

XI MENOPAUSE

SUSAN D. REED, M.D., M.P.H.
ELIZA L. SUTTON, M.D.

Definitions

The female reproductive system matures in a continuous, natural process from menarche to menopause, as the finite numbers of oocytes produced during fetal development are gradually lost to ovulation and senescence. Menopause is defined as the permanent cessation of menses¹; by convention, the diagnosis of menopause is not made until the individual has had 12 months of amenorrhea. Menopause is thus characterized by the menstrual changes that reflect oocyte depletion and subsequent reduction in ovarian hormone production. However, the manifestations that occur around the time of menopause are caused by the underlying ovarian changes, rather than by the cessation of menstruation itself. Therefore, a woman who has undergone a hysterectomy but who retains her ovaries will experience normal menopausal symptoms as oocyte depletion leads to hypoestrogenism, even though cessation of menstruation occurred with surgery.

Natural menopause occurs at or after 40 years of age and has no underlying pathologic cause [see Natural Menopause, below]. Induced menopause may occur after chemotherapy, pelvic radiation, or, most commonly, bilateral oophorectomy. Menopause is considered premature when it occurs before 40 years of age but is otherwise natural [see Premature Ovarian Failure, below].

The climacteric, a term now used infrequently, refers to the time of waning ovarian function associated with menstrual irregularity and vasomotor symptoms. Perimenopause is the time between the onset of the climacteric and the year after the last menses. Menopausal transition is replacing perimenopause and climacteric as the preferred term to describe the time of physiologic change around the cessation of ovarian function [see Figure 1].² Premenopause is the entire reproductive span before onset

of the menopausal transition, and postmenopause is the span of life after menopause.

In the past, natural menopause was considered to be an endocrinopathy, with the ovary depicted as a failing organ and estrogen considered the optimal therapy. Given that menopause is a normal transition in the lives of most women and that significant risks have been associated with postmenopausal hormone “replacement,” the viewpoint of menopause as an endocrinopathy is no longer espoused.

Natural Menopause

EPIDEMIOLOGY

The menopausal transition, which precedes menopause, has an average duration of 4 years, with a range of 0 to 10 years.^{3,5} The mean age at which menopause occurs in developed countries is 51 years^{4,6,7} and may be increasing.⁸ The standard deviation around this mean is about 2 years.^{4,9} Approximately 95% of women experience menopause by 55 years of age.⁴ Several factors appear to influence the age at which women experience menopausal symptoms and the final menstrual period; for example, menopause occurs approximately 1 year earlier in smokers^{6,7,10} and nulliparous women.^{6,7} Menopause may also occur earlier in women who have had ovarian cystectomies or unilateral oophorectomies.¹¹

PHYSIOLOGY AND GENETICS OF REPRODUCTIVE AGING

Ovarian follicular depletion, by means of atresia, is the final common pathway in female reproductive aging. At 5 months of fetal age, the ovaries contain their peak number of primordial follicles, totaling approximately two million. At birth, girls have one million primordial follicles, approximately 25% of which remain at puberty. During the reproductive years, many follicles will begin to develop during each ovulatory cycle; all but one, the dominant follicle, become atretic. An estimated 1,000 follicles remain in the ovaries of a woman 51 years of

Stages of reproductive aging	Reproductive Years			Menopausal Transition		Postmenopause		
	Early	Peak	Late	Early	Late*	Early*	Late	
				Perimenopause				
Duration of stage	Variable			Variable		1 yr	4 yr	Until demise
Menstrual cycles	Variable to regular	Regular		Variable cycle length (> 7 days different from normal)	≥ 2 skipped cycles and an interval of amenorrhea (≥ 60 days)	0	None	
Endocrine function (FSH levels)	Normal		Elevated or normal	Elevated or normal		↑	Elevated	

*Stages most likely to be characterized by vasomotor symptoms.

Final Menstrual Period

Figure 1 The Stages of Reproductive Aging Workshop (STRAW) reproductive staging system showing the relationship of the final menstrual period with menstrual cycle changes and FSH serum concentrations.² (FSH—follicle-stimulating hormone, ↑—elevated)

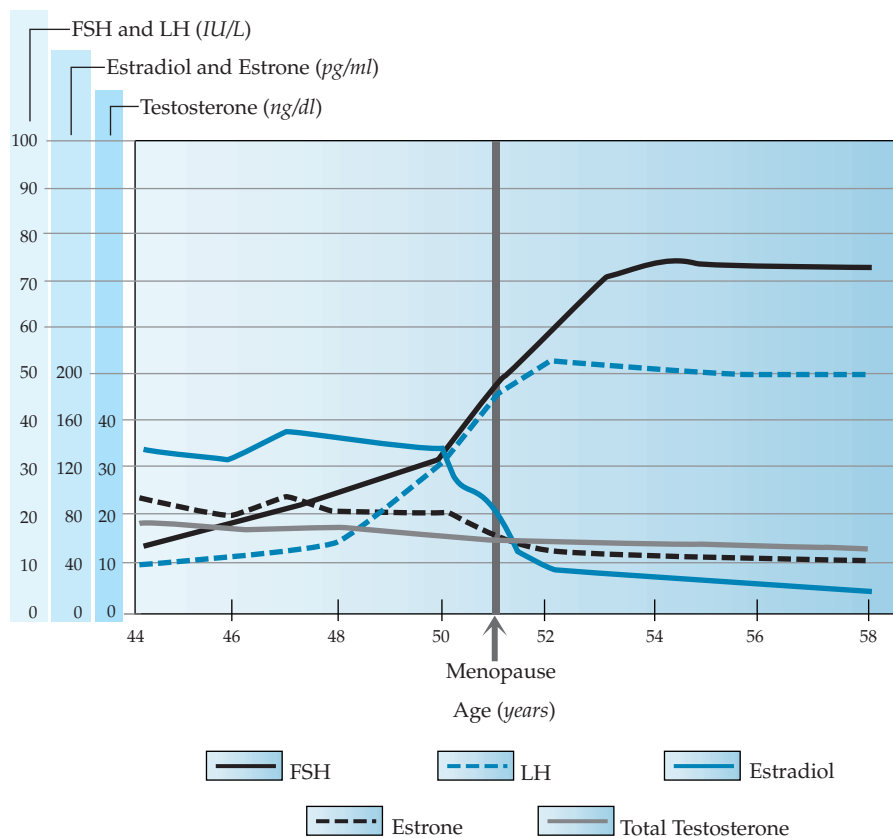


Figure 2 Approximate average serum concentrations of estradiol, estrone, FSH, LH, and total testosterone during the menopausal transition and postmenopause. A subtle rise in FSH occurs first, followed by a rise in LH and a decline in estradiol and estrone. There are no abrupt changes in testosterone, but a gradual continuous decline occurs that begins before the menopausal transition.¹³⁰

age.¹² Some poorly responsive follicles persist for a few years after the menopause.¹³ This progressive loss of follicles that accompanies aging is characteristic of all mammals studied to date; however, the controlling factors for this process have not been well defined.

Beginning as early as 10 to 15 years before menopause, the length of the menstrual cycle progressively decreases, owing to a shortening of the follicular phase of the cycle. The observed decrease in cycle length continues until the onset of the menopausal transition, when both the average cycle length and the standard deviation of cycle length begin to increase as follicles are depleted and ovulation occurs less frequently.^{4,14} Insufficient follicular development results in inadequate estrogen production. With little estrogen available to stimulate the endometrium, amenorrhea results.

There is good evidence that the timing of natural menopause is genetically programmed,¹⁵⁻¹⁷ but the specific genes involved are yet to be well defined. Common allelic variants of the estrogen receptor gene (estrogen receptor- α [ER- α] and ER- β) contribute to the variability in the timing of menopause.¹⁸ In addition, all of the steroid receptors, as well as the proteins and enzymes involved in steroid biosynthesis and metabolism, are known to be coded by polymorphic sites (genetic changes found in at least 1% of the population). This genetic variability adds to the complexity of the actions and interactions of the reproductive steroids and to the timing and extent of menopausal symptoms.

PHYSIOLOGIC CHANGES IN MENOPAUSE

Hormonal Changes

A subtle rise in the concentration of follicle-stimulating hormone (FSH) is the earliest and most consistent clinically measurable hormonal change noted in studies of reproductive aging.^{19,20} An FSH level measured during the early follicular stage of the menstrual cycle that is greater than two standard deviations above the mean level in women of reproductive age is a marker of impending menopausal transition.² Luteinizing hormone (LH) levels remain normal initially, but they eventually become elevated as ovarian steroid secretion falls and gonadotropin-releasing hormone (GnRH) increases [see Figures 2 and 3]. The early selective increase in FSH appears to be caused by decreased secretion of the hormone inhibin B by the ovarian granulosa cells and is a marker of follicular atresia. Inhibin A and B, hormones that are involved in directing follicular development and were first characterized in the 1990s, suppress pituitary FSH production.^{21,22} As anovulation predominates, FSH and LH remain chronically elevated (i.e., there is a 10-fold to 20-fold increase in the FSH level and a threefold to fivefold increase in the LH level),^{19,21,23} and estradiol levels fall below 50 pg/ml [see Figure 2].

The physiologic changes that are associated with menopause are predominantly reflected by changes in circulating levels of estrogens, androgens, and progesterone [see Figures 2 and 3]. The hormonal system is made more complex by fluctuations in steroid hormones that alternate between free and bound states. Sex hormone-binding globulin affects serum levels of all steroid

hormones, binding preferentially to testosterone, estrogen, and progesterone, in that order.

During the reproductive years, estradiol (E_2) is the principal estrogen, both in quantity and in potency; estrone (E_1) is present in a significant amount but is less potent than estradiol. Estriol (E_3), a weak estrogen, is a metabolite of estrone and estradiol. Despite diminished fertility and ongoing follicular atresia, the ovulatory cycles of women in the menopausal transition have normal to high concentrations of circulating estradiol and estrone. In fact, as women approach the menopausal transition, preovulatory estradiol levels can be higher than those seen in younger women.^{24,25}

After menopause, estradiol production drops by 90%,^{19,21} owing to follicular atresia [see Figures 2 and 3a]. What little estradiol is produced after menopause comes primarily from peripheral conversion of estrone. Estrone, the dominant estrogen after menopause, is produced through peripheral conversion of adrenal androstenedione by aromatase, primarily in adipose tissues [see Figure 3d]. Fatty breast tissue is a principal site of aromatase activity, but activity is also present in the brain, muscle, liver, and, minimally, the ovary of a postmenopausal woman.

As reproductive aging progresses, serum levels of androgens decrease but not to the extent that estrogen levels diminish. Androstenedione levels drop by approximately 50%,²⁶⁻²⁸ ovarian

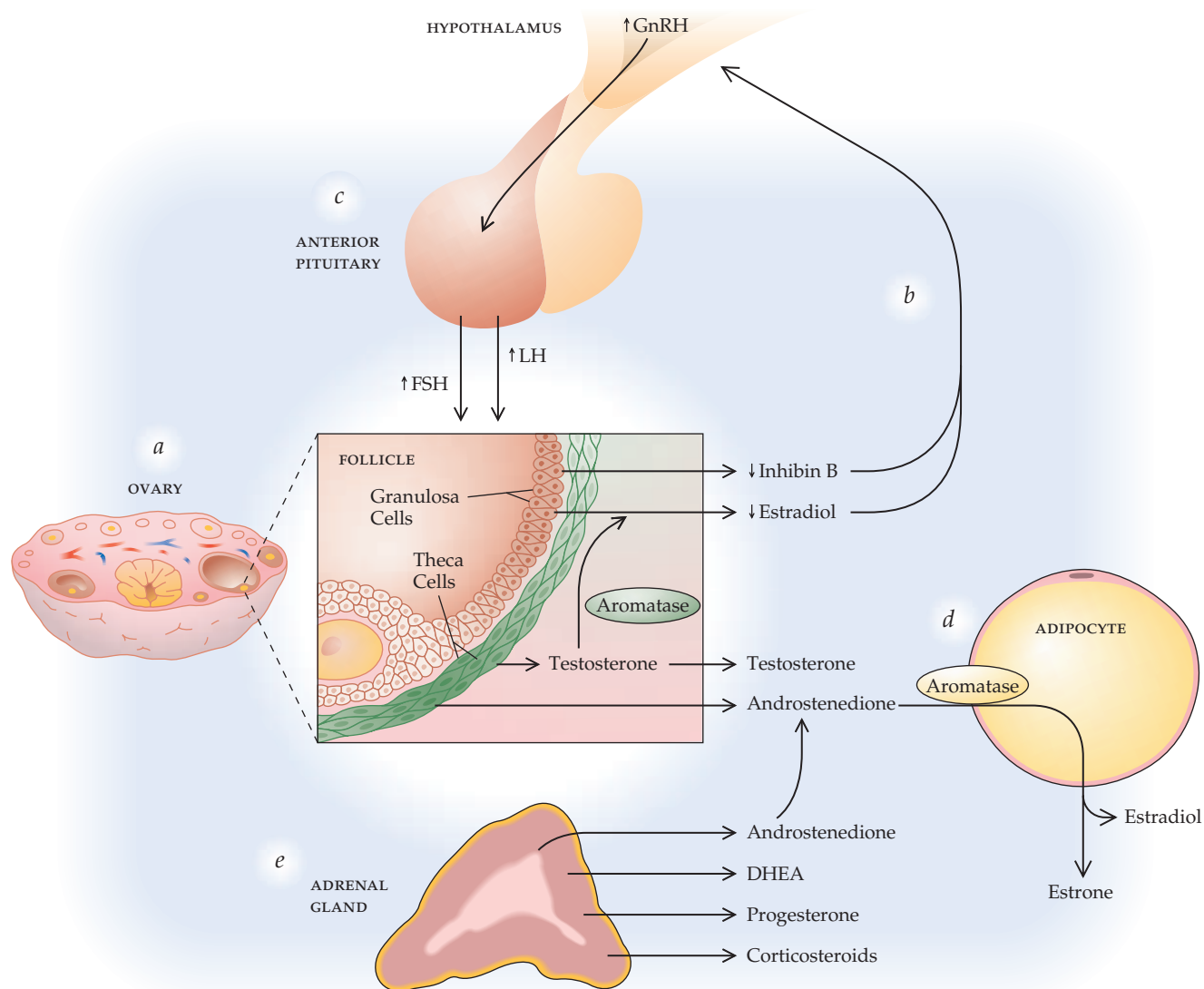


Figure 3 Multiple hormonal changes are associated with reproductive aging. (a) Within the ovary, secretion of inhibin B by granulosa cells decreases when a woman is in her mid-30s, and follicular depletion results in increasing rates of anovulation and diminished ovulatory surges of estradiol and estrone by her early 40s. Ovarian testosterone secretion continues; some ovarian testosterone is converted to estradiol by the enzyme aromatase, and the remainder is secreted as testosterone or the androgen precursor androstenedione. (b) In the menopausal transition, decreased circulating levels of inhibin and, subsequently, decreasing estradiol concentrations result in stimulation of the hypothalamus to increase secretion of GnRH. (c) Elevated circulating GnRH levels stimulate the anterior pituitary to increase secretion of FSH, followed by an increase in LH. Eventually, attempts by the brain to drive the ovary to produce estrogen fail, but production of androstenedione and testosterone by the ovarian theca cells continues in early menopause. (d) With diminished serum estrogen levels, adipocytes are stimulated to convert androstenedione to estrone via the enzyme aromatase. (e) Hormonal synthesis by the adrenal gland remains fairly constant, undergoing changes associated with aging, not menopause per se.

production declines [see Figure 3a], and adrenal output remains relatively constant [see Figure 3e]. Testosterone decreases by approximately 30% and continues to be secreted by the ovarian stroma, under the influence of LH [see Figure 3a].²⁶⁻²⁸ Serum concentrations of the adrenal androgen precursor dehydroepiandrosterone (DHEA) decrease with biologic aging, beginning before the final menstrual period [see Figure 3e].²⁶

During the reproductive years, the principal source of progesterone is the corpus luteum; small concentrations of progesterone continue to be produced by the adrenal gland after the menopause [see Figure 3e].

The overall changes in reproductive steroid hormones observed following menopause include the following:

- Negligible estradiol production by the ovary
- A shift from the ovary to the adrenal gland as the primary source of estrogen precursors
- Emergence of estrone as the dominant estrogen
- Continued testosterone production by the ovarian stroma
- An overall increase in the ratio of androgens to estrogens
- A decrease in progesterone levels resulting from anovulation

Target Tissues

During the past decade, remarkable advances in the understanding of steroid biosynthesis, metabolism, and receptor tissue specificity have occurred.²⁹ At least two estrogen receptors, ER- α and ER- β , and two progesterone receptors, PRA and PRB, have been identified. Estrogen receptors are found in the genitourinary, cardiovascular, and gastrointestinal tracts and in the brain, bone, and integument. Different tissues have a predominance of specific receptors, depending on the individual's endogenous hormonal profile. The complexity of the system leads to variations in the clinical manifestations of reproductive aging. Recent advances in the understanding of these complex physiologic processes have important implications for designing specific targeted therapies and have led to new classifications of pharmaceuticals: the selective estrogen receptor modulators (SERMs). Selective progesterone receptor modulators and selective androgen receptor modulators are also in development [see Preventive Health Care, *below*].

Endometrium During normal ovulatory cycles, progesterone, which is produced by the corpus luteum, causes the endometrium to mature to a secretory state. During the menopausal transition, endometrial shedding occurs less frequently because of anovulation, and oligomenorrhea results.⁴ Bleeding may be quite heavy in anovulatory cycles because estrogen is still produced, although at diminished levels, and stimulates the endometrium unopposed by progesterone. Furthermore, with increasing anovulation, longer cycles predominate and result in a thicker endometrium. Eventually, as anovulation predominates and estradiol production by the ovary becomes negligible, amenorrhea results.

Genitourinary epithelium The vagina is a principal target tissue for estrogen. Estrogen matures the vaginal epithelium, making it thicker and rugated. The estrogen-stimulated epithelial cells produce more glycogen, which in turn changes the bacterial flora and increases vaginal acidity.³⁰ Hypoestrogenism results in thinning of the vaginal and vulvar epithelium. The base of the bladder is also derived from müllerian tissue and likewise is estrogen sensitive. Epithelial changes in the bladder are similar to those occurring in the vagina and vulva and result in thin, pale, friable tissues.

Central and sympathetic nervous systems Fluctuations in estrogen levels are associated with hot flashes.³¹ Hot flashes are caused by thermoregulatory dysfunction that is most likely initiated by the hypothalamus in response to estrogen withdrawal. Small elevations in core body temperature are followed by peripheral vasodilation. This results in a sensation of warmth and perspiration, both of which occur at a core body temperature that is lower than normal.³² To be susceptible to hot flashes, a woman needs to have been exposed to reproductive levels of estrogen and then experience estrogen withdrawal. For example, women with Turner syndrome, who never attain reproductive levels of estrogen, do not experience hot flashes.

Alterations in dopamine, norepinephrine, and serotonin pathways³³⁻³⁵ associated with systemic estrogen fluctuations may contribute to the vasomotor symptoms experienced during the menopausal transition and postmenopause. In addition to hot flashes and diaphoresis, symptoms may include a sense of prickling of the skin, heart palpitations, and anxiety.

Sleep disruption from vasomotor instability can result in insomnia³⁶ and daytime fatigue, and it may also contribute to mood and other neuropsychiatric changes.³⁷ The prevalence of sleep-disordered breathing, including snoring and obstructive sleep apnea, increases after menopause,^{38,39} most likely because of the estrogen responsiveness of the upper airway musculature.⁴⁰ Other pathophysiologic alterations resulting in changes in cognition, mood, and sleep are not as well studied.

Women may experience a decline in libido during the menopausal transition or after the menopause.⁴¹ The contributing factors are complex and may include fatigue or stress (e.g., multiple responsibilities, including caretaking and employment), urogenital atrophy leading to dyspareunia, decreased testosterone levels [see Figure 2] (particularly in women who undergo surgical removal of both ovaries), sexual inactivity or dysfunction in a partner, and physical or emotional separation from a partner.

Bone Estrogen suppresses bone resorption. At the menopausal transition, bone resorption exceeds formation, and an accelerated loss in bone mass may occur.⁴² Bone mass may be lost at an annual rate of 3% to 5% in the first few years after the final menstrual period, but eventually, this rate of loss slows and continues at 1% to 2% a year.⁴³ Trabecular bone, the predominant type of bone in the spine, hip, and distal radius, is affected first and to a greater degree than cortical bone [see 3:VI Diseases of Calcium Metabolism and Metabolic Bone Disease].

Cardiovascular system Cardiovascular risks⁴⁴ and events⁴⁵ increase after menopause. Among the factors that contribute to an increased risk of cardiovascular events are the levels of low-density lipoprotein (LDL) cholesterol and apolipoprotein B, which are higher after menopause.⁴⁶ Estrogen receptors have been found in the muscularis of arteries in cardiovascular tissue.²⁹ Estrogens appear to have a direct vasodilatory effect on the coronary artery, mediated by the formation and release of endothelium-derived relaxing factor, reduction of endothelin levels, and the promotion of prostacyclin production.⁴⁷

Coagulation factors Menopause has been associated with increases in factor VII, factor VIII, plasminogen activator inhibitor-1 (PAI-1), and fibrinogen; all of these changes can lead to hypercoagulable states. Conversely, menopause has been associated with increased levels of antithrombin III and activated protein C, which may be beneficial in that these factors diminish

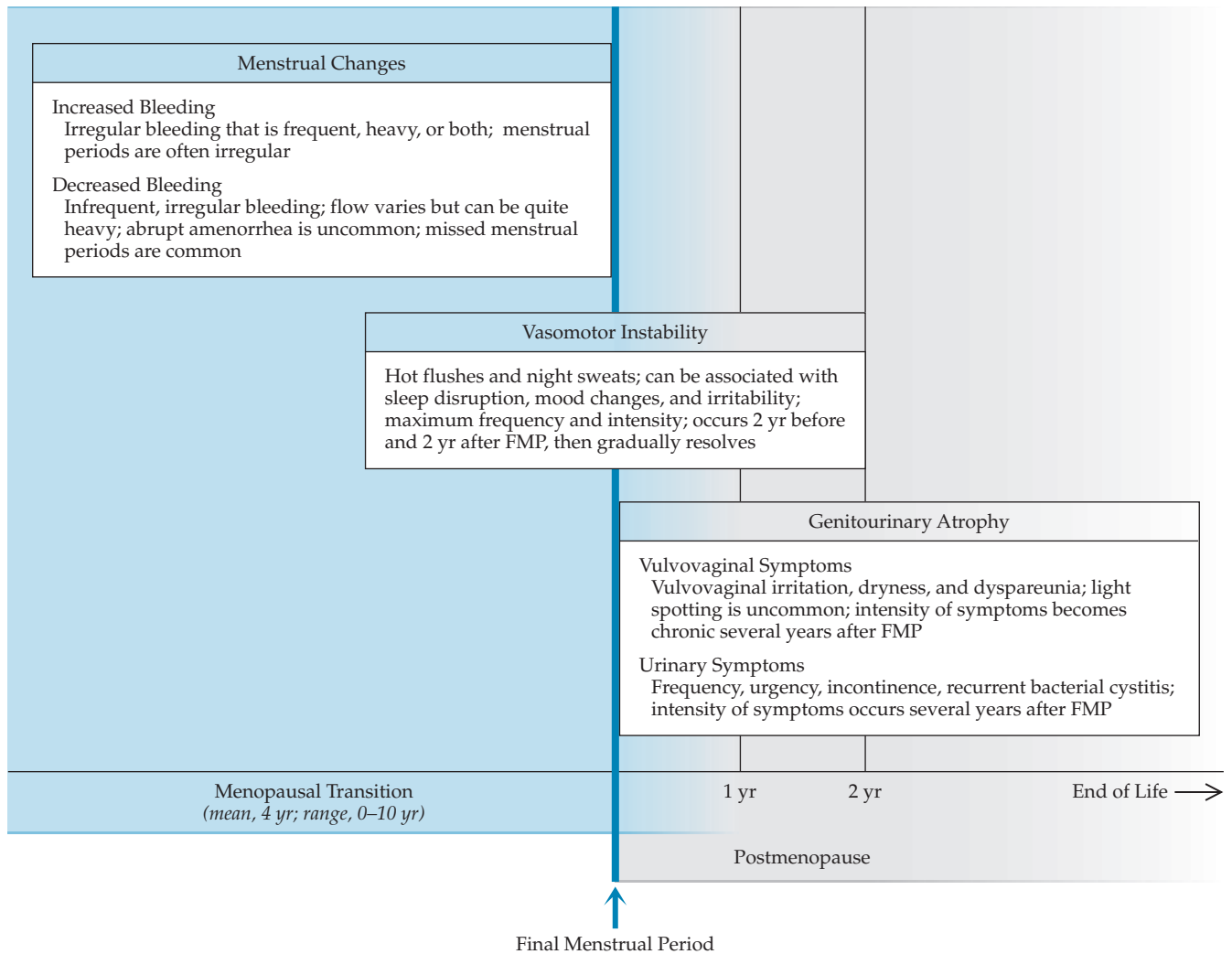


Figure 4 Characteristic symptoms of the menopausal transition and menopause. Peak vasomotor symptoms occur around the time of the final menstrual period. Menstrual changes are common before the menopause; abrupt amenorrhea preceded by normal cycles is unusual. Genitourinary atrophy is most common in postmenopause.

coagulation.⁴⁸ It is unknown whether these changes are caused by hypoestrogenism alone or by a combination of hormonal changes observed at the time of menopause.

Integument A decrease in the production of dermal collagen and a subsequent reduction in dermal thickness⁴⁹ result in significant changes in women's skin, including wrinkles and dryness. In addition, a reduced rate of cutaneous wound healing has been associated with diminished secretion of transforming growth factor- β 1 (TGF- β 1) by dermal fibroblasts.⁵⁰

Target-sensitive tissues and neoplastic growth Changes in the balance of reproductive hormones at the time of menopause have been associated with increased neoplastic growth in specific tissues. Hormonally sensitive neoplasms of the breast, colon, ovary, endometrium, and myometrium (leiomyoma) are widely recognized. Leiomyomas commonly increase in size during the menopausal transition but diminish in the postmenopausal period, presumably as a result of low levels of estradiol and progesterone. Other less common neoplasms occur in the gastrointestinal tract (esophageal and gastric)⁵¹; blood vessels; adipose and angiolymphatic tissues (angiomyolipoma,⁵² lymphangio-

myomatosis)⁵³; and the central nervous system (meningioma).⁵⁴ All of these neoplastic tissues have been found to have reproductive hormone receptors and appear to be sensitive to steroid hormones. Contrary to previous evidence, recent observations suggest that melanoma is not progesterone sensitive.⁵⁵

DIAGNOSIS

The diagnosis of menopausal transition may be suspected on the basis of symptoms (e.g., menstrual irregularity and vasomotor symptoms) in a woman older than 40 years [see Figure 4] well before it can be proven by FSH testing [see Laboratory Tests, below]. The clinical diagnosis of natural menopause is made if a woman is of an appropriate age and has had 12 months of amenorrhea accompanied by symptoms suggestive of ovarian failure, at which point the FSH serum concentration is so certainly elevated that testing is usually not useful.

Clinical Manifestations

Reproductive system changes The most common changes in the bleeding pattern in the menopausal transition are shortened cycle length, heavier flow (menorrhagia), and irregular cycle length (metrorrhagia). Intermenstrual bleeding may also oc-

cur, but it warrants specific attention because of its association with endometrial neoplasia in women older than 40 years [see Laboratory Tests, Biopsy, *below*]. A woman with vasomotor symptoms who has completely missed a menses is likely to experience her final menstrual period within the next 1 to 2 years.¹⁴ Menopause usually occurs several years after the onset of menstrual changes; however, about 10% of women experience abrupt onset of amenorrhea.^{3,4} Infertility and the cessation of menses are the only universal manifestations of menopause.

Genitourinary atrophy Genitourinary atrophy is typically mild and asymptomatic during the menopausal transition, but it is progressive and can become quite severe in the postmenopausal years.^{3,31} Atrophic vulvovaginitis can present as vaginal dryness, vulvovaginal pruritus, vaginal dyspareunia, or postcoital spotting. Atrophic urethritis and recurrent cystitis can manifest as dysuria, frequency, and incontinence.

Vasomotor symptoms Vasomotor symptoms (i.e., hot flushes and night sweats) are common manifestations of the menopausal transition; for example, 80% of white women experience vasomotor symptoms.⁵⁶ Women typically describe hot flushes as a strong sensation of warmth accompanied by flushing, a prickling sensation of the skin, and perspiration that seems to move from the trunk toward the head before it dissipates. These flushes are spontaneous, uncomfortable, and unpredictable, and they can occur any time of the day or night. Each episode is self-limited and typically lasts several minutes. A number of women describe feeling excessively warm in a more continuous pattern. The frequency of vasomotor symptoms may be represented by a bell-shaped curve that peaks around the time of the final menses.^{3,37} The occurrence of vasomotor symptoms usually ceases within 4 to 5 years from first onset, although 10% of women may suffer symptoms for much longer (up to 10 years).^{14,37}

Changes in libido, sleep, mood, and cognition Changes in mood, libido, and sleep may also occur but are variable in severity³⁷ and have a wider differential diagnosis. Snoring and daytime sleepiness suggest the possibility of obstructive sleep apnea. Women may complain of mildly diminished cognitive capacity, particularly during the menopausal transition; however, this has not been well studied.

Physical Examination

There are no pathognomonic physical findings in the menopausal transition. However, the physical examination may provide information that suggests the presenting symptoms are the result of an underlying pathologic condition and are not related to normal menopausal transition. Palpation of the thyroid gland and examination for physical signs of hypothyroidism or hyperthyroidism are warranted, particularly if menstrual irregularity, excessive diaphoresis, or neurocognitive changes are present. When intermenstrual bleeding is reported, speculum examination should be performed to rule out cervical or vaginal lesions, such as endocervical polyps. Bimanual pelvic examination is indicated when bleeding is heavy or frequent, to rule out the presence of adnexal masses and evaluate the uterus for fibroids; it is also indicated when pregnancy is possible. When the clinical presentation of oligomenorrhea or amenorrhea is not classic for the menopausal transition, prolactinoma may be suspected, in which case visual-field testing for bitemporal hemianopsia and breast examination for galactorrhea are appropriate. In addition,

inspection of the skin for needle tracks from possible injection use of heroin and evaluation for low body weight or significant weight loss may be useful, because these findings suggest a hypothalamic cause for oligomenorrhea or amenorrhea.

After menopause, vulvovaginal atrophy typically occurs. The vulvovaginal skin may appear pale, thin, and friable and may exhibit a loss of rugae and possible fissuring and erythema. The uterus is smaller, measuring 5 to 6 cm in length, and the ovaries are usually nonpalpable. The cervix may become stenotic and flush with the vagina.

Laboratory Tests

Urine or serum β -human chorionic gonadotropin (β -hCG) testing is crucial in the evaluation of any woman suspected to be in menopausal transition but who has the potential for pregnancy and who presents with a missed period, oligomenorrhea, or irregular vaginal bleeding with or without pain. In addition, testing for high-sensitivity thyroid-stimulating hormone (TSH) should be considered when menorrhagia, excessive diaphoresis, or neurocognitive changes—all potentially associated with the menopausal transition—suggest thyroid dysfunction. If the clinical picture suggests hemorrhagic diathesis, it may be helpful to obtain a platelet count, prothrombin time, and partial thromboplastin time. Additional evaluation for coagulopathies, such as von Willebrand factor, should follow, if appropriate.

With the onset of menstrual irregularity, there are wide variations in the production of FSH, estradiol, and LH.²³ Because of these wide variations, measurement of serum concentrations of these hormones is generally not useful during the menopausal transition and is not indicated unless the clinical situation is atypical and suggests an underlying condition. An elevated follicular-stage FSH level demonstrates that ovarian function is declining, but the FSH level cannot predict when the final menstrual period will occur.^{19,21,23} Once a woman has had 12 months without a menses, the FSH is reliably elevated at 25 IU/L, and the estradiol level is less than 50 pg/ml.

Oral contraceptive use during the menopausal transition will treat menopausal symptoms and mask menopause. Oral contraceptives suppress FSH; therefore, the FSH should be drawn on the seventh day of placebo pills or the seventh day of the pill-free week. If menopause has occurred, the serum FSH level will be greater than 25 IU/L when drawn on two separate occasions.

Measurement of FSH serum concentration can assist in the diagnosis of menopause in a woman with vasomotor symptoms who has had a hysterectomy without oophorectomy. FSH testing may also be appropriate in the evaluation of atypical clinical situations; for example, in a case of abrupt-onset amenorrhea in a 40-year-old woman with negative β -hCG testing, measurement of FSH, prolactin, and TSH concentrations should be performed to evaluate for premature ovarian failure, prolactinoma, or thyroid dysfunction [see Differential Diagnosis, *below*].

Tests of other body fluids Vaginal fluid pH is elevated after menopause, and vaginal cytology shows a decreased maturation index (increase in parabasal cells).³⁰ These tests are not typically performed, nor are they necessary, to establish the diagnosis of menopause. In evaluation of vaginal dyspareunia or vulvovaginal pruritus, vaginal fluid pH testing and microscopic examination of vaginal fluid (saline and 10% potassium hydroxide preparations) should be performed to rule out common vaginal infections such as candidiasis, trichomoniasis, or bacterial vaginosis. It should be noted that with genitourinary atro-

phy, the shift toward a more basic pH can precipitate bacterial overgrowth and concomitant infection.

Imaging Studies

No imaging study is useful in establishing the diagnosis of the menopausal transition or menopause, although pelvic ultrasound may be indicated in the diagnostic evaluation of women with abnormal vaginal bleeding before or after menopause. In women who present with metrorrhagia or menorrhagia during the menopausal transition, pelvic ultrasound can confirm a diagnosis of leiomyomas or endometrial polyps and can suggest a diagnosis of adenomyosis; however, ultrasound cannot rule out endometrial neoplasia in premenopausal women [see Biopsy, below]. In contrast, ultrasound can serve as a screening test for endometrial neoplasia in postmenopausal women who experience bleeding or spotting spontaneously or in conjunction with hormone therapy (HT). In a postmenopausal woman, a homogeneous endometrial thickness of 4 mm or less confers assurance that endometrial hyperplasia or cancer is not present in more than 96% of cases.⁵⁷⁻⁵⁹

Biopsy In the menopausal transition, endometrial biopsy should be performed in women who experience intermenstrual bleeding (i.e., bleeding at intervals of fewer than 21 days) or in obese women who present with menometrorrhagia. If the biopsy results are normal or if examination suggests leiomyoma or adenomyosis, ultrasonography should follow. Endometrial biopsy is also indicated in postmenopausal women at heightened risk for endometrial neoplasia (e.g., women with diabetes or obesity) who experience any bleeding after 12 months of amenorrhea or who have an ultrasound result that demonstrates an endometrium at least 4 mm in thickness.

DIFFERENTIAL DIAGNOSIS

Menstrual Changes

For women 45 to 55 years of age who are experiencing progressive oligomenorrhea, the most likely diagnosis is the menopausal transition, especially if there are associated vasomotor symptoms. In this setting, a wider differential diagnosis rarely needs to be considered. In younger women who have no vasomotor symptoms or whose menstrual changes are abrupt, a wider differential should be considered [see Premature Ovarian Failure, below]. The differential diagnosis for oligomenorrhea and secondary amenorrhea should always include pregnancy, prolactinoma, thyroid dysfunction, and medication or supplement use.

For women with excessive or intermenstrual bleeding, the differential diagnosis includes hypothyroidism, hyperthyroidism, blood dyscrasias, leiomyoma, adenomyosis, endometrial polyps, endometriosis, endometrial or cervical neoplasia, and hormone-secreting neoplasms such as granulosa cell ovarian cancer. Increased menstrual bleeding induced by medication or supplement use should also be considered.

Genitourinary Atrophy

Multiple conditions can cause genitourinary symptoms similar to those associated with hypoestrogenism occurring in the menopausal transition and menopause. Vulvovaginal symptoms (e.g., vaginal dryness, pruritus, dyspareunia, and postcoital spotting) may be caused by trichomonas vaginitis, yeast vulvovaginitis, bacterial vaginosis, desquamative inflammatory vagi-

nit, vestibulitis, allergic vulvovaginitis, and vulvar dysplasia or cancer. Urinary symptoms (e.g., dysuria, urinary frequency, and incontinence) may be caused by dietary bladder irritants, detrusor instability, urinary tract infection, and interstitial cystitis. The presence of isolated microscopic hematuria on urinalysis should prompt evaluation for neoplasia of the urinary tract.

Hot Flushes and Night Sweats

Hot flushes and night sweats may be symptoms of a number of disease processes, including hyperthyroidism, pheochromocytoma, carcinoid, and occult infection or neoplasm (e.g., tuberculosis, HIV), and lymphoma with B symptoms. Nonvolitional weight loss or documented fevers suggest a possible underlying disease. On the other hand, weight gain or existing obesity, which provides insulation against loss of body heat, may explain easy perspiration and a sensation of excess warmth in some women.

Changes in Libido, Sleep, Mood, and Cognition

The changes in libido, sleep patterns, mood, and cognition associated with the menopausal transition and menopause may also be induced by mood or anxiety disorders, thyroid dysfunction, and stress. Medications or other substances may cause insomnia, anxiety, mood abnormalities, cognitive changes, and sexual dysfunction. Other symptoms, such as fatigue, may be the result of an unrecognized sleep disorder (e.g., obstructive sleep apnea and restless legs syndrome), an inflammatory or neoplastic process, or multiple sclerosis. New cognitive dysfunction may be the first manifestation of dementia.

MENOPAUSAL TRANSITION AND POSTMENOPAUSAL SYMPTOM MANAGEMENT

Management of women experiencing menopausal symptoms is best approached by (1) defining the reproductive phase² of the patient [see Figure 1]; (2) identifying the menopausal symptoms for which treatment is desired [see Figure 4]; and (3) identifying the medical conditions that might influence management options [see Sidebar Internet Resources for Information on Menopause].

The menopausal transition and menopause do not warrant management in and of themselves. However, women who experience bothersome symptoms may want to consider treatment. HT is effective in controlling symptoms of the menopausal transition and menopause, but it carries risks [see Hormone Therapy Risks and Benefits, below].

The Food and Drug Administration has recommended that HT be used only for women with symptoms severe enough to warrant its use and at the lowest dose and for the shortest duration required to ease the menopausal transition. The FDA further recommends that tissue-targeted therapies be used whenever possible.⁶⁰

Because of the potential risks associated with HT, it is recommended that all women taking HT be evaluated on an annual basis. The woman who is taking HT should be instructed to refrain from taking HT 1 week before the annual assessment to allow the physician and patient to evaluate the current severity of symptoms. Women who choose to stop HT may require a slow taper, ranging from 3 to 6 months, for successful cessation. Women on HT are encouraged to attempt cessation after 5 years of use.

Uterine Bleeding

Vaginal bleeding during the menopausal transition is best managed (after appropriate evaluation) with low-dose, combi-

nation oral contraceptives (containing 20 µg ethinyl estradiol) or a progestin intrauterine device; both protect against pregnancy and reduce menstrual blood loss. The overall effect of ethinyl estradiol at 20 µg/day is estimated to be three to four times that of 0.625 mg/day of conjugated estrogen; head-to-head trials comparing the clinical effects of the two estrogens do not exist. Although the chance of pregnancy is low (< 1% after age 50),⁶¹ pregnancy may occur during the menopausal transition. Women 40 to 49 years of age have a rate of unintended pregnancy that is now higher than that of any other age group, even teenagers⁶²; thus, it is important to address the issue of contraception with every potentially fertile woman until she has experienced 12 months of amenorrhea. Oral contraceptives can be discontinued and symptoms reassessed at approximately age 50 [see Laboratory Testing, *above*]. Those with persistent and severe vasomotor symptoms and amenorrhea may be transitioned to postmenopausal HT.

Genitourinary Atrophy

Symptoms of genitourinary atrophy may be present during the menopausal transition but typically become more prominent after menopause. Symptoms of genitourinary atrophy usually improve within 2 weeks after initiation of estrogen therapy and should be controlled after 1 to 3 months of use.⁶³ Estrogen can be administered topically with excellent local effect. Vaginal estrogen creams result in little or no systemic absorption when used at extremely low doses of less than one-eighth applicator (< 0.15 mg conjugated estrogen cream) and one-sixteenth applicator (< 0.025 mg estradiol cream); a full applicator of vaginal estrogen cream can deliver a dose equivalent to that of an oral formulation, although the rate of absorption varies considerably. Initial therapy constitutes nightly application for 2 to 6 weeks; thereafter, maintenance doses can be applied one to three times a week, depending on the severity of symptoms. Use of low-dose vaginal creams does not necessitate the use of a progestin; however, cessation of therapy results in the return of genitourinary atrophy. Low-dose vaginal estrogen rings effectively treat genitourinary atrophy with little or no systemic absorption and no significant endometrial stimulation.

Nonhormonal alternatives include lubricants for use during intercourse and vaginal moisturizers.

Vasomotor Symptoms

Estrogen is highly effective for the treatment of vasomotor symptoms. For women in the menopausal transition who are at risk for pregnancy and who have heavy or frequent menses, treatment with low-dose oral contraceptives provides amelioration of vasomotor symptoms, control of bleeding, and contraception. Cyclical HT is preferable for women in the menopausal transition who are predominantly anovulatory and who do not need contraception, because it provides lower doses of hormones than oral contraceptives. Continuous HT, which is commonly used in women who are approximately 12 months from the final menstrual period, is often associated with bothersome bleeding patterns in women in earlier stages of the menopausal transition.

Low-dose oral contraceptives and HT result in prompt resolution of symptoms within 1 to 2 weeks in 80% of women; they should be titrated to the lowest dose possible to achieve acceptable symptom relief. Systemic administration of estrogen can be achieved orally, transdermally (in the form of a gel or patch), or transmucosally (at a higher dose via the use of a vaginal ring).

Internet Resources for Information on Menopause

General Information about Menopause for Clinicians and Patients

North American Menopause Society

<http://www.menopause.org>

Women's Health Initiative

<http://www.whi.org>

Alternative Therapies for Management of Menopausal Symptoms

University of Washington School of Medicine, Department of Family Medicine, on Complementary and Alternative Medicine

<http://www.fammed.washington.edu/predoctoral/CAM>

ConsumerLab.com

<http://www.consumerlab.com>

The Longwood Herbal Task Force

<http://www.mcp.edu/herbal>

Natural Medicines Comprehensive Database

<http://www.naturaldatabase.com>

Some formulations include progestins. Implants and intramuscular injections are less preferable forms of delivery because they release extremely high levels of HT at the time of administration or placement. The lowest doses of estrogens found to be effective for vasomotor symptoms include oral conjugated estrogen 0.03 mg, oral estradiol 0.5 mg, and transdermal estradiol 0.025 mg.

Several nonhormonal alternatives for treatment of vasomotor symptoms may have some efficacy. These include venlafaxine,^{64,65} selective serotonin reuptake inhibitors (SSRIs) (e.g., fluoxetine and paroxetine),⁶⁶⁻⁶⁸ and gabapentin.⁶⁹ Less evidence supports the use of clonidine^{70,71} and vitamin E⁷² as being effective in the control of vasomotor symptoms. Results from controlled clinical trials evaluating the effectiveness of phytoestrogens (including dietary soy) for vasomotor symptoms vary, but most studies indicate that the use of phytoestrogens offers no significant improvement over placebo in reducing the frequency of hot flashes.⁷³ Black cohosh, a possible phytoestrogen, may be effective, but no large controlled trials have been conducted.⁷⁴ Progestin alone is effective^{75,76} but is not recommended because of a potential increased risk of breast cancer.⁷⁷ Behavioral modification^{78,79} and increased exercise^{78,80} may diminish the severity of hot flashes. Red clover extract, dong quai, evening primrose oil, and Siberian ginseng have not been found to be effective in small randomized, controlled trials. Other botanicals purported to be effective, including valerian, motherwort, and chasteberry, have not been studied in clinical trials.⁸¹

Libido, Sleep, Mood, and Cognition

Treatment of sexual dysfunction depends on the underlying etiology. If the cause of decreased libido is not predominantly psychosocial, testosterone therapies have been shown, in some circumstances, to improve sexual function, interest and frequency of desire, and psychological well-being.^{82,83} There are no FDA-approved products for diminished libido in women; however, esterified estrogen combined with methyltestosterone is commonly used. Vaginal estrogen therapy, if indicated, can play an important role in the treatment of diminished sexual function resulting from urogenital atrophy.⁶³

Vasomotor instability may contribute to disruption of sleep;

thus, estrogen is effective for some women who begin to experience insomnia during the menopausal transition. Alternative therapies include short-term zolpidem and low-dose trazodone.

Estrogen may be beneficial in the treatment of depression in the menopausal transition.⁸⁴ Estrogen alone, without an antidepressant, does not appear to be sufficient to treat significant clinical depression in postmenopausal women.⁸⁵ However, some investigators support the use of estrogen as an adjunct to other therapies, such as SSRIs, particularly in older women.⁸⁶

MANAGEMENT CONSIDERATIONS

Risks and Benefits of Hormone Therapy

Although the risks and benefits of using HT for the relief or prevention of symptoms in women in the menopausal transition have not been evaluated in clinical trials, information has been established on the risk-to-benefit profile of short-term and long-term use of HT for postmenopausal women 50 to 79 years of age. Historically, it was believed that the estrogen deprivation that accompanies menopause increases the risk of some chronic diseases—specifically, heart disease, osteoporosis, and dementia. On the basis of observational data, long-term postmenopausal HT was recommended during the 1980s and 1990s not only for symptom relief but also to reduce the risk of chronic disease and to prolong life. However, two large randomized, controlled trials (i.e., Heart and Estrogen/Progestin Replacement Study [HERS]⁸⁷ and the Women's Health Initiative [WHI])^{88,89} called this practice into question. HT is no longer recommended for primary or secondary prevention of these conditions in women older than 50 years.

HERS demonstrated no evidence to support the use of HT for the secondary prevention of heart disease⁸⁷; more important, WHI found that HT use conferred an increased risk of cardiovascular disease,⁹⁰ stroke,⁹¹ dementia,⁹² thromboembolism,⁸⁸ and breast cancer⁹³ in women 50 to 79 years of age. Striking discrepancies in the findings of the randomized trials and the earlier nonrandomized (observational) studies can be explained by selection biases in participants in the observational studies. In the

observational studies, women opting for HT therapy tended to be healthier and of higher socioeconomic status than non-HT users. In addition, these women were more likely to be carefully screened for chronic disease before starting HT and, therefore, had a lower risk of developing chronic disease than nonusers of HT.⁹⁴ The selection biases inherent in the observational studies were virtually eliminated in the randomized trials.

Counseling about the risks of postmenopausal HT use should now be based on the evidence provided by WHI.^{88,89,91-100} The WHI postmenopausal estrogen and progestin therapy (EPT) and estrogen therapy (ET) trials are discussed in greater detail below.

Estrogen and progestin therapy The WHI prematurely halted its clinical trial of EPT in 2002; participants had been followed for an average of 5.2 years. The trial randomized over 16,000 postmenopausal women who were 50 to 79 years of age to take either conjugated equine estrogen (0.625 mg/day) plus medroxyprogesterone acetate (2.5 mg/day) or placebo. The study was halted because the rates of adverse events (i.e., cardiovascular events, stroke, thromboembolism, and breast cancer) were 1% higher in the intervention group and overshadowed the reduced risk of osteoporotic fractures and colon cancer.⁸⁸ There was no difference in overall or disease-specific mortality between the HT and placebo groups. The study reported the following risks: (1) thromboembolic events were highest in the first year and remained elevated over 5 years (absolute risk difference, 21/10,000/yr); (2) ischemic cardiac events were highest in the first year and remained elevated and statistically unchanged thereafter (absolute risk difference, 7/10,000/yr); (3) stroke risk was not elevated in the first year, rose slightly in the second year, and remained elevated through year 5 (absolute risk difference, 8/10,000/yr); and (4) breast cancer risk was not appreciably higher in years 1 to 3 but became elevated in year 4 (absolute risk difference, 8/10,000/yr), with the increased breast cancer risk being strongest in the approximately 25% of women who had taken HT before enrolling in the study [see Table 1]. The EPT portion of the WHI study showed a

Table 1 WHI Findings: Outcomes Associated with Use of Combined Estrogen and Progestin and Estrogen Alone in Healthy Postmenopausal Women

Outcomes	Combined Estrogen and Progestin*		Estrogen Alone†	
	Relative Risk (95% CI)	Absolute Risk Difference‡	Relative Risk 95% (CI)	Absolute Risk Difference‡
Adverse/neutral				
Deep vein thrombosis ^{88,89}	2.07 (1.49–2.87)	13	1.47 (1.04–2.08)	6
Pulmonary embolism ^{88,89}	2.13 (1.39–3.25)	8	1.34 (0.87–2.06)	11
Coronary artery disease ^{89,90}	1.24 (1.00–1.54)	7	0.91 (0.75–1.12)	5
Ischemic stroke ^{89,91}	1.44 (1.09–1.90)	8	1.39 (1.10–1.77)	12
Breast cancer ^{89,93}	1.24 (1.01–1.54)	8	0.77 (0.59–1.01)	7
Probable dementia ^{§95,98}	2.05 (1.21–3.48)	23	1.49 (0.83–2.66)	12
Beneficial/neutral				
Colorectal cancer ^{88,89,100}	0.56 (0.38–0.81)	6	1.08 (0.75–1.55)	1
All fractures ^{88,89,96}	0.76 (0.69–0.85)	44	0.70 (0.63–0.79)	56
Mortality ^{88,89}	0.98 (0.82–1.18)	1	1.04 (0.88–1.22)	3

*Patients received 0.625 mg/day of conjugated estrogen and 2.5 mg/day of medroxyprogesterone acetate.

†Hysterectomized patients received 0.625 mg/day of conjugated estrogen.

‡Annual per 10,000 women.

§Ages: 65–79 yr.

CI—confidence interval

reduction in the risk of hip fractures (absolute risk difference, 6/10,000/yr)⁹⁶ and colorectal cancer (absolute risk difference, 6/10,000/yr).¹⁰⁰

The Women's Health Initiative Memory Study (WHIMS), a substudy of the WHI continuous combined HT intervention trial, observed the effect of HT on memory and cognition in women 65 to 79 years of age (average age, 73 years).^{92,95} A reduction in memory and thinking abilities (as measured by the Modified Mini-Mental State Examination)⁹⁵ and an increase in dementia of all types (absolute risk increase, 2/1,000/yr) were observed in women who took HT.⁹²

Estrogen therapy The estrogen-only arm of WHI was halted prematurely in early 2004 because of increased risk of stroke; participants had been followed for an average of 6.8 years.⁸⁹ Over 10,000 women 50 to 79 years of age were randomized to receive 0.625 mg/day of conjugated equine estrogen or placebo. As in the EPT portion of WHI and HERS, the ET portion of the WHI trial found that estrogen use conveyed an increased risk of deep vein thrombosis (1.47 relative risk; 95% confidence interval [CI], 1.04 to 2.08) and stroke (1.39 relative risk; 95% CI, 1.10 to 1.77) [see Table 1]. Women taking ET had 12 more strokes and six more events of deep vein thrombosis a year than the women taking placebo. The study showed a reduction in the incidence of hip fractures (0.61 relative risk; 95% CI, 0.41 to 0.91) and an unanticipated, though not statistically significant, reduction in breast cancer incidence, a finding that requires further investigation. Observational studies support an increased risk of thromboembolism,¹⁰¹⁻¹⁰³ cholecystitis,¹⁰⁴ and breast cancer⁷⁷ in women taking ET.

In contrast to the EPT portion of the WHIMS study, women taking estrogen alone did not have a statistically increased risk of dementia.⁹⁸ For women taking ET, as compared with placebo, the risk of having a 10-unit decrease in the Modified Mini-Mental State examination scores (greater than two standard deviations) was 1.47 (95% CI, 1.04 to 2.07). The risk was greater in women with lower cognitive function at initiation of ET.⁹⁹

Type, route of administration, and dose of HT Two observational studies^{77,105} and a population-based study from Southern California¹⁰⁶ have increased current understanding of the type, route of administration, and dose of HT with associated breast cancer risk. The findings are as follows: (1) use of estrogen therapy confers greater risk than nonuse^{77,107}; (2) use of estrogen plus progestin confers greater risk than use of estrogen alone^{77,105,106}; (3) risk increases with duration of estrogen use^{77,105,106}; (4) risk with estrogen use is increased in women with low or normal body mass index but not in overweight and obese women¹⁰⁵; (5) increased risk of breast cancer is associated with any dose and type of commonly used estrogen (i.e., conjugated estrogen and estradiol) and progestin (i.e., medroxyprogesterone acetate, norethisterone, and levonorgestrel/norgestrel); and (6) transdermal formulations of estrogen also confer increased risk.⁷⁷ Surprisingly, the use of tibolone, a synthetic steroid with estrogenic, progestogenic, and androgenic properties that is marketed in Europe for its favorable effect on breast symptoms (e.g., tenderness and mastalgia), was also associated with a greater risk of breast cancer than nonuse of steroid hormones.⁷⁷ Current evidence indicates that all forms of HT are associated with an increased risk of breast cancer.

Transdermal delivery of estrogen may not be safer if administration is long term; however, transdermal patches and trans-

mucosal delivery systems (including estrogen vaginal rings that provide systemic levels of estrogen for treatment of vasomotor symptoms) avoid the first-pass effect through the liver and may carry a lower risk of thromboembolism,^{48,102,108,109} elevation of bile acids,¹¹⁰ and hypertriglyceridemia¹¹¹ than oral estrogen. Studies of moderate- to high-dose regimens suggest that transdermal systems may have a more favorable effect on the coagulation pathway¹¹² and C-reactive protein¹¹³ than oral products. Transdermal and transmucosal products have been shown to be effective as treatment for vasomotor symptoms¹¹⁴ and maintenance of bone mineral density.¹¹⁵

Given the newly appreciated risks of oral progestins,^{77,88} alternative approaches to progestin therapy are gaining popularity. There is a widely held belief that natural progesterone is better than synthetic progestins, but this hypothesis has never been studied. Lower-dose oral micronized progesterone formulations have been widely used in Canada and Europe and were evaluated in the Postmenopausal Estrogen/Progestin Intervention (PEPI) trial.¹¹⁶ The PEPI study of 596 postmenopausal women found that micronized progesterone combined with estrogen sufficiently diminished the hyperplastic endometrial changes associated with estrogen-only therapy.¹¹⁶ No other randomized clinical trials exist to better inform us about risks and safety of micronized progesterone, particularly with respect to breast cancer. Likewise, over-the-counter transdermal progesterone creams have not been studied in this regard.

In addition, attention has been directed at nonsystemic therapies. Off-label use of a progestin intrauterine system (IUS) (20 µg/day of levonorgestrel) in postmenopausal women taking estrogen provides low systemic levels of progestin and attenuation of endometrial stimulation by estrogen.¹¹⁷ Intrauterine levonorgestrel at doses of 10 µg and 14 µg/day have been studied in Europe.^{117,118} No increased risk of endometrial hyperplasia or cancer has been observed in women taking estrogen with a progestin IUS in place.¹¹⁷ Vaginal application of progesterone creams result in local uterine and systemic effects.¹¹⁹

Preventive Health Care

The menopausal transition offers women and their health care providers the opportunity to review and focus on preventive health care measures, including basic health habits, such as regular exercise, good nutrition with calcium and vitamin D supplementation, and avoidance of smoking [see Table 2].

WHI demonstrated that HT is effective for the prevention of osteoporotic fractures and colorectal cancer in postmenopausal women, but the risks outweigh the benefits⁸⁸ [see Table 1]. The prevalence of certain medical conditions (e.g., dementia, coronary artery disease, breast cancer, colon cancer, and diabetes mellitus) increase with age, rising more steeply after loss of ovarian function. Recommended management for these conditions is almost always nonhormonal. HT is not indicated for primary prevention of disease, unless a woman at high risk for osteoporosis chooses HT over other options after consideration of the risks and benefits.⁶⁰ Two chronic disease processes associated with hypoestrogenism and aging greatly impact women's health in the postmenopausal years, namely cardiovascular disease and osteoporosis. Cardiovascular disease is the leading cause of death in women in the United States, and osteoporosis is a major cause of morbidity. The management of these diseases is discussed more fully elsewhere [see 16:IX Cardiovascular Disease in Women and 3:VI Diseases of Calcium Metabolism and Metabolic Bone Disease].

Table 2 Preventive and Screening Measures for Common Conditions in Postmenopausal Women

Condition	Prevention	Early Detection
Dementia	Participation in cognitive leisure activities Regular exercise Treatment of hypertension Statins and possibly other lipid-lowering agents Long-term NSAID use* Avoidance of HT initiation in postmenopause†	
CAD	Smoking cessation Regular exercise Diet high in nuts, whole-grains, and total fiber (especially water-soluble fiber), folate, and marine n-3 fatty acids Diet low in saturated fat, <i>trans</i> fatty acids, and glycemic load Daily, low-dose alcohol Prevention and treatment of hypertension, diabetes mellitus, and hypercholesterolemia Consideration of low-dose daily aspirin if risk of CAD events is $\geq 0.7\%/yr$ Avoidance of HT initiation in postmenopause Statins, aspirin, and beta blockers for secondary prevention (underutilized)	
Breast cancer	Minimal exposure to HT (estrogen and/or progestin) Regular exercise Avoidance of increase in weight and waist circumference Weight loss if overweight/obese Reduction of alcohol intake to 0–20 g/day Raloxifene* if at average risk, or tamoxifen if risk $\geq 1.67\%/yr$	Screening mammography every 1–2 yr, with or without clinical breast exam regardless of age until clinically significant comorbid conditions
Osteoporosis	Adequate calcium and vitamin D intake Weight-bearing exercise Thiazide* diuretics Antiresorptive treatment before first osteoporotic fracture Antiresorptive treatment after osteoporotic fracture HT† if intolerant of or unresponsive to first-line agents	Screening DEXA at age 65 (earlier if risk factors)
Colon cancer	High-fiber diet for primary, but not secondary, prevention of polyps Aspirin* if personal history of adenoma or colon cancer Removal of adenomatous polyps HT* effective but not advised for this indication†	Periodic screening‡ by fecal occult blood testing or sigmoidoscopy
Diabetes mellitus	Regular exercise Weight loss if overweight/obese Metformin, acarbose, and possibly thiazolidinediones for those at high risk HT† effective but not advised for this indication	

*Off-label indication.

†Increased risk of adverse outcomes has been demonstrated for HT initiation in the postmenopausal years. HT is not advised for the primary prevention of disease, because associated risks outweigh benefits for most women; in limited cases, HT may be used for prevention of osteoporosis, after consideration of all other options. HT should be used only for severe and debilitating symptoms, in the lowest dose and most directed therapy possible, and for the shortest time necessary to accomplish symptom control.

‡The United States Preventive Services Task Force (USPSTF) recommends screening for colon cancer starting at age 50 using either annual fecal occult blood testing, sigmoidoscopy (periodicity unspecified), or both.

HT—hormone therapy CAD—coronary artery disease DEXA—dual x-ray absorptiometry NSAID—nonsteroidal anti-inflammatory drug

Premature Ovarian Failure

Premature ovarian failure (POF) is defined as menopause that occurs before 40 years of age that is not iatrogenically induced. The prevalence of POF is approximately 1%.¹²⁰ The Study of Women Across the Nation (SWAN) investigated risk factors associated with POF¹²¹ and found that ethnicity influences risk: POF occurs in 1.1% of white women and 1.4% of African-American and Hispanic women, but it occurs in only 0.5% of Chinese-American women and 0.1% of Japanese-American women. Higher body mass index is associated with increased likelihood of POF, especially in African-American

women. Disability and current smoking are associated with greater risk in white women.

ETIOLOGY

There is good evidence to suggest that the timing of the age of menopause is genetically programmed^{15,16} and that genes play a significant role in the etiology of premature ovarian failure.¹²⁰ Rare genetic and chromosomal causes of premature ovarian failure include familial predisposition, FSH receptor mutations, galactosemia, 17 α -hydroxylase deficiency, alterations in gonadotropin structure or function, and structural alterations of the X

chromosome (e.g., Turner syndrome mosaicism). A common genetic cause of POF is the fragile X premutation. Up to 3% to 5% of women with POF are carriers of the fragile X premutation, the most common cause of mental retardation in males.¹²² Approximately 16% of women who are fragile X premutation heterozygotes have POF.¹²³

Premature menopause may be immune-mediated in 30% to 50% of women with POF.¹²³ Family history is often positive for autoimmune conditions,¹²⁴ and other autoimmune diseases may be present in the patient herself,¹²⁴ including autoimmune thyroiditis, type 1 diabetes mellitus, autoimmune hemolytic anemia, Addison disease, hypoparathyroidism, idiopathic thrombocytopenic purpura, Crohn disease, myasthenia gravis, rheumatoid arthritis, systemic lupus erythematosus, vitiligo, and polyendocrine failure.

DIAGNOSIS

Clinical Manifestations

The presentation of premature ovarian failure is identical to that observed in natural menopause, with the exception that POF occurs before 40 years of age. It is more common, however, for women with POF to experience waxing and waning of symptoms over longer periods than it is for women who have natural menopause, and some women will ovulate several years after a diagnosis of POF is made.

Physical Examination

A targeted examination for women with oligomenorrhea or secondary amenorrhea is described elsewhere [see Natural Menopause, Physical Examination, *above*]. Less common etiologies of POF, such as Turner Syndrome (i.e., short stature, webbed neck, shield chest, small fourth metacarpal, and minimal breast development with normal hair distribution), can be detected with a specifically targeted physical examination. Findings of other autoimmune conditions often associated with POF [see Etiology, *above*] may be present in some women, including signs of thyroid disease (i.e., enlarged, asymmetrical, or nodular thyroid gland; dry skin; lateral eyebrow thinning; delayed relaxation phase on deep tendon reflexes; and myxedema), adrenal dysfunction (i.e., hyperpigmentation and orthostatic hypotension), and systemic lupus erythematosus (i.e., synovitis or malar rash). Galactorrhea suggests an elevated prolactin (PRL) prolactinoma [see Differential Diagnosis, *below*].

Laboratory Tests

Ovarian failure is most accurately confirmed by measurement of serum FSH. In women with incipient ovarian failure, FSH levels are often between 15 and 25 IU/L and can fluctuate. Complete ovarian failure is associated with repeated serum FSH levels greater than 25 IU/L. Therefore, FSH levels persistently greater than 25 IU/L (drawn on at least two separate occasions) can be useful in making the diagnosis of POF. Testing of urine or serum β -hCG, TSH, and prolactin concentrations should not be deferred if indicated in the evaluation of oligomenorrhea or secondary amenorrhea [see Natural Menopause, Laboratory Tests, *above*]. If a diagnosis of POF is made, consideration of genetic testing for a premutation allele of fragile X may be advisable, providing that this information would benefit family members and that the patient agrees to testing. If a woman younger than 30 years is diagnosed with POF, a karyotype test should be considered to rule out Turner syndrome mosaicism. When POF

may be caused by autoimmunity, the complete blood count (CBC), erythrocyte sedimentation rate (ESR), rheumatoid factor (RF), antinuclear antibody (ANA), glucose, calcium, and phosphorus levels can point to associated autoimmune conditions that may not otherwise be clinically apparent.

DIFFERENTIAL DIAGNOSIS

Hypergonadotropic amenorrhea can be caused by thyroid dysfunction, hyperprolactinemia, heroin addiction, and the use of some antidepressant and antipsychotic medications.

MANAGEMENT

All women with POF should be treated with exogenous estrogen, either in the form of a low-dose estrogen-progestin combination contraceptive or a postmenopausal HT formulation to manage symptoms and decrease the risk of osteoporosis and osteopenia. Bone mineral density should be obtained at baseline and followed at intervals of 3 to 5 years. It is recommended that women continue estrogen replacement until at least age 50 (approximately the time of natural menopause). Progestin therapy is recommended for women who have a uterus. Women who are at risk for unintended pregnancy should receive exogenous estrogen and progestin in the form of a contraceptive. For those desiring pregnancy, artificial reproductive technology is available. In vitro fertilization utilizing donor eggs and hormonal manipulation to mature the endometrium result in successful pregnancy in women with POF as often as in women with infertility from other causes.¹²⁵

Treatment with oral contraceptives in the general population is associated with an increased risk of thromboembolic disease, cardiovascular disease in smokers, and stroke in women with migraine headaches or hypertension.¹²⁶ The risks of using oral contraceptives and postmenopausal HT in women with POF has not been specifically studied.

COMPLICATIONS AND PROGNOSIS

The chance of spontaneous pregnancy in POF is estimated to be less than 10%.¹²⁷ Women with POF may be at higher risk for younger onset of cardiovascular disease.¹²⁸ It is estimated that women with POF who do not take estrogen have a lower background risk of breast cancer and thromboembolism than the general population.¹²⁹ New onset of autoimmune disorders is not uncommon after the diagnosis of POF has been made.

Early-age mortality may occur in women with POF because of autoimmune phenomena, cardiovascular disease, and osteoporosis. A few epidemiologic studies suggest that an earlier age at menopause is associated with substantially increased mortality^{128,129}; thus, careful screening for and management of chronic disease processes associated with hypoestrogenism [see Table 2] may be important for sustaining long-term health and quality of life. In addition, careful management of any coexisting autoimmune disorder and reduction, when possible, of potential risks posed by medications used to treat such disorders (e.g., corticosteroids) may be crucial for the long-term health of affected women.

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The progestin intrauterine system and esterified estrogen combined with methyltestosterone have not been approved by the FDA for uses described in this chapter.

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Acknowledgments

Figure 1 Modified from "Executive Summary: Stages of Reproductive Aging Workshop (STRAW)," by M. R. Soules, S. Sherman, E. Parrott, et al., in *Fertility and Sterility* 76:874, 2001.

Figure 3 Seward Hung.