of HT is critical**, and this has also been supported by basic science studies, which have found that early exposure to estrogen decreased the possibility of brain damage from free radicals and also promoted maintenance of neuronal and synaptic activity. However, prospective trials in younger women still have not been able to confirm the older observational data, suggesting a cognitive benefit of estrogen. Therefore this area remains somewhat inconclusive. In summary, **although early treatment with estrogen in younger women at the onset of menopause *may* be beneficial for cognition as it is with certain types of mood (although not proved yet), later treatment (e.g., after age 65) has no benefit and may even be detrimental, depending on the regimen of hormones used.**

Collagen and Other Tissues

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. 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**. 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 (Dunn, 1997). There is a possible bimodal effect with high doses of estrogen causing a reduction in skin thickness. The supportive effect of estrogen on collagen has

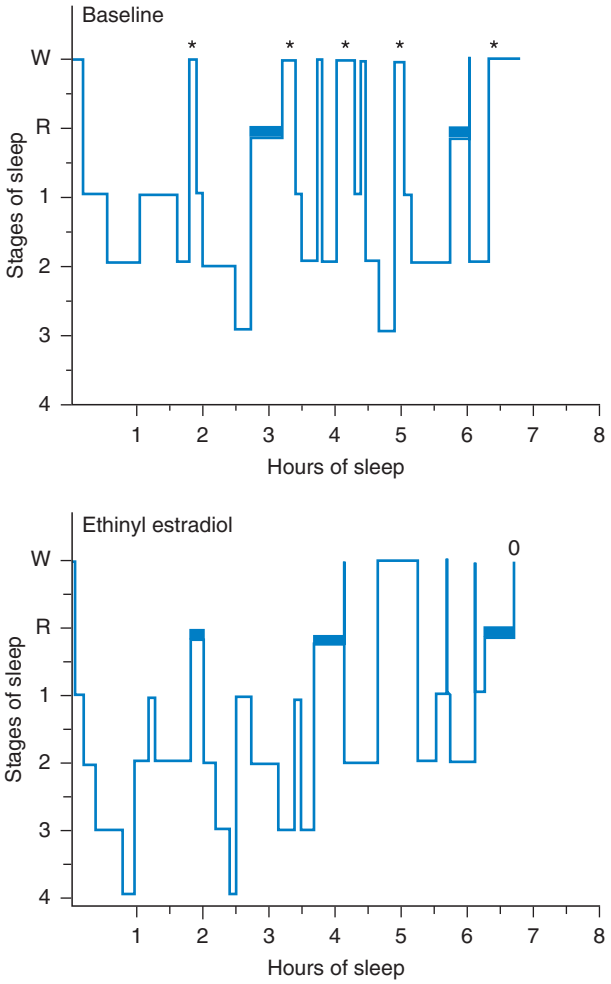


Fig. 14.20 Sleep grams measured in a symptomatic patient before and after a 30-day administration of ethinyl estradiol, 50 μg four times daily. (Modified from Erlik Y, Tataryn IV, Meldrum DR, et al. Association of waking episodes with menopausal hot flushes. *JAMA.* 1981; 245:1741.)

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 symptoms (Falconer, 1996). Vaginal estrogen has also been shown to reduce recurrent urinary tract infections. Symptoms of urinary incontinence and irritative bladder symptoms occur in 20% to 40% of perimenopausal and postmenopausal women. Uterine prolapse and other gynecologic symptoms related to poor collagen support, as well as urinary complaints, may improve with estrogen therapy. Although estrogen generally improves symptoms, urodynamic changes have not been shown to be altered. Estrogen has also been shown to decrease the incidence of recurrence of urinary tract infections. Restoration of bladder control in older women with estrogen has been shown to decrease the need for admission to nursing homes in Sweden. 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 (TGF-β) (Ashcroft, 1997).

Although still not completely settled, it appears that oral estrogen does not improve stress urinary incontinence in postmenopausal women and may even cause such symptoms in previously asymptomatic older women. Estrogen may, however, improve urge and other irritative urinary symptoms.

TABLE 14.2 Genitourinary Syndrome of Menopause (GSM): Symptoms and Signs

Symptoms	Signs
Genital dryness	Decreased moisture
Decreased lubrication with sexual activity	Decreased elasticity
Discomfort or pain with sexual activity	Labia minora resorption
Postcoital bleeding	Pallor/erythema
Decreased arousal, orgasm, desire	Loss of vaginal rugae
Irritation/burning/itching of vulva or vagina Dysuria	Tissue fragility/fissures/petechiae
Urinary frequency/urgency	Urethral eversion or prolapse Loss of hymenal remnants Prominence of urethral meatus Introital retraction Recurrent urinary tract infections
Supportive findings: pH > 5, increased parabasal cells on maturation index, and decreased superficial cells on wet mount or maturation index.	

Modified from Portman DJ, Gass MLS. Genitourinary syndrome of menopause: new terminology for vulvovaginal atrophy from the International Society for the Study of Women's Sexual Health and The North American Menopause Society. *Menopause.* 2014;21:1063-1068.

Genitourinary Syndrome of Menopause

Genitourinary syndrome of menopause (GSM) is now the accepted terminology and replaces terms such as atrophic vaginitis or vulvovaginal atrophy. The definition encompasses subjective and objective findings of the vulva, vagina, and lower urinary tract. The constellation of established symptoms and signs may be found in Table 14.2 (Portman, 2014).

Vulvovaginal complaints are often associated with estrogen deficiency. During 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. With this change, an increase in sexual complaints also occurs, with an incidence of dyspareunia of 41% in sexually active 60-year-old women. Estrogen deficiency results in a thin, paler vaginal mucosa. The moisture content is low, the pH increases (usually >5), and the mucosa may exhibit inflammation and small petechiae.

With estrogen treatment, particularly when used locally, vaginal cytologic changes have been documented, transforming from a cellular pattern of predominantly parabasal cells to one with an increased number of superficial cells. Along with these changes, the vaginal pH decreases, the vaginal blood flow increases, and the electropotential difference across the vaginal mucosa increases to that found in premenopausal women. Vaginal DHEA (0.25% to 1.0%) has been used with some suggested efficacy; the mechanism is presumed to be the local conversion of DHEA into estrogen, with possibly some other modulating effects as well (Heo, 2019).

Ospemifene 60 mg, a selective estrogen receptor agonist (SERM), has been approved as an oral treatment for vulvovaginal atrophy. This SERM has particular properties of acting as an agonist in the vagina and as an antagonist in other tissues such as the breast.

The approach to urinary symptoms will be addressed in different chapters.

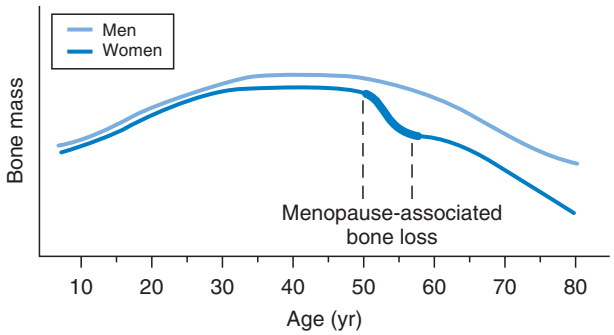


Fig. 14.21 Bone mass by age and sex. (Modified from Finkelstein JS: Osteoporosis. In: Goldman L, Bennet JC, eds. *Cecil Textbook of Medicine.* 21st ed. Philadelphia: Saunders; 1999:1366-1373; and Riggs BL, Melton LJ III. Involutional osteoporosis. *N Engl J Med.* 1986;314:1676.)

Bone Health

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 perimenopause from 1.5 years before menopause to 1.5 years after menopause, and 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. Loss of **trabecular bone** (spine) is greater with estrogen deficiency than is loss of **cortical bone**.

Postmenopausal bone loss leading to osteoporosis is a substantial health care problem. In Caucasian women, 35% of all postmenopausal women have been estimated to have osteoporosis based on BMD. Furthermore, the lifetime fracture risk for these women is 40%. The morbidity and economic burden of osteoporosis is well documented. Interestingly, some data 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. 14.21) is key to ensuring that the subsequent loss of bone mass with aging and estrogen deficiency does not lead to early osteoporosis. E_2 together with GH and insulin-like growth factor-1 act to double bone mass at the time of puberty, 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. Although 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.

However, even in men estrogen appears to be important for bone health in that in male individuals with aromatase deficiency (inability to convert androgen to estrogen) osteoporosis ensues (Carani, 1997).

Estrogen receptors are present in osteoblasts, osteoclasts, and osteocytes. Both ERα and ERβ are present in cortical bone, whereas ERβ predominates in cancellous or trabecular bone (Bord, 2001). However, the more important actions of E_2 are believed to be mediated via ERα. Estrogens suppress bone turnover and maintain a certain rate of bone formation. Bone is remodeled in functional units, called *bone multicenter units* (BMUs), where resorption and formation should be in balance. Multiple sites of bone go through this turnover process over time. Estrogen decreases osteoclasts by increasing apoptosis, thus reducing their life span. The effect on the osteoblast is less consistent, but E_2 antagonizes glucocorticoid-induced osteoblast apoptosis. Estrogen deficiency increases the activities of remodeling units, prolongs resorption, and shortens the phase of bone formation. It also increases osteoclast recruitment in BMUs, and thus resorption outstrips formation. The molecular mechanisms of estrogen action on bone involve the inhibition of production of proinflammatory cytokines, which increase with a decrease in estrogen at menopause, leading to increased bone resorption (Pacifici, 1996). These cytokines include interleukin-1, interleukin-6, tumor necrosis factor-α, colony-stimulating factor-1, macrophage colony-stimulating factor, and prostaglandin E_2, all of which may contribute to increased resorption. E_2 also upregulates TGF-β in bone, which inhibits bone resorption. Receptor activation of nuclear factor kappa B (NFκB) ligand (RANKL) is responsible for osteoclast differentiation and action. A scheme for how all these factors interact has been proposed (Fig. 14.22) (Riggs, 2000). In women, Riggs has suggested that bone loss occurs in two phases. With estrogen levels declining at the onset of menopause, an accelerated phase of bone loss, which is predominantly of cancellous bone, occurs. Approximately 20% to 30% of cancellous bone and 5% to 10% of cortical bone can be lost in a span of 4 to 8 years. Thereafter, a slower phase of loss (1% to 2% per year) ensues, during which more cortical bone is lost. This phase is thought to be induced primarily by secondary hyperparathyroidism. The first phase is also accentuated by the decreased influence of stretching or mechanical factors, which generally promotes bone homeostasis, as a result of estrogen deficiency. Genetic influences on bone mass are more important for the attainment of peak bone mass (heritable component, 50% to 70%) than for bone loss. Polymorphisms of the vitamin D receptor gene, TGF-β gene, and the Spl binding site in the collagen type 1 Al gene have all been implicated as being important for bone mass (Nguyen, 2000).

Bone mass can be detected by a variety of radiographic methods (Table 14.3). Dual-energy x-ray absorptiometry (DEXA) 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.

Various biochemical assays are also available to assess bone resorption and formation in both blood and urine (Table 14.4). At present, serum markers appear to be most useful for assessing changes, with antiresorptive therapy having less variability compared with the urinary assessments. Although these biochemical measurements cannot reliably predict bone mass, they may be useful as markers of the effectiveness of treatment. For example, an increased resorption marker may decrease within months into the normal range with an antiresorptive therapy, whereas it takes 1 to 2 years to see a change in BMD with DEXA.

Fracture risk is determined not only by bone mass but by many factors, the most important of which is bone strength. This in turn is determined by bone mass and by bone turnover, for which biochemical assessments may be helpful. **A research method employs a high-resolution quantitative computed tomography of bone, which is intended to provide a "virtual" bone biopsy.** This may be available in the future. **The World Health Organization (WHO) has made available an algorithm to predict the 10-year fracture risk of men and women living around the world. This model, called *FRAX,* can be assessed at www.shef.ac.uk/FRAX and is calculated based on individual patient history data and the results from DEXA.** Although there are other assessment tools as well, FRAX is perhaps the most used, but it requires a DEXA measurement. The FRAX tool is used as a rationale for pharmacologic therapy. For example, with osteopenia, if the FRAX score shows a **10-year risk of hip fracture of more than 3% or a 10-year risk of any other osteoporotic fracture of more than 20%, treatment should be initiated**.

In terms of the use of DEXA, U.S. Preventative Task Force guidelines suggest screening with DEXA at age 65 or older in

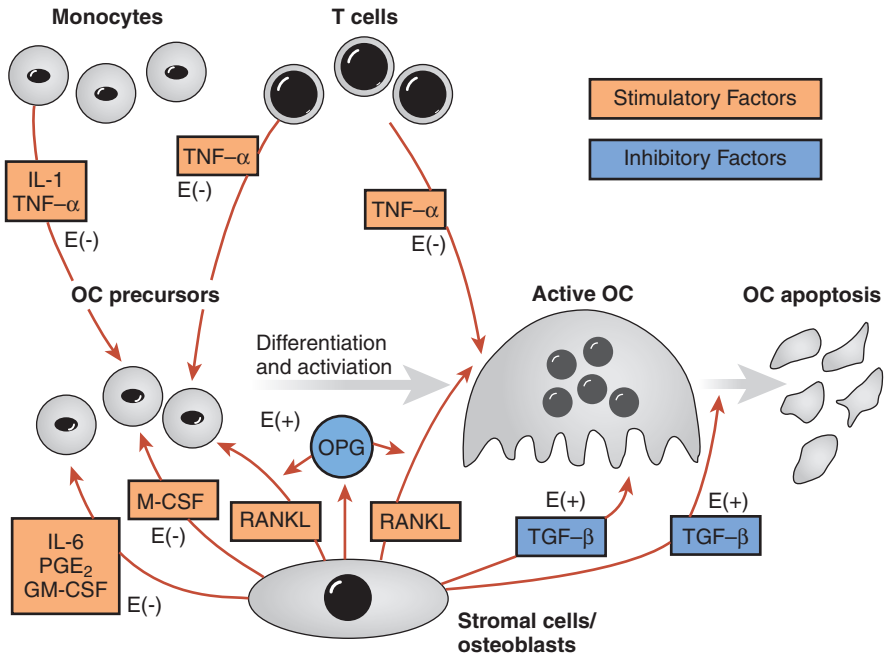


Fig. 14.22 Model for mediation of effects of estrogen *(E)* on osteoclast formation and function by cytokines in bone marrow microenvironment. Stimulatory factors are shown in orange and inhibitory factors are shown in blue. Positive (+) or negative (−) effects of E on these regulatory factors are shown 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,* macrophage colony-stimulating factor; *OC,* osteoclast; *OPG,* osteoprotegerin; *PGE_2*, prostaglandin E_2; *RANKL,* receptor activation of B ligand; *TGF-β*, transforming growth factor beta; *TNF-α*, tumor necrosis factor alpha. (Modified from Riggs BL. The mechanisms of estrogen regulation of bone resorption. *J Clin Invest.* 2000;106:1203.)

TABLE 14.3 Techniques for the Detection of Bone Mass

		Precision in	Examination and Analysis	Estimated
		Effective		
Technique	**Anatomic Site of Interest**	**Vivo (%)**	**Time (min)**	**Dose**
Equivalent (uSv)				
Conventional radiographs	Spine, hip 2000	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

Modified from van Kuijk C, Genant HK. Detection of osteopenia. In: Lobo RA, ed. *Treatment of the Postmenopausal Woman: Basic and Clinical Aspects.* 2nd ed. Philadelphia: Lippincott Williams & Wilkins; 1999:287-292.
NA, Not applicable.

all women and in younger women with traditional risk factors for fracture (U.S. Preventive Services Task Force, 2018). These traditional risk factors include advanced age, previous fracture, glucocorticoid therapy, parental history of hip fracture, low body mass, cigarette smoking, excessive alcohol use, rheumatoid arthritis and secondary osteoporosis as a result of factors such as hypogonadism/POI, malabsorption, and liver disease.

Many agents are now available for preventing osteoporosis. Guidelines for initiating treatment are history of a fracture, osteoporosis as determined on DEXA, or osteopenia with FRAX scores, as noted earlier. It is important to make a distinction about using various agents for the *prevention* of osteoporosis (e.g., in a woman who has risk factors and is osteopenic: T score greater than −2.5) as opposed to using drugs to *treat* established osteoporosis (T scores greater than −2.5).

TABLE 14.4 Bone Turnover Markers

Marker	Specimen
BONE RESORPTION MARKERS	
Cross-linked N-telopeptide of type I collagen (NTX)	Urine, serum
Cross-linked C-telopeptide of type I collagen (CTX)	Urine ($\alpha\alpha$ and $\beta\beta$ forms), serum ($\beta\beta$ form)
MMP-generated telopeptide of type I collagen (ICTP or CTX-MMP)	Serum
Deoxypyridinoline, free and peptide bound (fDPD, DPD)	Urine, serum
Pyridinoline, free and peptide bound (fPYD, PYD)	Urine serum
Hydroxyproline (OHP)	Urine
Glycosyl hydroxylysine (GylHyl)	Urine, serum
Helical peptide (HelP)	Urine
Tartrate resistant acid phosphatase	Serum, plasma
5b Isoform specific for osteoclasts (TRACP 5b)	
Cathepsin K (Cath K)	Urine, serum
Osteocalcin fragments (uOC)	Urine
Bone Formation Markers	
Osteocalcin (OC)	Serum
Procollagen type I C-terminal propeptide (PICP)	Serum
Procollagen type I N-terminal propeptide (PINP)	Serum
Bone-specific alkaline phosphatase (bone ALP)	Serum

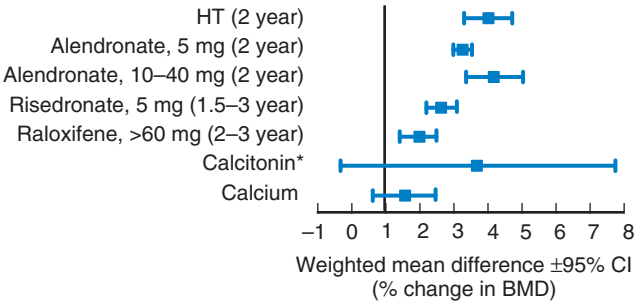


Fig. 14.23 Meta-analysis of osteoporosis therapies: total hip bone mineral density (BMD). *CI,* Confidence interval; *HT,* Hormone therapy. (From Cranney A, Guyatt G, Griffith L, et al. Meta-analyses of therapies for postmenopausal osteoporosis. IX: summary of meta-analyses of therapies for postmenopausal osteoporosis. *Endocr Rev.* 2002;23:570; data from Cranney A, Tugwell P, Wells G, et al. Meta-analyses of therapies for postmenopausal osteoporosis. I. Systematic reviews of randomized trials in osteoporosis: introduction and methodology. *Endocrine Rev.* 2002;23:496.)

The use of estrogen depends on whether there are other indications for estrogen treatment and whether there are any possible contraindications. Estrogen has been shown to reduce the risk of osteoporosis and to reduce osteoporotic fractures. A dose equivalent of 0.625 mg of conjugated equine estrogens (CEEs) was once thought to be necessary for the prevention of osteoporosis, but we now know that lower doses (0.3 mg of CEE or its equivalent) in combination with progestogens, or even with adequate calcium alone, can prevent bone loss, although there are no long-term fracture data with lower-dose therapy. Whether the addition of progestogens by stimulating bone formation increases bone mass beyond that produced by estrogen alone is unclear. The androgenic activity of certain progestogens such as norethindrone acetate (NET) also has been suggested to play a role by stimulating bone formation. Fig. 14.23 provides data on changes in BMD at the hip using various agents (Cranney, 2002). Companion figures from the same review (not shown) provide data on vertebral and other nonvertebral fractures. Although these data from an earlier meta-analysis have been updated, the graphic comparisons are basically unchanged. A more recent network meta-analysis suggests that for prevention of hip fracture, compared with placebo, only the following agents have efficacy: romosozumab, an anabolic agent (relative risk [RR], 0.44); alendronate (RR, 0.61); zoledronate (RR, 0.60); risedronate (RR, 0.73); denosumab (RR, 0.56), estrogen/progestogen (RR, 0.72); and calcium with vitamin D (RR, 0.81) (Barrionuevo, 2019).

SERMs such as **raloxifene**, droloxifene, and tamoxifen all have been shown to decrease bone resorption. Raloxifene has been shown to decrease vertebral fractures in a large prospective trial (Ettinger, 1999). All of these agents are used for *prevention*. In younger women, one complicating factor is that agents such as raloxifene may induce hot flushes; however, they do afford some protection for breast cancer risk because they act as estrogen antagonists at the level of the breast. SERMs such as raloxifene act as a low-dose estrogen and can prevent vertebral fractures but not hip fractures. **Tibolone** (structurally related to 19-nor progestins) has also been shown to be an effective treatment for the prevention of 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 as a result of its metabolites. The drug does not seem to cause uterine or breast cell proliferation and also is beneficial for vasomotor symptoms. It prevents osteoporosis and has been shown to be beneficial in treatment of osteoporosis as well at a dose of 2.5 mg daily.

Bisphosphonates have been shown to have a significant effect on the *prevention and treatment* of osteoporosis, using similar doses for both indications. With this class of agents (etidronate, alendronate, risedronate, ibandronate, and zoledronic acid), incorporation of the bisphosphonate with hydroxyapatite in bone increases bone mass. The skeletal half-life of bisphosphonates in bone can be as long as 10 years, and their effects on the skeleton are sustained for a few years after discontinuation, which does not occur with other agents. These agents reduce both spine and hip fractures (see Fig. 14.23). 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 (Cummings, 1998). Similar data are available for **risedronate** (35 mg weekly). **Ibandronate** has been approved as a once-a-month treatment (150 mg), and some data to date support the reduction in vertebral fractures. It can also be injected (3 mg) every 3 months. **Zoledronic acid 5 mg is available as an intravenous infusion** (over 15 minutes) once a year for the treatment of osteoporosis and every 2 years for prevention. **This class of medications has the property of causing esophageal irritation, and care must be taken in administering the oral doses in an upright position with a full glass of water.**

Some concern has been raised about bisphosphonates and osteonecrosis of the jaw, fractures of long bones such as the femur with long-term use, and atrial fibrillation. Jaw problems only occur with high doses when poor dentition is present. Femur

fractures with long-term use are extremely rare, and atrial fibrillation, although statistically increased with bisphosphonate use, is also rare. Nevertheless, we do not have long-term data (>10 years), and these drugs should not be used for more than 10 years and not with another antiresorptive agent. Their use in younger postmenopausal women (<60 years) should be limited unless there is significant osteoporosis present.

RANKL secreted by osteoblasts causes bone resorption (see Fig. 14.22). **Denosumab** is a monoclonal antibody that binds up RANKL, thus preventing bone resorption. It is an effective treatment for osteoporosis, and although it can also be used for prevention, it is largely viewed as a secondary agent, particularly for women intolerant to other treatments. Denosumab 60 mg is administered subcutaneously every 6 months, and it is effective both at the vertebrae and at the hip, with an efficacy that is similar to or greater than that of the bisphosphonates. Unlike the bisphosphonates, however, the effects wear off immediately after discontinuation of treatment. Although denosumab does not carry the small risks of jaw osteonecrosis and long bone fractures, as an immune therapy, long-term effects of immune modulation are not known.

Calcitonin (50 IU subcutaneous injections daily or 200 IU intranasally) has been shown to inhibit bone resorption, and vertebral fractures have been shown to decrease with calcitonin therapy. Long-term effects, however, have not been established, and this is not a first-line therapy today.

Fluoride has been used for women with osteoporosis because it increases bone density. 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.

Intermittent parathyroid hormone (PTH) (teriparatide, abaloparatide) is effective at increasing bone mass in women with significant osteoporosis. In a randomized trial lasting 3 years, average bone density increased in the hip and spine, with fewer fractures observed. This is a second-tier therapy reserved for severe cases of osteoporosis. Teriparatide at 20 μg needs to be injected subcutaneously on a daily basis for no longer than 18 months (Murad, 2012).

Romosozumab, mentioned earlier, an anabolic agent that is a **monoclonal antibody against sclerostin, is** now approved for the treatment of severe osteoporosis. Sclerostin is a product of osteocytes and inhibits bone formation; thus **romosozumab, as an antibody, increases bone formation and reduces fractures.** Like teriparatide, it is a second-line therapy in patients with an intolerance to other drugs and for severe osteoporosis. Romosozumab 210 mg injected subcutaneously once monthly performed as well as or better than teriparatide in head to head clinical trials.

Adjunctive measures for prevention of osteoporosis are calcium, vitamin D, and exercise.

It should be noted that with all the drug therapies noted here, women should not be deficient in calcium or vitamin D, and supplements are usually required.

Calcium with vitamin D, used together, has been shown to increase bone only in older individuals and was found to be better than placebo for preventing hip fractures in the meta-analysis reviewed earlier. However, this will not be sufficient to prevent bone loss in younger women at the onset of menopause, and these modalities alone are not thought to be effective for the treatment of osteoporosis. A woman's total intake of elemental calcium should be 1500 mg daily if no agents are being used to inhibit resorption, and 400 to 800 IU of vitamin D should also be ingested. Caution should be exercised in prescribing excessive calcium, particularly in older individuals, because this has been linked to coronary events. Exercise has been shown to be beneficial for building muscle and bone mass and for reducing falls.

There has been a realization that many women in the United States are **vitamin D deficient**, particularly those in the northern parts of the country because of less sunlight exposure. Vitamin D may also be important as an antimitotic agent that may prevent certain types of cancer. Although there is some controversy about what a normal vitamin D level should be, a blood level of 25-hydroxyvitamin D (25[OH]D) less than 30 ng/mL usually warrants supplemental treatment with 25(OH)D.

Although it is clear that women with established osteoporosis (fractures or a T score of −2.5 or greater) should receive an antiresorptive agent (usually a bisphosphonate), there is more controversy regarding initiating preventive strategies in patients with T scores in the osteopenia range (–1.0 to −2.5) unless there are significant risk factors, as noted earlier. Many women, however, may sustain fractures when in this range of T scores. Age and risk factors largely help determine the need to treat those with osteopenia. In this setting, depending on the age of the woman, her family history, and whether she has vasomotor symptoms, she may be offered HT, a SERM, or a bisphosphonate. **The FRAX algorithm should be used as a guide to therapy.**

DEGENERATIVE ARTHRITIS

Degeneration of intervertebral discs is a process that occurs rapidly after menopause. This is consistent with changes in collagen, as noted previously. There is evidence that this is benefited by estrogen after menopause.

Osteoarthritis is a source of significant distress. **Estrogen is powerful inhibitor of damage to chondrocytes**. The WHI study found that estrogen alone (but not combination hormone therapy) significantly decreased osteoarthritis. A 2018 Korean health assessment study showed that knee osteoarthritis was reduced by 30% in users of HT (Jung, 2018). However, much more work is needed in this area.

CARDIOVASCULAR EFFECTS

Women have a very low incidence of CVD before menopause, but after menopause the risk increases significantly. Data from the Framingham study have shown that the incidence is three times lower in women before menopause than in men (3.1 per 1000 per year in women ages 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 resulting from 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.**

Although CVD becomes more prevalent only in the later years after 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 two- to threefold, and oophorectomy before age 35 increases the risk sevenfold (Lobo, 2007).

When the possible reasons for the increase in CVD are examined, the most prevalent finding is an accelerated rise in total cholesterol in postmenopausal women. The changes of weight, blood pressure, and blood glucose with aging, although important, are not thought to be as important as the rate of rise in total cholesterol, which is substantially different in women after menopause 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 lipoprotein (a). High-density lipoprotein cholesterol (HDL-C) levels trend downward with time, but these changes are small and inconsistent relative to the increases in LDL-C.

Coagulation balance is not substantially altered as a counterbalance of changes occurs. Some procoagulation factors increase (factor VII, fibrinogen), but so do counterbalancing factors such

as antithrombin III, plasminogen, protein C, and protein S. 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. Most of these latter changes primarily are due to the fairly rapid reduction in estrogen levels, in that with estrogen all these parameters (generally) improve, and coronary arterial responses to acetylcholine are dilatory, with a commensurate increase in blood flow.

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, some membrane effects are mediated by estrogen.

Overall, the direct vascular effects of estrogen are considered to be as important, or more important, than the changes in lipid and lipoproteins after menopause. Although replacing estrogen has been thought to be beneficial for the mechanisms previously cited, these beneficial arterial effects may only be seen in younger (stage +1[a-c]) postmenopausal women (Fig. 14.24) (Mendelsohn, 2005). Women with significant atherosclerosis or risk factors such as those studied in secondary prevention trials, who have established atherosclerosis and prior coronary disease, do not respond well to this treatment because of coronary plaque burden (see Fig. 14.24), which prevents estrogen action. 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. Another mechanism is the significant conversion of cholesterol to 27-OH cholesterol, which also impedes estrogen's production of nitric oxide (Fig. 14.25).

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, although the data are mixed, and high doses of estrogen with or without progestogen cause a deterioration in insulin sensitivity. 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. Whether 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. Several trials including data from both hormonal trials of the WHI have shown a reduction in the development of diabetes with HT (Bonds, 2006; Lobo, 2014).

These consistently strong basic science and clinical data for the protective effects of estrogen on the cardiovascular system together with strong **epidemiologic evidence for a protective effect of estrogen** (Fig. 14.26) led to the belief that estrogen should be prescribed to prevent CVD in women. Clinical trial data, however, have refuted this notion in women with established disease, as noted previously. **Results from several randomized trials in women have failed to show a protective effect in women with established coronary disease**. Furthermore**, a trend toward increased cardiovascular events (early harm) has been observed in this setting** in some women within the first 1 to 2 years. The WHI trial, which compared CEE/medroxyprogesterone acetate (MPA) with placebo, came to similar conclusions. Though considered to be a primary prevention trial, it studied participants in a large range of ages (mean age 63). These women did not have vasomotor symptoms and

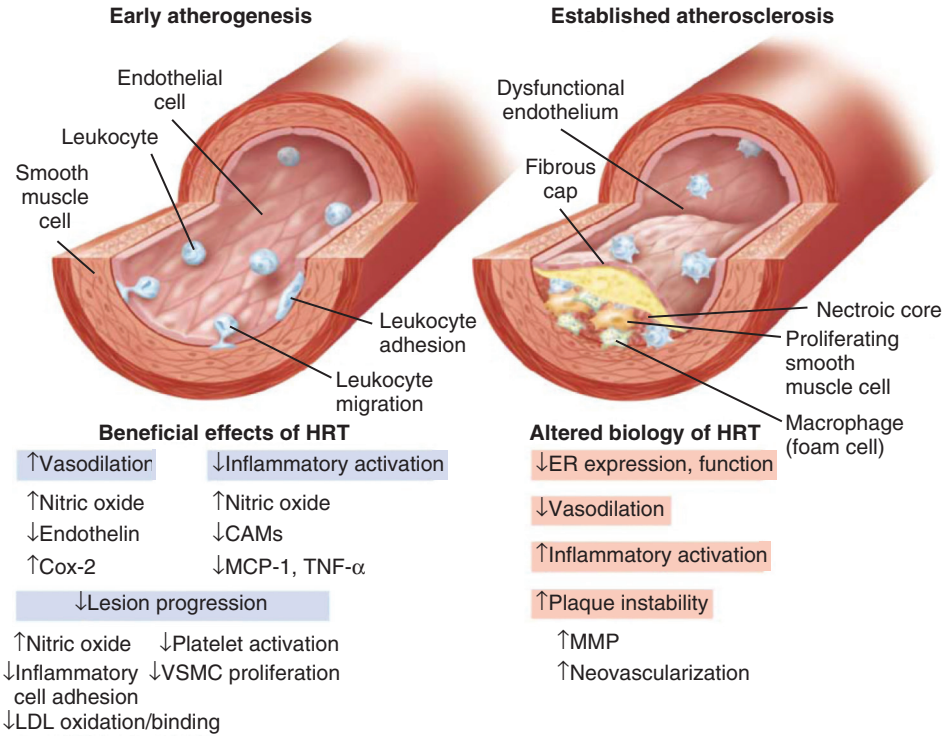


Fig. 14.24 Mechanisms of benefit of hormonal therapy with estrogen in early menopause (relatively clean coronary vessels) and the lack of effect in older women and those with significant atherosclerotic plaque burden. *CAM,* Cellular adhesion molecule; *Cox-2,* cyclooxygenase 2; *ER,* estrogen receptor; *HRT,* hormone replacement therapy; *LDL,* low-density lipoprotein; *MCP-1,* Macrophage chemoattractant protein -1; *MMP,* matrix metalloproteinase; *TNF-α*, tumor necrosis factor alpha; VSMC, vascular smooth muscle cell. (From Mendelsohn ME, Karas RH. Molecular and cellular basis of cardiovascular gender differences. *Science* 2005;308(5728): 1583-1587.)

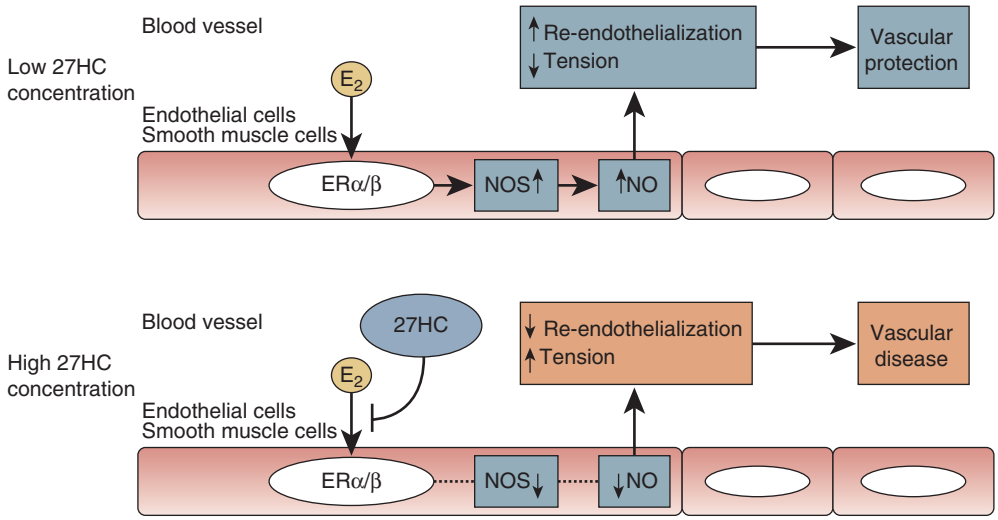


Fig. 14.25 Hypothesis of how elevated (27-hyroxycholesterol, 27HC) can influence the effect of estradiol (E_2). *ER,* Estrogen receptor, *NO,* nitric oxide, *NOS,* nitric oxide synthetase. (From Umetani M, Domoto H, Gormley AK, et al. 27-Hydroxycholesterol is an endogenous SERM that inhibits the cardiovascular effects of estrogen. *Nat Med.* 2007;13(10):1185-1192.)

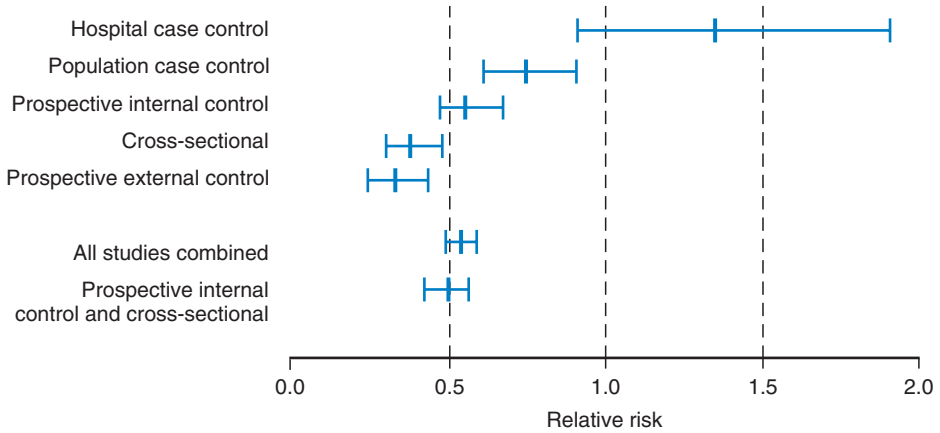


Fig. 14.26 Estrogen replacement therapy and coronary heart disease. Relationship between relative risk and study type. (Modified from Stampfer MJ, Colditz GA. Estrogen replacement therapy and coronary heart disease: a quantitative assessment of the epidemiologic evidence. *Prev Med.* 1991;20:47.)

had more risk factors than the healthy women studied in observational cohorts, as shown in Fig. 14.26.

The protective effect of estrogen demonstrated in the observational trials such as the Nurse's Health Study (NHS) (see Fig. 14.26) occurred predominantly in young, healthy, symptomatic women. Table 14.5 compares the demographics of the participants of the WHI and the NHS. Trials carried out in a monkey model have shown 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. 14.27). This has been called the *timing hypothesis*, in which early intervention shows benefit and late intervention with hormonal therapy is possibly harmful for the cardiovascular (CV) system. This has been shown in clinical trial data (see later) and also pertains to the beneficial effects of estrogen on glucose tolerance and insulin sensitivity.

The perception of coronary harm and other risks in older women receiving combined CEE/MPA in WHI led to widespread confusion and concern about HT in general and led to most women stopping HT and not starting it even when there were significant symptoms. As will be discussed later, **more** recent **data now have confirmed that HT is safe for young, healthy women, and it is particularly indicated in women**

TABLE 14.5 Demographics of Women in WHI and NHS

	WHI	NHS
Mean age or age range at enrollment (years)	63	30-55
Smokers (past and current)	49.9%	55%
Body mass index (BMI: mean)	28.5 kg/m^2	25.1 kg/m^2
Aspirin users	19.1%	43.9%
Menopausal symptoms	Rare	Common

NHS, Nurse's Health Study; *WHI,* Women's Health Initiative.

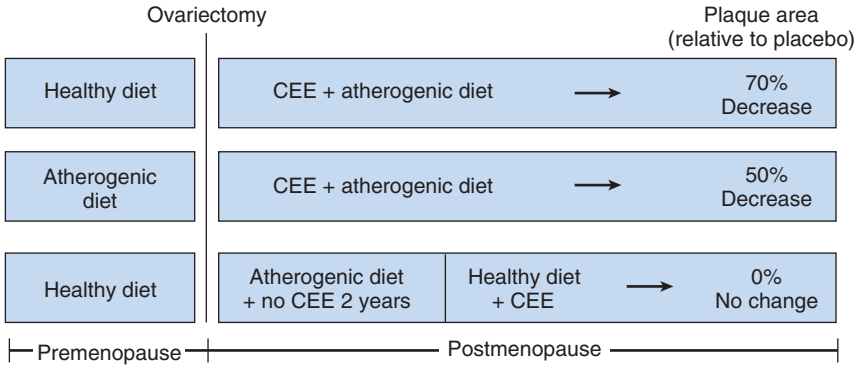


Fig. 14.27 Importance of timing of intervention on the effect of estrogens on atherogenesis in nonhuman primates. *CEE*, Conjugated equine estrogen. (Modified from Clarkson TB, Anthony MS, Jerome CP. Lack of effect of raloxifene on coronary artery atherosclerosis of postmenopausal monkeys. *J Clin Endocrinol Metab*. 1998;83:721; data from 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*. 1997;17:217; 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*. 2001a;86:41; and Williams JK, Anthony MS, Honore EK, et al. Regression of atherosclerosis in female monkeys. *Arterioscler Thromb Vasc Biol*. 1995;15:827.)

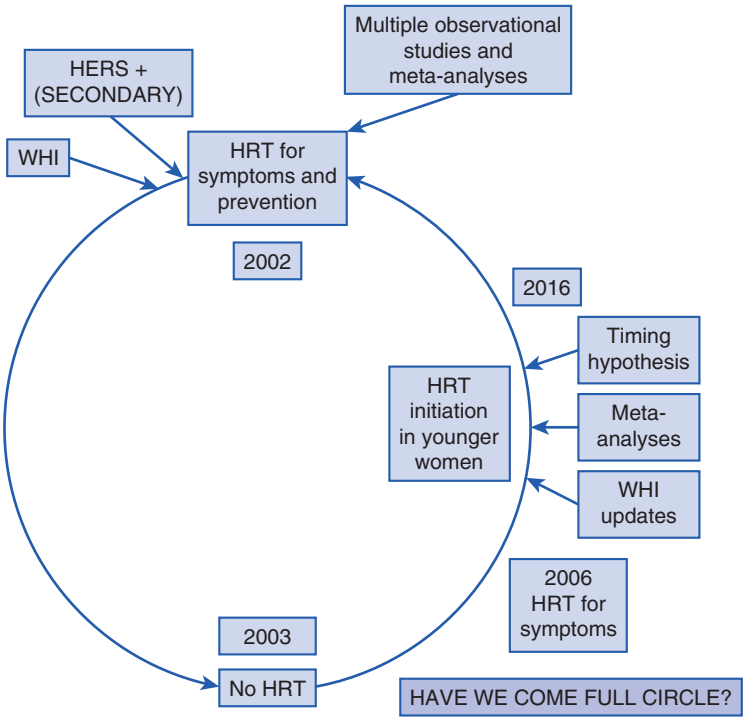


Fig. 14.28 Diagrammatic depiction asking whether we have come full circle in the prescribing of hormone replacement therapy (HRT). HRT use before 2002, based on strong epidemiologic data and meta-analyses, was for symptom control and prevention. HRT use essentially stopped soon thereafter. Some limited use for symptoms began again around 2006. The suggestion in the figure is that the use should be coming around full circle based on new data as depicted by the arrows. *HERS*, Heart Estrogen/progestin Replacement Study; *WHI*, Women's Health Initiative. (From 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 2016;254:282-290.)

with symptoms. It appears we have come full circle as many of the original concepts of cardioprotection and reduction in all-cause mortality with estrogen have been once again confirmed from the randomized trials, when one examines the effects in younger women close to menopause (Lobo, 2016) (Fig. 14.28). However, what we have learned from the WHI is that although younger women benefit, older women do not (the timing hypothesis) and may endure harm, as several secondary prevention trials (in women with established coronary disease) have shown. No clear explanation exists for what may cause the observed "early harm," but these effects were not observed in those women receiving statins concurrently. This finding suggests that HT (in the doses used) may lead to plaque destabilization and thrombosis in some women with established (although possibly

silent) coronary disease. The molecular mechanisms for this effect may be due to estrogen upregulating matrix metalloproteinase-9 and inhibiting its natural inhibitor within the mural area of the plaque; the resultant disruption of the gelatinous covering then leads to thrombosis. The antiinflammatory effects of statins inhibit this process. Additional lessons learned from WHI and more recent data are findings that **estrogen** is what is protective, and **progestogens**, depending on the type and dose, are likely to attenuate or eliminate any protective effect and also may be implicated in the risk of breast cancer.

What Are the Current Data on the Effects of Estrogen and Estrogen/Progestogen on the Cardiovascular System?

Data from WHI first reported that the younger women, aged 50 to 59, receiving CEE alone had a significantly reduced coronary score. In 2007 the WHI reported that women aged 50 to 59 receiving CEE and CEE/MPA (combined analysis) had a significant 30% reduction in all-cause mortality (Rossouw, 2007). Subsequently pooled analyses of prospective studies, including data from the WHI, showed a statistical benefit in the reduction of coronary disease with estrogen in women less than 10 years from menopause or younger than age 60 years. A Bayesian meta-analysis (looking at retrospective and prospective studies) showed consistent data for a reduction in all-cause mortality of about 30% in younger women receiving hormonal treatment (Salpeter, 2009) (Fig. 14.29).

As discussed previously, the 13-year follow-up data from the WHI, including the intervention and follow-up phases of the trial, showed a significant benefit in younger women receiving CEE alone (Manson, 2013) (Fig. 14.30). The data with CEE/MPA were in the same direction for mortality but were less robust. These data have been updated for 18 years of follow-up, but the data have not changed in any substantial way. The most recent follow-up data regarding estrogen alone in younger women, at this writing, suggests an additional benefit for women who had experienced a bilateral salpingo-oophorectomy (Manson, 2019). Mortality at the 18-year follow-up was substantially and significantly lower in users of estrogen.

Several prospective trials in younger women deserve some discussion. A prospective trial in Denmark of 1000 recently postmenopausal women who received E_2 alone or E_2 and norethindrone (in women with a uterus) or no treatment for up to 10 years, with follow-up for up to 16 years, showed significant coronary benefit (Schierbeck, 2012). Cardiovascular death, myocardial infarction, and hospitalizations for congestive heart failure were significantly reduced in users of HT (Fig. 14.31). ELITE tested the "timing" hypothesis by treating women who were within 6 years of menopause and another group of women who were more than 10 years past menopause. Oral E_2 1 mg or placebo was used in both groups, with vaginal progesterone for endometrial protection. The primary endpoint was carotid intima media thickness, which was significant reduced in recently menopausal women but not in the older women, confirming the hypothesis (Hodis, 2014) (Fig. 14.32).

A Cochrane analysis reviewed cardiovascular (CV) and overall mortality with HT and found no change in mortality when all ages and both primary and secondary prevention trials were combined (Boardman, 2015). **However, in women less than 10 years from menopause the data were consistent with findings noted previously, with significant protective effects of 30% in all-cause mortality and 40% to 50% protection from CV mortality**. However, a significant increase was noted in venous thromboembolism (VTE), which is well known to occur with oral therapy (as also occurs with oral contraceptives) but does not affect mortality. Stroke was not affected in this younger population. The complications of VTE and potentially of ischemic stroke are discussed later.

The two risk areas for CVD, even in younger women, at least potentially, are VTE and ischemic stroke. **It is now accepted that there is a two- to threefold increase in venous thrombosis risk with oral hormonal therapy**. However, the prevalence of this risk is low, particularly in young, healthy women. This two- to threefold risk is similar to that with the use of oral contraceptives. For pulmonary embolism risk, in women aged 50 to 60 years, the background risk is approximately 10 to 20 events per 100,000 woman-years. Thus with HT the twofold increase may result in 40 events per 100,000 woman-years, which is less than the rate in normal pregnancy (approximately 60/100,000 women). This risk is related to age, weight, dose, and route of administration of estrogen. It has also been suggested that some progestogens increase this risk further, although this has not been established. Most events (deep vein thrombosis or pulmonary emboli) occur early (within the first year) and decrease thereafter, suggesting an aberrant thrombophilic interaction with oral estrogen. The risk has been found not to be increased with transdermal estrogen (Canonico, 2008) (Fig. 14.33), which warrants consideration of the use of transdermal therapy in more high-risk women (e.g., those with obesity or hypertension).

Stroke (ischemic, not hemorrhagic) was found to be increased in the WHI trials (both HT and estrogen therapy [ET]). There was an approximately 30% increase over the 5 to 6 years of the trial, but this outcome was confined primarily to older women in the trial. These data are similar to data from the NHS trial where even younger women had a very small but statistically increased risk of ischemic stroke with standard doses of oral estrogen. The increase in younger women is extremely small and may not be statistically significant. In the 13-year follow-up data from the WHI (Manson, 2013) and in the Cochrane review (Boardman, 2015), stroke was not significantly increased in the younger age groups. Thus although a rare event, ischemic stroke risk may be increased in women taking standard doses of oral estrogen (women using CEE at 0.625 mg or more) but not with lower doses (e.g., CEE 0.3 mg). Similarly, transdermal therapy has not been associated with an increased risk. These and other data point to a thrombotic risk with oral estrogen (in susceptible women). The mechanism of ischemic stroke risk in younger women is not likely to be due to atherosclerosis, as it is in coronary disease in older women, but is due to acute thrombosis (Lobo, 2011) (Fig. 14.34). The thrombosis risk in younger women, much like the risk of venous thrombosis, likely is due to an aberrant interaction of estrogen with thrombotic factors, at times because of an underlying thrombophilia.

In summary, there should be no concern regarding increased cardiovascular risk for young, healthy women at the onset of menopause who are contemplating HT for treatment of symptoms. In this setting there is no evidence of increased risk, and indeed these women may be found to benefit from a cardiovascular standpoint.

CANCER RISKS IN POSTMENOPAUSAL WOMEN

Just as CVD is a concern for women after menopause, the risk of cancer also increases with time after menopause, but this is a function of aging and not a consequence of menopause per se. ***Prevention*** requires healthy lifestyle measures and screening for early detection, which will be emphasized again later in the chapter.

Although breast cancer is generally believed to be the leading cause of death in postmenopausal women, in fact it is lung cancer. Indeed, mortality from breast cancer tends to decrease after menopause, on an age-specific basis, but cardiovascular mortality increases, and these lines transect around the time of menopause (Fig. 14.35). The gynecologist should be well

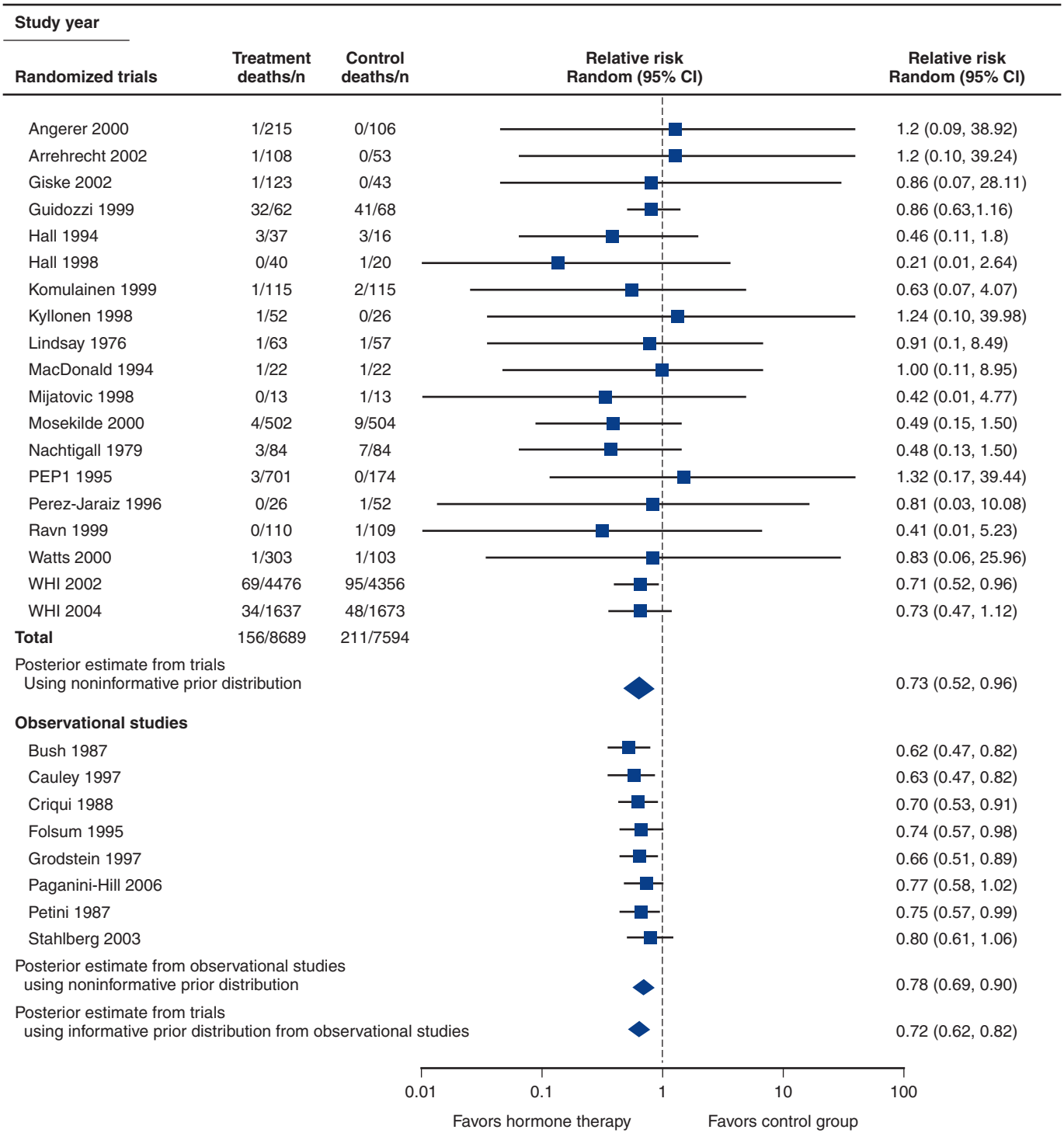


Fig. 14.29 Bayesian meta-analysis of reduction in mortality with hormone therapy in younger women. *CI,* Confidence interval; CI, confidence interval; *PEP1,* Postmenopausal Estrogen/Progestin Interventions study; *WHI,* Women's Health Initiative. (Modified from Salpeter SR, Cheng J, Thabane L, et al. Bayesian meta-analysis of hormone therapy and mortality in younger postmenopausal women. *Am J Med.* 2009;122(11): 1016-1022.)

versed in the epidemiology of and preventive strategies for breast, lung, cervical, endometrial, ovarian, and colorectal cancer. Further discussions of these cancers may be found in Part IV (Gynecologic Oncology) of this text. What follows is a discussion of the potential effects of HT on endometrial, breast, ovarian, and colorectal cancer.

Endometrial cancer is a common cancer in postmenopausal women and is increased in women using **unopposed estrogen therapy**. Although a woman's risk for endometrial cancer with unopposed estrogen use is two- to eightfold higher than that for the general population, precursor lesions (primarily endometrial hyperplasia) signal the presence of an abnormality in most

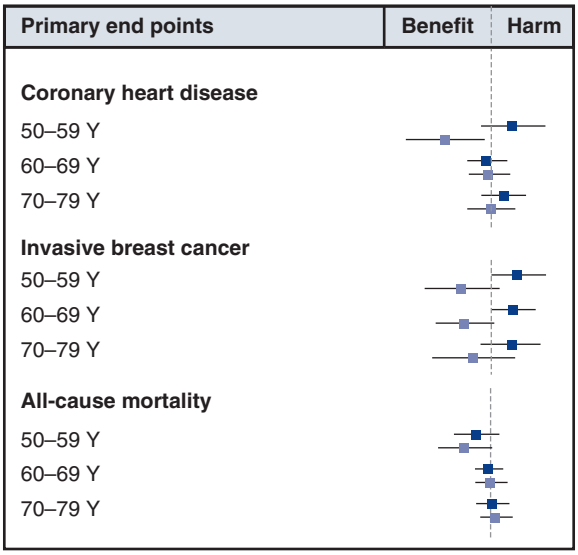
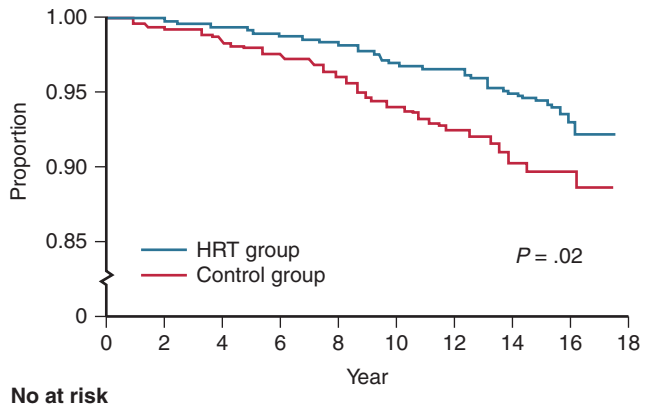


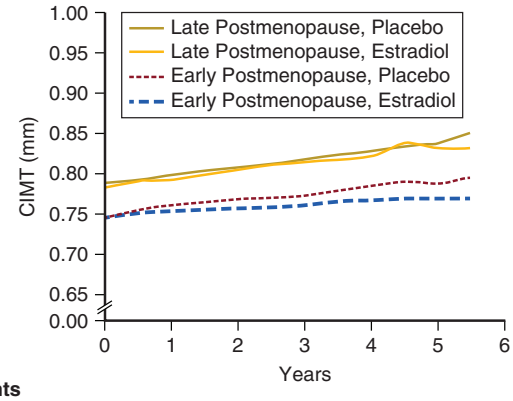
Fig. 14.30 Cumulative 13-year follow-up data, intervention and follow-up phases with conjugated equine estrogen (CEE) and CEE/medroxyprogesterone acetate (MPA) arms of the Women's Health Initiative in different age groups *(CEE, light blue; CEE/MPA, dark blue).* (Modified from Manson JE, Chlebowski RT, 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(13):1353-1368, 2013.)



No at risk

HRT	502	502	498	496	483	487	484	477	155
Control	504	502	497	492	484	475	466	455	90

Fig. 14.31 Sixteen-year follow-up of women randomly allocated to hormone therapy (HT) showing a reduction in death, heart failure, and myocardial infarction (MI). (Modified from Schierbeck IL, Renmark L, Tofteng CL, et al. Effect of hormone replacement therapy on cardiovascular events in recently postmenopausal women: randomized trial. *BMJ.* 2012;345:e6409.)



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

Fig. 14.32 Carotid intima media thickness (CIMT) changes in younger and older postmenopausal women treated with estradiol versus placebo (the ELITE trial). Younger women, but not older women, with *early* initiation of estradiol had significant attenuation of CIMT. (From Hodis HN, Mack WJ, Henderson VW, et al. Vascular effects of early versus late postmenopausal treatment with estradiol. *N Engl J Med.* 2016;374: 1221-1231.)

patients, and the cancer is usually well differentiated and hormonally responsive, as are hyperplasias.

One study showed that the risk of endometrial hyperplasia was 20% after 1 year of using 0.625 mg of oral CEE. In another study, the 3-year postmenopausal Estrogen/Progestin Interventions Trial, this risk of hyperplasia 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 risk. Use of CEE alone at 0.3 mg/day for 2 to 3 years results in a hyperplasia risk of 5% to 10%. With the same dose of esterified estrogens (which are less potent), no hyperplasia was found after 2 years.

The risk for endometrial cancer in women taking estrogen and progestogen is similar to that of women in the general population because combination therapy merely eliminates the excess risk attributed to estrogen; a few studies, however, have suggested a lower risk of endometrial cancer with **continuous combined hormone treatment**. It is important to remember that some endometrial cancers occurring in postmenopausal women are not hormonally related; thus some women may develop a **serous** type of cancer (poorly differentiated) while on HT, making continuous surveillance important. It could be argued that these serous cancers, which are usually receptor negative, may have arisen independently of HT use.

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. 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.

Risk of Breast Cancer With Estrogen Use

Several studies and meta-analyses have shown a borderline or small statistical increase in the risk of breast cancer (RR, l.2 to l.4) after approximately 5 years of estrogen use. This risk is related to the dose of estrogen and to duration of use. Data have pointed to the addition of progestogen as a major contributor to this increased risk of breast cancer. A 2019 meta-analysis did not reach different conclusions, but several important papers were missing from this analysis. (Collaborative Group, 2019). There is some biologic plausibility to this notion in that progesterone in the normal luteal phase increases breast mitotic activity and HT increases mammographic tissue density relative to ET alone. Several small case-control studies found no increase with ET alone, but the same studies showed a statistically significant increase with progestogen use (in the range of a 1.3 or l.4 RR). In the WHI trial, the increase

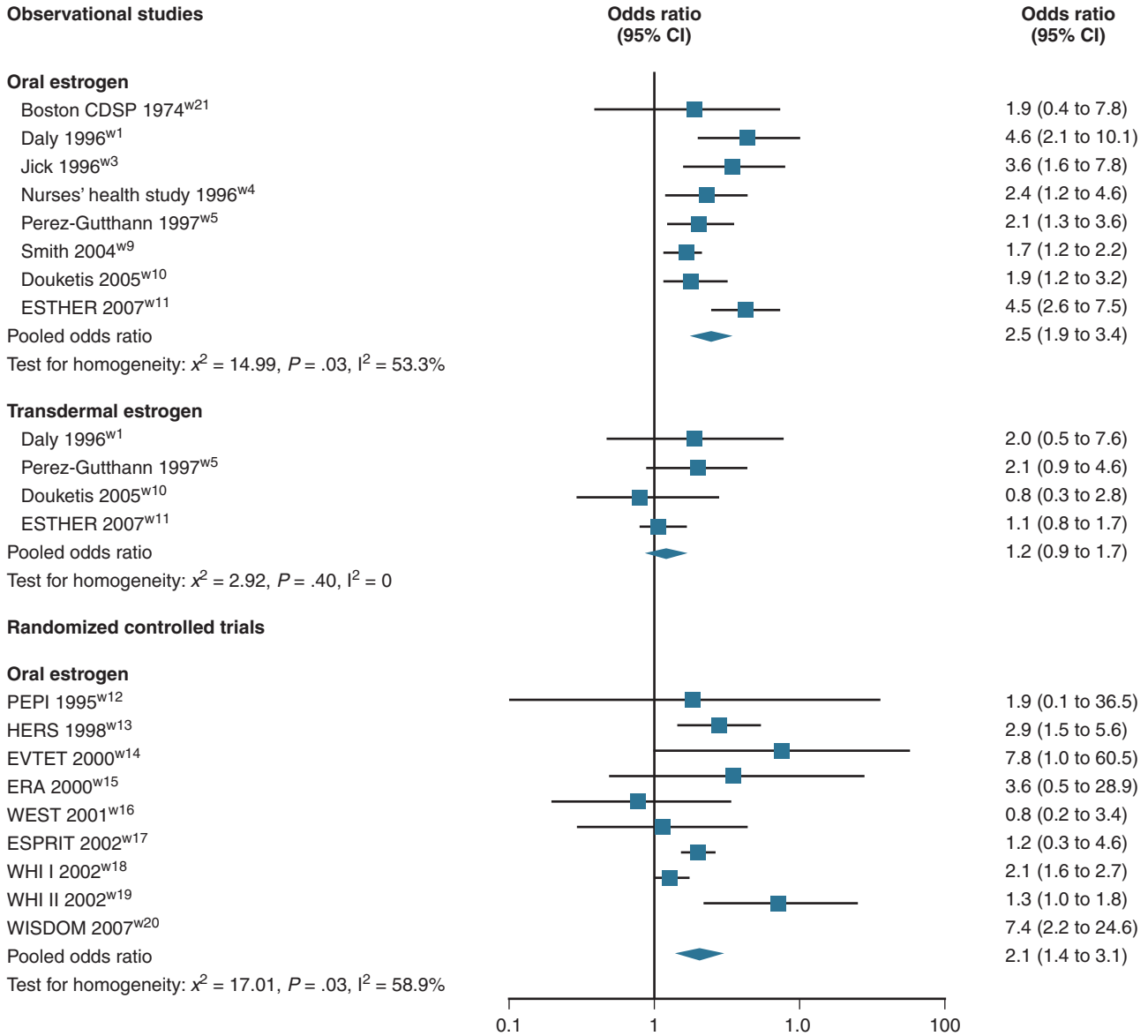


Fig. 14.33 Meta-analysis of various studies showing no increased risk of thrombosis with transdermal therapy. *CI,* Confidence interval; *w,* week. (Modified from Canonico M, Plu-Bureau G, Lowe GD, et al. Hormone replacement therapy and risk of venous thromboembolism in postmenopausal women: systematic review and meta-analysis. *BMJ.* 2008;336(7655):1227-1231.)

in breast cancer risk was of borderline significance with CEE/MPA (hazard ratio [HR], 1.24 [1.01 to 1.54]). A reanalysis by Anderson and coworkers found that when correcting for variables known to affect breast cancer risk, the average risk was no longer statistically significant: 1.20 (0.94 to 1.53) (Anderson, 2006). It is important to note that the total duration of therapy is very important for the risk with estrogen/progestogen therapy. In the WHI trial the significant increase over 5 years was only found in prior users of HT, suggesting a longer cumulative effect. *There was no statistical increase over 5 years with CEE/MPA in women in the WHI trial who had not used HT in the past* (Anderson, 2006). A large collaborative case-control study also has shown that continuous combined estrogen-progestogen therapy is associated with increased breast cancer risk over time.

The effect of estrogen/progestogen therapy and breast cancer risk is thought to be one of promotion, rather than carcinogenesis per se. Occult breast tumors are extremely common in breast tissue and take up to 10 years of slow growth to be clinically detectable. It has been suggested that certain doses of estrogen, and particularly estrogen/progestogen therapy, stimulate the growth of these occult receptor positive tumors, which shortens the time to clinical detection, thus allowing them to be recognized as a consequence of HT. Using the modeling of growth kinetics by Santen and applying these numbers to findings in the WHI lends credence to this notion (Santen, 2012).

In the estrogen-only arm of the WHI, after 6½ years there was a borderline significant ***decrease* in breast cancer risk** (HR, 0.77 [0.59 to 1.01]). In a more complete analysis of these findings, Stefanick and associates found the risk to be significantly decreased for ductal cancer (0.71 [0.52 to 0.99]), and **in a sensitivity analysis among adherent women, the decrease was statistically significant (0.67 [0.47 to 0.9])** (Stefanick, 2006) (Fig. 14.36). Thus although it is unclear why there should be a decrease in breast cancer risk, we may conclude that standard-dose ET

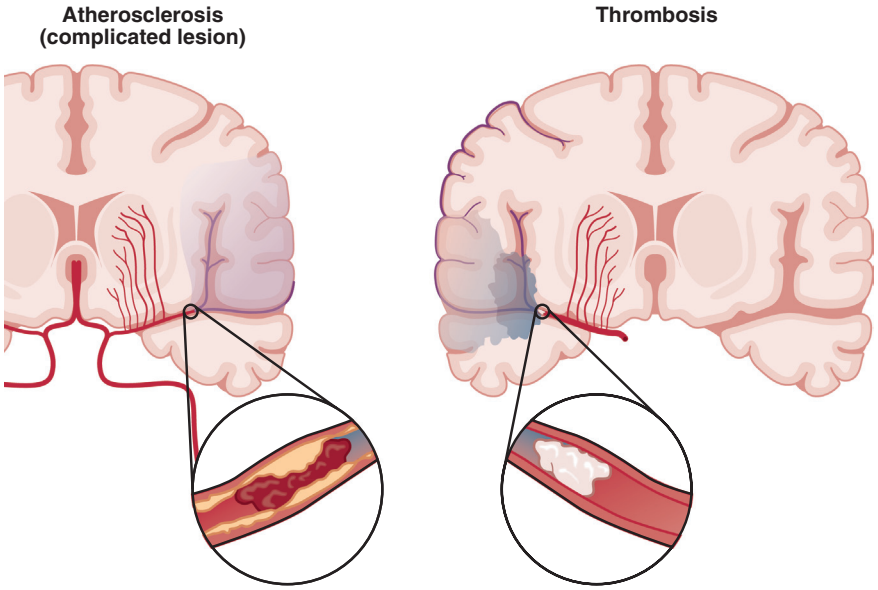


Fig. 14.34 Mechanisms of ischemic stroke risk with estrogen in older women as a result of atherosclerosis with complicated lesions *(left)* and as a result of thrombosis in younger women *(right)*.

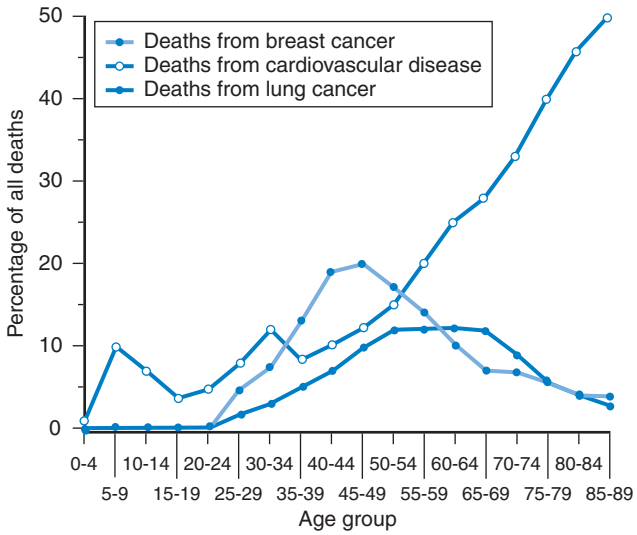


Fig. 14.35 Risks of breast cancer and lung cancer versus cardiovascular disease in various age categories. (Modified from Phillips KA, Glendon G, Knight JA. Putting the risk of breast cancer in perspective. *N Engl J Med.* 1999;340:141. Copyright 1999 Massachusetts Medical Society.)

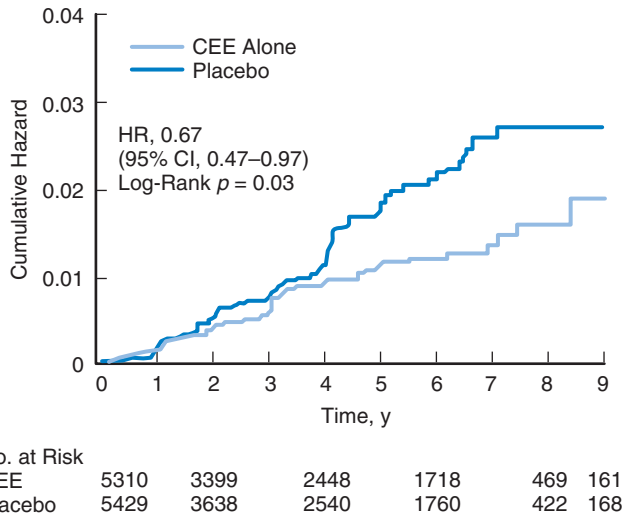


Fig. 14.36 Cumulative hazard for invasive breast cancer: sensitivity analysis. *CEE,* Conjugated equine estrogen; *CI,* confidence interval; *HR,* hazard ratio. (From Stefanick ML, Anderson GL, Margolis KL, et al. Effects of conjugated equine estrogens on breast cancer and mammography screening in postmenopausal women with hysterectomy. *JAMA.* 2006;295:1647.)

(0.625 mg CEE) is not associated with a risk of breast cancer except for very long-term users. In an analysis from the NHS, Chen and colleagues found that this risk only increases significantly after 20 years (Table 14.6). This risk is predominantly seen in lean women because women who are overweight or obese already have an increased risk of breast cancer, which is not further increased. A theory proposed by Jordan has suggested that the decrease in risk is confined to women who did not receive hormones immediately after menopause, but some time later. **The theory suggests that this lag allowed the occult breast cancers to undergo apoptosis when later exposed to estrogen, thus decreasing the risk of breast cancer**.

The promotional effect of hormones and breast cancer is thought to be enhanced by the use of progestogens. Some observational data from France have shown that use of natural progesterone may not enhance the risk as has been noted with synthetic progestins (Fournier, 2008).

Putting these risks into perspective is important for patient counseling. The background risk for breast cancer in a woman between the ages of 50 and 60 is 2.8 per 100 women. According to data from the WHI, the overall relative risk for women taking CEE/MPA for 5 years was approximately 1.24. Note that this applies to women who had also used hormones in the past, as noted earlier. **This 24% increase translates into an overall risk of 3.47 per 100 women, less than 1% greater than the background risk**. This risk is expected to be even lower with different regimens, including lower-dose therapy, and potentially with different progestogens, such as natural progesterone, which

TABLE 14.6 Risk of Invasive Breast Cancer by Duration of ET Use among All Postmenopausal Women Who Had Undergone Hysterectomy and Those with ER+/PR+ Cancer Only*

ET Use and Duration (Years)	All Postmenopausal Women							
	Who Had Undergone Hysterectomy				ER+/PR+ Cancers Only			
	All		Screened Cohort†		All		Screened Cohort†	
	Cases	Risk	Cases	Risk	Cases	Risk	Cases	Risk
Never	226	1.00	104	1.00	87	1.00	48	1.00
Current								
<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

From Chen WY, Manson JE, Hankinson SE, et al. Unopposed estrogen therapy and the risk of invasive breast cancer. *Arch Intern Med.* 2006;166:1027.
*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; 1-2 children and age at first birth 23-25 years; 1-2 children and age at first birth 25 years; ≥3 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,* unopposed estrogen therapy.

has been shown in observational studies not to increase the risk. A relative risk of 1.24 for breast cancer is less than that for obesity alone (3.3) or for being a flight attendant (1.87) because of the increase in cosmic radiation. Furthermore, for estrogen alone there is probably no increased risk at moderate to low doses for up to 20 years of exposure, as noted by Chen and colleagues. **The risk of breast cancer is much higher with certain endogenous risk factors such as obesity and increased breast density than it is with any type of HT** (Fig. 14.37).

With some exceptions in the literature, **most reports have shown that the mortality rate in users of ET/HT is improved compared with those women not receiving hormones** who are diagnosed with breast cancer. Fig. 14.38 depicts the 10-year follow-up data from WHI with women receiving CEE alone; both breast cancer mortality and total mortality were reduced in users of estrogen (Anderson, 2012). It should be appreciated that women receiving HT are likely to have (and should have) closer surveillance (examinations and mammography); accordingly, most tumors, if they occur, will be detected at an early stage.

Family history and genetic mutations (e.g., *BRCA1* and *BRCA2*) substantially increase the risk of a woman developing breast cancer. However, the literature suggests that the use of HT does not increase this risk further. Nevertheless, for many women it is unacceptable to consider a potentially promotional effect of using HT, and they may opt for risk reduction strategies such as the use of tamoxifen or other SERMs.

If there is a concern regarding hormones and breast cancer, it is with larger doses, a longer duration, and specifically the use of a progestogen. Accordingly, for longer-term therapy, if warranted (>5 years), lower doses of estrogen should be used, and progestogen exposure should be minimized.

Ovarian Cancer

Several studies have suggested an increased risk of ovarian cancer with long-duration use of estrogen or estrogen/progestogen therapy. However, the data are inconsistent, and the purported risk is less than a twofold relative risk. Prospective randomized trials such as the WHI have found no statistical increase in risk. A 2015 meta-analysis suggested a modest risk of 30% to 40% (Collaborative Group, 2019). In this analysis it is unclear if adequate attention was paid to confounders, and there was no association with length of exposure regarding risk, which does not make sense physiologically. Further, estrogen and estrogen/progestogens both carried some risk, whereas use of oral contraceptives are known to decrease ovarian cancer risk. According to this meta-analysis, **the risk was calculated to be approximately 1 extra case of ovarian cancer per 1000 women over 5 years, which suggests if this association is real, it is extremely rare.**

Colorectal Cancer

The third most common cancer in women, colorectal cancer, is often preventable by the detection and treatment of polyps. Women older than 50 should have a colorectal evaluation by some means (detection of occult blood, sigmoidoscopy, or a colonoscopy). **Data have been fairly consistent in identifying a reduction in risk with the use of hormones.** Several meta-analyses have shown an approximate **33% decrease in risk,** as did the observational data from the NHS and the prospective randomized trial data of the CEE/MPA arm of the WHI. It is unclear why in the ET arm of WHI a decrease was not observed. No definitive mechanism for this protective effect has been found, although several theories have been advanced (e.g., changes in the composition of bile acids, antiinflammatory effects).

Other Cancers

More attention is being paid to lung cancer, in part because it is the leading cause of cancer mortality in women. The data on HT, however, have not been consistent and are without convincing evidence of any increased risk of lung cancer with HT use.

DISEASE PREVENTION AFTER MENOPAUSE

Because all major diseases, including CVD, obesity, metabolic diseases (particularly diabetes), cancer, and AD, as well

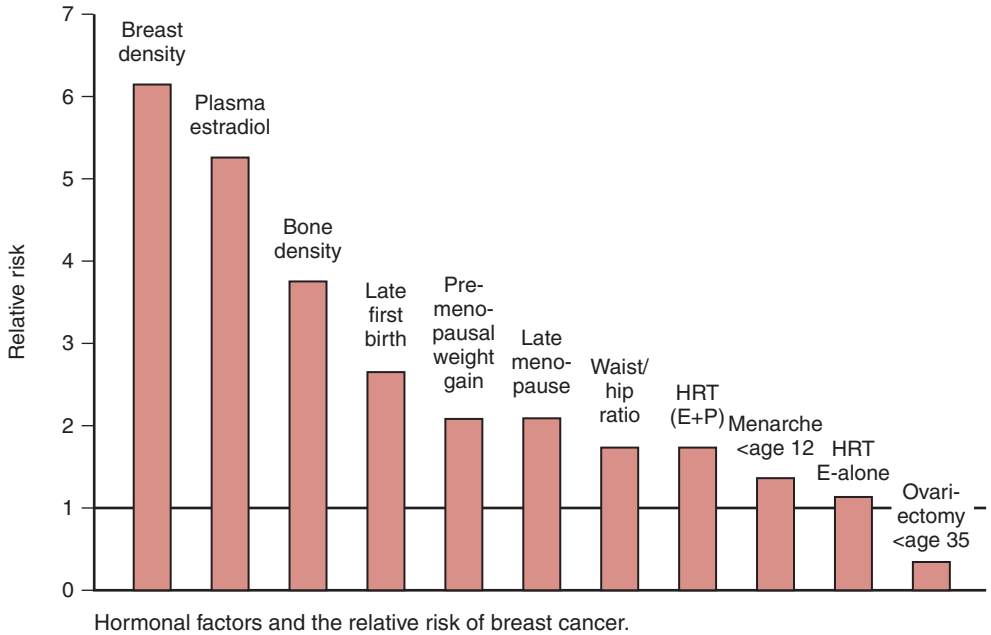


Fig. 14.37 Risks of breast cancer with various exposures and endogenous traits, particularly increased breast density. *E,* Estrogen; *HRT,* hormone replacement therapy; *P,* progestogen. (Modified from Gompel A, Santen RJ: Hormone therapy and breast cancer risk 10 years after the WHI. *Climacteric.* 2012;15(3):241-249.)

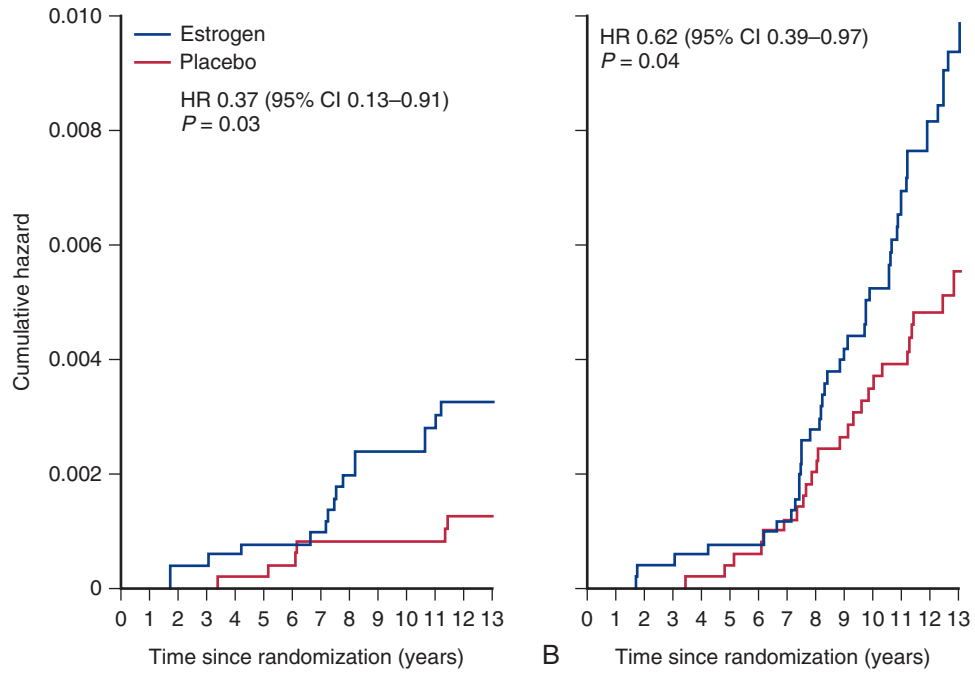


Fig. 14.38 In women with breast cancer, women taking estradiol (E_2) had significantly reduced mortality; breast cancer (**A**) and total (**B**). *CI,* confidence interval; *HR,* hazard ratio. (Modified from Anderson GL, Chlebowski RT, Aragaki AK, et al. Conjugated equine oestrogen and breast cancer incidence and mortality in postmenopausal women with hysterectomy: extended follow-up of the Women's Health Initiative randomized placebo-controlled trial. *Lancet Oncol.* 2012;13(5):476-486.)

as cognitive decline increase after menopause, menopause itself heralds an important opportunity to screen for and prevent many of these problems (Lobo, 2014).

Details of this approach may be found in the review cited, but in essence it stresses the introduction of screening procedures for these disorders and then beginning prevention strategies such as prescribing diet and exercise regimens and the consideration of HT. Primary strategies for the prevention of CVD in men, such as statins and aspirin, have not been shown to be of benefit in women (Lobo, 2014). Thus apart from lifestyle measures, there are no good prevention strategies for women, with the possible exception of HT. As discussed previously, in a young healthy

population of women close to menopause, estrogen-based therapy has been shown to significantly decrease coronary disease and mortality, with minimal to rare risks of adverse outcomes. As Fig. 14.28 shows, the use of HT was considered for prevention until the time of the various secondary prevention trials (such as the Heart and Estrogen/Progestin Replacement Study [HERS]) and then the WHI, and this concept is now being reconsidered, although it remains controversial. Table 14.7 lists a compilation of several studies and meta-analyses that are **remarkably consistent in showing a reduction in mortality in younger women receiving estrogen after menopause, which strengthens the argument for considering the use of estrogen for prevention.**

Because "early harm" was reported in **older women** taking standard doses of CEE/MPA in secondary prevention trials and in the WHI, it has been suggested (by some) that women have a cardiovascular risk assessment before initiating HT. **The American Heart Association (www.heart.org) offers an easy-to-use rapid risk assessment calculator, which defines women at low risk if they have a less than 7.5% chance of sustaining a myocardial infarction in 10 years.** Although some investigators have questioned the validity of this approach, risk assessment is not an unreasonable course in general, along the lines of stressing the need for *prevention* after menopause. Because most of the CV-related risks of HT relate to oral therapy, "higher"-risk women may benefit more by being placed on transdermal estrogen.

In summary, apart from the need to screen carefully for all diseases at the onset of menopause and stressing healthy lifestyle measures, the decision to initiate HT should be straightforward in symptomatic women who will benefit more in terms of absolute numbers of women affected by treatment (see Fig. 14.39). Fig. 14.39, generated from newer data and data from the WHI in the 50- to 59-year-old age group, shows the absolute benefits and risks associated with the use of estrogen, strongly emphasizing benefits. However, when these absolute numbers are compared with the benefit of the reduction in hot flushes in women receiving estrogen, the latter appears to be the predominant effect (Fig. 14.40). The decision to use HT at the onset of menopause probably applies for women who are at greater risk for osteoporosis as well, based on family history and their physical characteristics. Otherwise, it is not unreasonable to consider HT in otherwise healthy women with adequate counseling and discussion of the risks and benefits. This should be an individual decision. For some women, the fear of breast cancer, particularly in those with some family history of the disease, will overshadow any potential benefits, and this view has to be respected. Women who decide to initiate HT should be made aware that this need not be a long commitment, and therapy should be reassessed annually based on needs and symptoms.

Finally, the data to date regarding protection are strongest for the use of estrogen; certain progestogens may eliminate or attenuate the benefit, and some progestogens increase the promotional risk of breast cancer. Philosophically, therefore, HT should be about using the lowest amount of a progestogen necessary to prevent endometrial disease.

TABLE 14.7 Consistency in the Reduction in All-Cause Mortality in Younger Women Receiving Estrogen at the Onset of Menopause

Study	Point Estimate (Relative Risk)
Observational meta-analysis	0.78 (0.69-0.90)*
Randomized trials meta-analysis	0.73 (0.52-0.96)*
Bayesian	0.72 (0.62-0.82)*
WHI combined groups	0.70 (0.62-0.82)†
WHI 13-year cumulative CEE	0.78 (0.59-1.03)‡
WHI 13-year cumulative CEE/MPA	0.88 (0.70-1.1)‡
Cochrane meta-analysis	0.70 (0.52-0.95)§
Finnish registry data (pre-WHI)	0.57 (0.48-0.66)‖
Finnish registry data (post-WHI)	0.46 (0.32-0.64)‖

*Salpeter SR, Cheng J, Thabane L, et al. Bayesian meta-analysis of hormone therapy and mortality in younger postmenopausal women. *Am J Med.* 2009;122(11):1016-1022.

†Rossouw JE, Prentice RL, Manson JE, et al. Postmenopausal hormone therapy and cardiovascular disease by age and years since menopause. *JAMA.* 2007;297(13):1465-1477.

‡ 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.* 2013;310:1353-1368.

§ Boardman HMP, Hartley L, Main C, et al. Hormone therapy for preventing cardiovascular disease in post-menopausal women (review). *Cochrane Database Syst Rev.* 3:CD002229, 2015.

‖Tuomikoski P, Lyytinen H, Korhonen P, et al. Coronary heart disease mortality and hormone therapy before and after the Women's Health Initiative. *Obstet Gynecol.* 2014;124: 947-953. (Coronary mortality including all women but with similar point estimates as in women <60 years.)

CEE, Conjugated equine estrogen; *MPA,* medroxyprogesterone acetate; WHI, Women's Health Initiative.

Hormone Regimens

The various hormonal preparations and osteoporosis drugs that are available for treatment are listed in Box 14.3. A more complete list may be found in the Consumer section of the North American Menopause Society website at www.menopause.org. For the clinician and patient, as noted earlier, the decision to start estrogen therapy need not involve a long-term commitment. For short-term treatment of symptoms, estrogen should be used at a low dose that can control hot flushes or can be administered via the vaginal route for symptoms of dryness or dyspareunia. There are no definitive data on what doses are necessary for CV protection, but whereas low doses of estrogen may be sufficient to prevent bone loss (discussed earlier), the doses necessary to afford CV protection may need to be higher, although there are no definitive data. Therefore lower doses are still recommended, which are sufficient for symptom control.

Oral estrogen results in higher levels of E_1 than E_2; this is true for oral micronized E_2 as well as oral E_1 products. CEE is a mixture of at least 10 conjugated estrogens derived from equine pregnant urine. E_1 S is the major component, but the biologic activities of equilin, 17α-dihydroequilin, and several other B-ring unsaturated estrogens, including δ5 dehydroestrone, have been documented. Table 14.8 compares the standard doses of the most commonly prescribed oral estrogens and the levels of E_1 and E_2 achieved. Much of the following clinical information may be found in systematic reviews.

Synthetic estrogens, given orally, are more potent than natural E_2. Ethinyl estradiol is used in oral contraceptives, with a dose of 5 μg being equivalent to the standard ET doses used (0.625 mg CEE or 1 mg micronized E_2). Standard ET doses are five or six times less than the amount of estrogen used in oral contraceptives. Although there are incomplete data available to compare the equivalencies of CEE and micronized E_2 (because of different end organ effects and the mixture of estrogens in CEE, which are difficult to measure), 0.625 mg CEE is probably equivalent to 1.5 mg of micronized 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 (e.g., an increase in procoagulation factors and an increase in C-reactive protein),

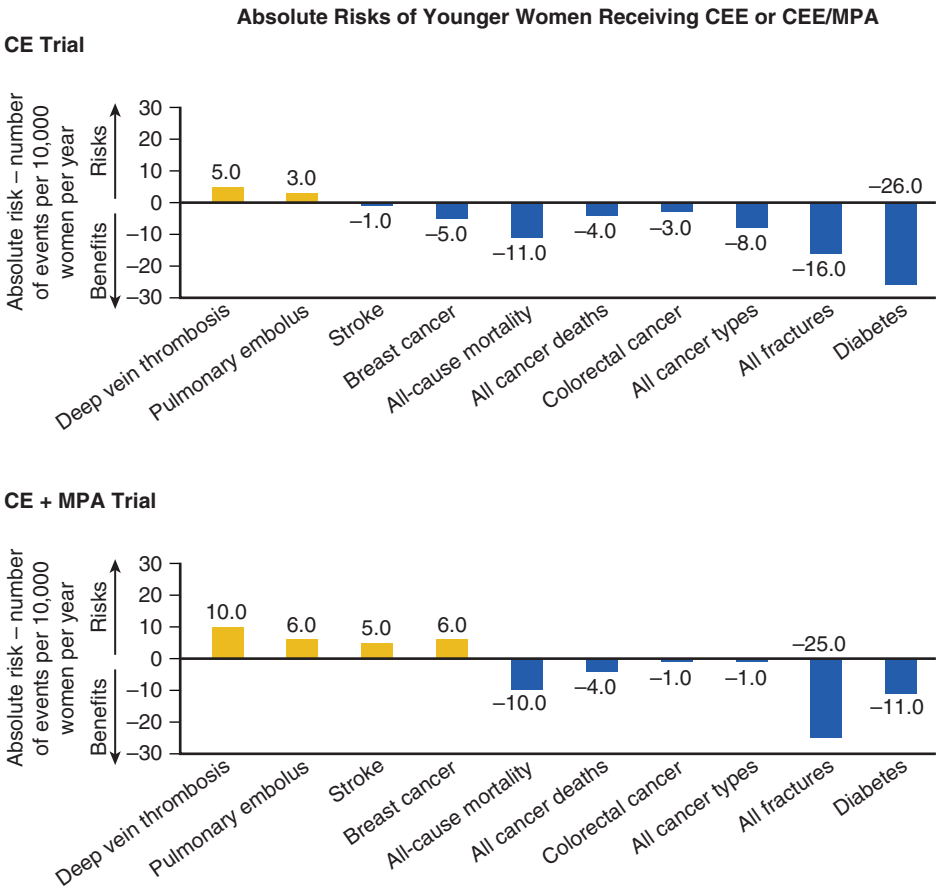


Fig. 14.39 Absolute risks in younger women receiving estrogen or estrogen/progestogen. *CEE,* Conjugated equine estrogen; *MPA,* medroxyprogesterone acetate. (Data from Women's Health Initiative; modified from Lobo RA, Pickar JH, Stevenson JC, Mack WJ, Hodis HN. Back to the future: hormone replacement therapy as part of a prevention strategy for women at the onset of menopause. *Atherosclerosis.* 2016;254:282-290.)

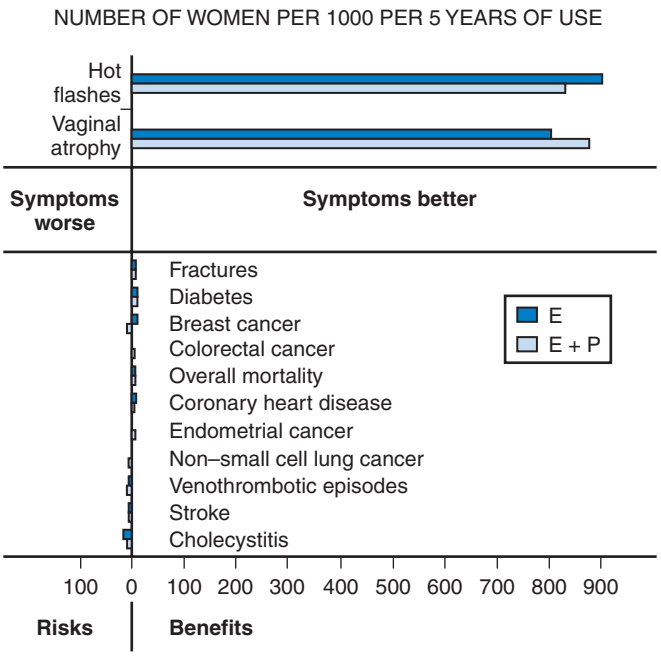


Fig. 14.40 Putting risks and benefits in perspective for the 50- to 59-year-old. (Modified from Santen R. Endocrine Society position paper. *J Clin Endocrinol Metab.* 2010;95[7 Suppl 1]:s1-s66.)

whereas other changes are beneficial (an increase in HDL-C and a decrease in fibrinogen and plasminogen activator inhibitor-1).

E_2 can be administered in patches, gels, lotions, sprays, and subcutaneously. These routes of administration are not subject to major hepatic effects as with oral therapy. Accordingly, there is no increase in C-reactive protein and minimal if any change in coagulation factors, but there is also only a minimal increase in HDL-C. Patches are available in doses from 0.014 mg to 0.1 mg, available for administration once or twice weekly. An ultra-low dose patch (0.014 mg/day) has been marketed for osteoporosis prevention in older women and not for treating hot flushes. Matrix patches are preferable to the older alcohol-based preparations because there is less skin reaction and estrogen delivery is more reliable. Whereas levels of E_2 with oral therapy may vary widely among women and within the day (peaks and valleys), levels with transdermal therapy are more constant within each woman, yet values achieved may vary from woman to woman based on absorption and metabolic characteristics. With the 0.05-mg patch, E_2 levels should be in the 40 to 50 pg/mL range, but a woman can have a value as high as 200 pg/mL or a level that is less than 20 pg/mL. This issue of interpatient variability is based on skin absorption, metabolism, and body distribution. Accordingly, regardless of symptomatic control, it is valuable to assess at least once what the E_2 level is in a woman using a patch. This becomes more critical for women in whom the clinician wishes to keep the levels low, because of concerns of thrombosis, for example, or that sufficient E_2 is being delivered if the patch is being used for the prevention of osteopenia or osteoporosis.

BOX 14.3 Hormonal and Osteoporosis Treatments: Available and Approved for Use in Postmenopausal Women

ESTROGENS

Oral

CEE, 0.3, 0.45, 0.625, 0.9, 1.25, and 2.5 mg
Piperazine estrone sulfate, equivalent of 0.625, 1.25, and 2.5 mg
Esterified, 0.3, 0.625, 0.9, 1.25, and 2.5 mg
Micronized estradiol, 0.5, 1, and 2 mg

Transdermal

Estradiol patches, 0.014, 0.025, 0.0375, 0.05, 0.75, and 0.10 mg/day
Estradiol gels, 0.25 to 1.5 mg/day various brands
Estradiol spray, 1.53 mg/day

Vaginal

Cream, CEE (0.0625%), estradiol (0.01%)
Estradiol ring, 2 mg: release for atrophy 7.5 μg/day for 3 months
Estradiol acetate ring for vasomotor symptoms: 50 to 100 μg/day for 3 months
Estradiol hemihydrate (tablet) 10 μg: 1 tablet per day for 2 weeks, then twice/week
Estradiol soft gel inset, 4 μg and 10 μg: daily use for 2 weeks, then twice/week

Parenteral

Intramuscular injections should be avoided

PROGESTINS

Oral

Medroxyprogesterone acetate, 2.5, 5, and 10 mg
Norethindrone acetate, 5 mg
Micronized progesterone, 100 and 200 mg

Vaginal

Micronized progesterone, 100 mg
Progesterone gel, 4% and 8%

COMBINATIONS

Oral

CEE + MPA (0.625 mg) + MPA (2.5 or 5 mg)
CEE + MPA (0.3 mg + MPA, 1.5 mg)
Micronized estradiol (1 mg) + norethindrone, acetate (0.5 mg); or 0.5 mg with 0.1 norethindrone acetate
Micronized estradiol (1 mg) + 0.5 mg drospirenone; or 0.5 mg estradiol and 0.25 mg drospirenone
Ethinyl estradiol (5 μg), norethindrone acetate (1 mg or 2.5 μg), and 0.5 mg norethindrone acetate
CEE + bazedoxifene (SERM), 0.45 + 20 mg/day
Micronized estradiol (1 mg) + micronized progesterone (100 mg) in single tablet

Transdermal

Patch, 0.05 mg estradiol with 140 μg or 250 μg norethindrone acetate
Patch, 0.045 mg estradiol with levonorgestrel 0.015 mg

ANDROGENS

Oral

Esterified estrogen and methyl testosterone (0.625/1.25 mg and 1.25/2.5 mg)

Transdermal

Patch, 150 μg/300 μg, approved outside the United States

OTHER NONHORMONAL PRODUCTS

Ospemifene (SERM), 60 mg/day for vulvovaginal atrophy
Paroxetine (SSRI), 7.5 mg/day for vasomotor symptoms

MEDICATIONS FOR OSTEOPOROSIS

Bisphosphonates

Alendronate, 5 and 10 mg daily; 35 and 70 mg weekly
Risedronate, 5 mg; 35 mg weekly
Ibandronate, 150 mg monthly and 3l mg IV every 3 months
Zoledronic acid 5 mg once yearly
Etidronate, 200 mg (intermittent)

Selective Estrogen Receptor Modulators (SERMs)

Raloxifene, 60 mg

Others for Osteoporosis

Tibolone, 2.5 mg (not approved in the United States)
Denosumab, 60 mg subcutaneously every 6 months
Human parathyroid hormone 1-34; 20 μg subcutaneously daily
Romosozumab 105 mg × 2 (prefilled syringes) subcutaneously once/month

CEE, Conjugated equine estrogens; *IV,* intravenously; *MPA,* medroxyprogesterone acetate.

TABLE 14.8 Mean Serum Estradiol (E_2) and Estrone (E_1)

	Level (pg/mL)	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.

Note also that many commercial assays for E_2 are not reliable and do not accurately reflect E_2 status, although sensitive assays using mass spectroscopy have been incorporated into clinical assays.

In women with GSU, vaginal therapy is most appropriate. Cream formulations of E_2 or CEE are available, as well as tablets, inserts, and an estrogen ring. With creams, systemic absorption occurs but with levels that are one-fourth 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, inserts and rings) are available that have been designed to limit systemic absorption. A Silastic ring is available that delivers E_2 to the vagina for 3 months with only minimal systemic absorption. A vaginal preparation of DHEA (prasterone 6.5 mg vaginal inserts) has also been approved for use to treat dyspareunia. DHEA as a prehormone relies on local (vaginal) conversion to other androgens and estrogen, which may exert a beneficial local effect. Prasterone has been found to be equivalent in efficacies to other hormonal preparations (Heo, 2019).

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.** For women who are totally intolerant of progestogens (regardless of the dose and route of administration) and take unopposed estrogen, even at lower doses, periodic endometrial sampling is necessary. In this setting, endometrial thickness by ultrasound may be a guide.

Dealing With Side Effects

Apart from the thrombotic risks of larger doses of oral estrogen (discussed previously), there may be an "idiosyncratic" blood pressure response to oral estrogen. This has been described primarily with the use of CEE and occurs about 5% of the time. Estrogen typically causes no change in blood pressure and often can lower blood pressure, even in women with hypertension. A hypertensive response is often dealt with by changing the dose, preparation, or route of administration. The important clinical point is that blood pressure should be checked after initiation of therapy.

Other somatic effects of estrogen include potential breast tenderness, fluid retention, and bloating (more common with progestogens). All these symptoms are easily dealt with by changing the dose or preparation and potentially by changing the route of administration as well. There should be a great deal of flexibility in the prescribing of estrogen because there is no ideal product for all women.

Use of a Progestogen

There are many ways to administer progestogens. The most commonly used oral progestins are medroxyprogesterone acetate (MPA) in doses of 2.5 and 5 to 10 mg, norethindrone (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. Larger doses of estrogen may require larger doses and particularly more prolonged regimens of a progestogen. In the sequential administration of progestogens, the number of days (length of exposure) is more important than the dose. Thus, if a woman is receiving oral ET continuously, a regimen of at least 10 to 12 days' 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 are common. In some women on this regimen, amenorrhea is never completely achieved. The most common combinations in the United States are single tablets containing 0.45 or 0.625 mg CEE with 1.5 and 2.5 mg MPA, respectively, and 5 μg of E_2 with 1 mg NET and 1 mg micronized E_2 with 0.5 mg NET. The Food and Drug Administration (FDA) has approved a single capsule containing E_2 1 mg with natural progesterone 100 mg for daily dosing. Transdermal patches E_2 and NET or E_2 and levonorgestrel are also available.

Progesterone administered vaginally (in low doses) avoids systemic effects and results in high concentrations of progesterone in the uterus. This can be accomplished with capsules, suppositories, or a 4% gel. Intrauterine delivery of progestogens is ideal for targeting the uterus and minimizing systemic effects. However, the only marketed product, the Mirena intrauterine system, delivers too high a dose of levonorgestrel (52 mg in the system) for lower doses of estrogen therapy; a 13.5-mg system (Skylar) has been made available. Progestogens, particularly when taken orally, may lead to problems of continuance or compliance because of adverse effects, including mood alterations and bleeding. This requires flexibility in prescribing habits. Most short-term clinical trials have demonstrated an attenuating effect of progestogens on cardiovascular endpoints that are improved with estrogen; these effects include lipoprotein changes (an attenuation of the rise in HDL-C) and arterial and metabolic effects, and potentially a further increase in thrombotic risk. The cardiovascular effects found in the WHI with CEE alone and CEE with MPA, which showed a more favorable effect without MPA, also suggest some detrimental effects of added progestogen. However, two different populations of women were studied in the two WHI trials, which limits any direct comparison. The most inert progestogens, such as micronized progesterone, or vaginal delivery of progesterone should have the fewest attenuating effects. As noted earlier, it is most likely that progestogen exposure is what increases the risk of breast cancer with HT. Natural micronized progesterone was found not to increase the risk of breast cancer in several French observational studies (Fournier, 2008). Progestogens should not be used in women who have had a hysterectomy.

Androgen Therapy

In a subtle way, some women are relatively androgen deficient or insufficient. Clinicians have proposed adding androgen to ET or HT for complaints or problems relating to libido and energy that are not relieved by adequate estrogen. Although well-controlled trials using parenteral testosterone have shown benefit in younger oophorectomized women, there have been few data showing a benefit to using more physiologic therapy. Data using a testosterone patch or pellet (with near physiologic levels) have indicated improvement in several scales of well-being and sexual function (Simon, 2005). A 2019 systematic review and meta-analysis showed that testosterone is both safe and efficacious when used to treat low sexual desire in women (Islam, 2019). Although testosterone is typically administered nonorally, 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. The latter findings correlated with an increase in circulating unbound testosterone levels. **At present, androgen therapy should be individualized and considered for those women who have symptoms that are not adequately relieved with traditional hormonal therapies.** Measuring testosterone before therapy is not helpful in making this determination, but it is essential to monitor testosterone levels during therapy because the normal range of testosterone is narrow in women and there is a tendency to get higher levels, which can lead to adverse effects, particularly masculinizing symptoms such as acne and hirsutism. Administration of DHEA at 25 to 50 mg/day may also be an option for raising endogenous testosterone, but data have not shown it to be beneficial for symptoms such as hypoactive sexual desire.

Another SERM-like compound that is used worldwide but is not approved in the United States is tibolone. This progestogen-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. There is also limited (or no) uterine stimulation. However, there is suppression of HDL-C, but at the same time a decrease in triglycerides. In monkeys no deleterious effect of tibolone on coronary arteries was identified.

"Bioidentical" Hormone Therapy

It has become popular to have compounding pharmacies dispense a mixture of "bioidentical" hormones in a cream or suspension for topical administration. These preparations usually contain one or more estrogens, progesterone, testosterone, and often other precursors such as pregnenolone. **As an unregulated industry, without approval by the FDA, there is inadequate**

quality control for these products, with batch-to-batch variation and the inclusion of some steroid hormones that may not be necessary. Claims that these compounded products are safer than pharmaceutical grade hormones is completely unsubstantiated. Nevertheless, use of these preparations has dramatically increased since the reports from the WHI, with the perception that they are safer. Ironically, during this time, as use of traditional hormone products has decreased, an increased incidence of endometrial cancer has been witnessed (Constantine, 2019). Also, "titrating" preparations to salivary hormone levels is not accurate and has never been validated. Indeed micronized E_2, orally or as a transdermal product, and micronized progesterone are bioidentical products approved by the FDA and should be first-line therapies. Several major societies have come out with strong statements against the use of compounded bioidentical preparations, and there is a combined statement from the American Society for Reproductive Medicine (ASRM) and the American College of Obstetricians and Gynecologists (ACOG) (Practice Committee, 2012).

Tissue Selective Estrogen Complex Concept

The tissue selective estrogen complex (TSEC) concept is a newer therapy for menopause that pairs together an estrogen and a SERM, which when complexed together have specific and different tissue properties than either one would exert independently. A specific SERM, bazedoxifene (BZA)—which has agonistic effects (acting like an estrogen) on bone, antagonistic effects on the uterus and breast, and minimal effects on the central nervous system (CNS)—when paired with CEE maintains the effects of CEE on reducing hot flushes, yet prevents endometrial hyperplasia. Accordingly, a progestogen is not needed, and this continuous regimen results in a low rate of vaginal bleeding. It is beneficial for osteoporosis protection and at least theoretically should be safer for the breast as well (Kagan, 2012). It is available as a combination product of CEE 0.45 mg and 20 mg of BZA.

ALTERNATIVE THERAPIES FOR MENOPAUSE

There are several nonhormonal alternatives for symptoms of menopause, which are listed in Box 14.4, although none of these is as effective as estrogen. Nevertheless, for women who cannot or choose not to take a hormonal preparation, some of these are viable substitutes. Because there is a fairly significant placebo effect in the reduction in hot flushes (up to 40% reduction), at least in the short term, randomized trials against placebo are necessary to establish efficacy.

Not listed here, because this list includes nonhormonal preparations, rather than estrogen or estrogen/progestogen regimens, there is an established efficacy of using progestogens alone. MPA 10 to 20 mg, and NET 5 to 10 mg (as well as other progestogen regimens) used alone have shown some benefit in women with hot flushes, but this is less beneficial than the use of estrogen and has more side effects, particularly with more long-term therapy (>3 months). Also, if a woman cannot or will not take estrogen, it is unlikely that she would take a progestogen alone. Therefore this is often an impractical choice for dealing with symptoms.

BOX 14.4 Nonhormonal Therapies for Vasomotor Symptoms

Antidepressants (SSRIs/SNRIs)
Gabapentin
Clonidine
Isoflavones, red clover, black cohosh
Cognitive behavior therapy
Acupuncture
Stellate ganglion block

SNRI, selective norepinephrine reuptake inhibitor; *SSRI,* selective serotonin reuptake inhibitor.

Antidepressants (Selective Serotonin Reuptake Inhibitors/Serotonin Norepinephrine Reuptake Inhibitors)

Several well-controlled clinical studies have demonstrated efficacies of several antidepressant drugs for hot flushes that were initially used in women with breast cancer. These include fluoxetine (20 mg), venlafaxine (75 mg), paroxetine (12.5 mg, 25 mg), and escitalopram (10 mg, 20 mg). Apart from some side effects, such as nausea, dry mouth, and sexual dysfunction, all these agents are superior to placebo in reducing hot flushes. However, only one product, paroxetine, is approved by the FDA, at a lower dose of 7.5 mg. This has a moderate effect, and in breast cancer patients it may interfere with tamoxifen therapy.

Gabapentin

Gabapentin has been shown to be superior to placebo in doses ranging from 300 to 900 mg. Side effects include somnolence, dizziness, fatigue, and ataxia, which are dose related. If doses are titrated up to 2400 mg (a very large dose), the efficacy has been shown to be similar to that of CEE at 0.625 mg (Reddy, 2006).

Antihypertensives

Clonidine has been the most studied antihypertensive, but methyldopa also has efficacy over placebo in reducing hot flushes. Typically a 0.1-mg patch is used daily. There is an obvious hypotensive response, and the efficacy is not very large, precluding its routine use unless the patient is also hypertensive.

Phytoestrogens

It has been suggested that 30% to 60% of women with symptoms at menopause seek "natural" therapies, and the majority are botanicals such as phytoestrogens. 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.

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 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, although the literature on this issue is mixed. In placebo-controlled trials, red clover and black cohosh have been found to have similar effects as placebo (Fig. 14.41) (Geller, 2009).

With doses of 30 to 40 mg of soy isoflavone, cholesterol levels may be reduced, but this is not a consistent finding. Phytoestrogens do not appear to have much of an effect on bone loss or on vaginal atrophy.

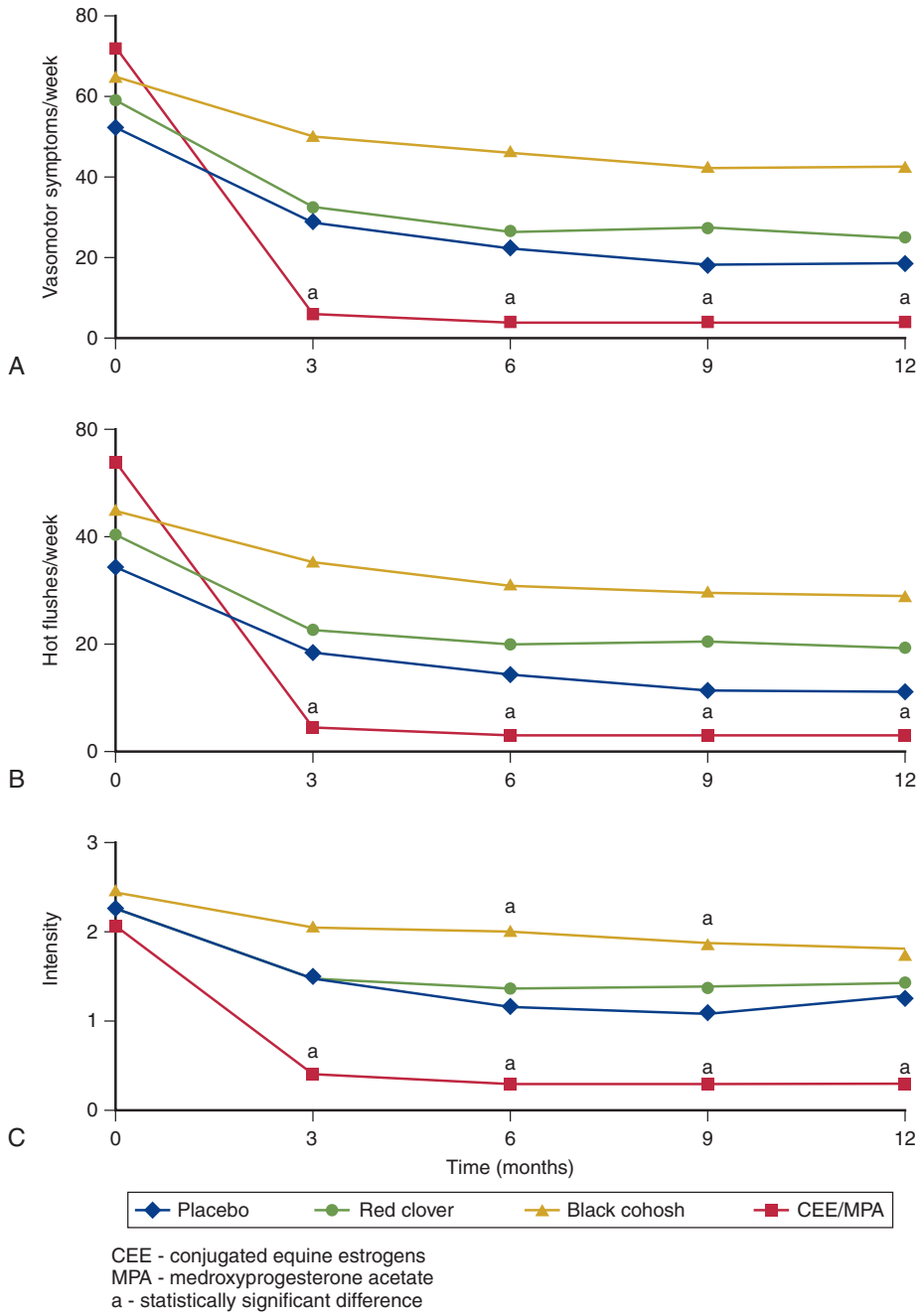


Fig. 14.41 A, Number of vasomotor symptoms per week. **B,** Number of hot flushes per week. **C,** Intensity of the hot flushes. Black cohosh and red clover are not different from placebo. *E*, Estrogen; *P*, progestogen. (Modified from Geller SE, Shulman LP, van Breemen RB, et al. Safety and efficacy of black cohosh and red clover for the management of vasomotor symptoms: a randomized controlled trial. *Menopause.* 2009;16(6): 1156-1166.)

Cognitive Behavioral Therapy

"Talk therapy," which teaches coping skills that may change one's cognitive appraisal of the symptoms, may be beneficial (van Driel et al., 2019). It is not clear if this treatment is sustained over time.

Acupuncture

Acupuncture has been used in several trials to assess the treatment of hot flushes and other menopausal symptoms. A meta-analysis confirmed that acupuncture may be effective in alleviating the frequency and severity of hot flushes (Chiu, 2015).

Stellate Ganglion Blockade

Although somewhat invasive, needle injection of the stellate ganglion has been shown to be effective in some women, such as those being treated for breast cancer. In one study, image-guided stellate ganglion blockade with 5 mL of 0.5% bupivacaine was shown to be beneficial compared with sham injection with saline for vasomotor symptoms (Walega, 2014).

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Full references and Suggested readings for this chapter can be found on ExpertConsult.com.

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