# Menopause

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Updated: Apr 7, 2014

## Practice Essentials

Menopause is diagnosed after 12 months of amenorrhea.[1, 2] Hormonal changes and clinical symptoms occur over a period leading up to and immediately following menopause; this period is frequently termed the climacteric or perimenopause but is increasingly referred to as the menopausal transition.[1, 2]

### Essential update: Postmenopausal calcium/vitamin D supplementation appears to increase 25OHD3 levels and improve lipid profiles

Schnatz et al evaluated the effect of increased levels of serum 25-hydroxyvitamin D3 (25OHD3) from calcium/vitamin D supplementation on the lipid profiles of 600 postmenopausal women randomly selected from the Women's Health Initiative Calcium/Vitamin D Trial. They found that daily supplementation with 1,000 mg of elemental calcium and 400 IU of vitamin D3 significantly increased concentrations of 25OHD3 and decreased levels of low-density lipoprotein cholesterol.[3] Moreover, women with higher concentrations of 25OHD3 had higher levels of high-density lipoprotein cholesterol but lower triglyceride levels.

### Clinical effects

During the menopausal transition, physiologic changes in responsiveness to gonadotropins and their secretions occur, with wide variations in hormone levels. Women often experience a range of symptoms, including the following:

- Hot flashes or flushes (most common)
- Insomnia
- Weight gain and bloating
- Mood changes
- Irregular menses
- Mastodynia
- Depression
- Headache

The temporal pattern of symptoms is as follows:

- Symptoms may begin up to 6 years before the final menstrual period and continue for a variable number of years after the final menstrual period[1, 2, 4]
- As the postmenopause years progress, with an accompanying loss of ovarian response to gonadotropins, associated affective symptoms of menopause also decline

On pelvic examination, the effects of gonadal hormone depletion (which may be noted before menopause in some women) are as follows:

- With loss of estrogen, the vaginal epithelium becomes redder as the epithelial layer thins and the small capillaries below the surface become more visible
- Later, as the vaginal epithelium further atrophies, the surface becomes pale because of a reduced number of capillaries
- Rugation diminishes, and the vaginal wall becomes smooth
- The menopausal ovary diminishes in size and is no longer palpable during gynecologic examination
- The uterus becomes smaller
- Fibroids, if present, become less symptomatic, sometimes shrinking to the point where they can no longer be palpated on manual pelvic examination
- In older women, a general loss of pelvic muscle tone occurs, sometimes manifested as prolapse of reproductive or urinary tract organs

Urogenital effects of diminished hormone levels are as follows:

- A decrease in urine pH leading to a change in bacterial flora may result in pruritus and a malodorous discharge
- Vaginal changes often result in insertional dyspareunia
- Endometriosis and adenomyosis are alleviated
- Atrophic cystitis, when present, can mimic a urinary tract infection

## Menopause markers

Laboratory markers of menopause include the following:

- An increase in serum follicle-stimulating hormone (FSH) and decreases in estradiol and inhibin are the major endocrine changes that occur during the transition to menopause[1, 2]
- FSH levels are higher than luteinizing hormone (LH) levels, and both rise to even higher values than those seen in the surge during the menstrual cycle
- The FSH rise precedes the LH rise; FSH is the diagnostic marker for ovarian failure, while LH is not necessary to make the diagnosis
- The large cyclical variation of estradiol and estrone observed during the menstrual years ceases, and fluctuation in levels is small and inconsequential, with the mean value being considerably lower
- No specific changes in thyroid function related to menopause have been found

*Endometrial changes*

- Endometrial biopsy can show a range of endometrial appearances, from mildly proliferate to atrophic
- No secretory changes are observed after menopause, because no ovulation occurs and therefore no corpus luteum forms to produce progesterone
- Endometrial hyperplasia is a sign of hyperstimulation by estrogen from either endogenous sources or replacement therapy and may be a precursor of endometrial cancer
- Endometrial hyperplasia can also be suggested by ultrasonographic findings (ie, endometrial thickness >5 mm), which are useful for excluding hyperplasia and cancer of the endometrium in postmenopausal women

## Osteoporosis

Bone loss accelerates in the late menopausal transition and continues for the first few years after menopause.[5] Postmenopausal women and elderly women should be treated early and on a long-term basis unless a contraindication to such treatment exists.

Current treatment options for preventing fractures among postmenopausal women with osteoporosis include the following:

- Bisphosphonates (alendronate, etidronate, ibandronate, risedronate, zoledronic acid)
- Selective estrogen receptor modulators (SERMs; eg, raloxifene)
- Calcium
- Vitamin D
- Calcitonin
- Monoclonal antibodies
- Hormonal medications
- Estrogen therapy (considered a second-line therapy for osteoporosis[6] )

### Replacement therapy

The main reasons for treating symptoms of the menopausal transition and actual menopause are as follows:

- To provide relief of vasomotor symptoms
- To reduce the risk of unwanted pregnancy
- To avoid the irregularity of menstrual cycles
- To preserve bone
- To lower the risk of disease
- To improve quality of life

*Disease risk*

In the Women's Health Initiative (WHI), greater safety and possible benefit from hormone or estrogen therapy for women in their 50s, with potential harm for older women, were observed with respect to the following[7] :

- Coronary artery disease (CAD)
- Total myocardial infarction
- Colorectal cancer
- Total mortality
- Global index of chronic diseases

Although immediate use of hormone or estrogen therapy in the early postmenopausal time may reduce the risk of CAD, the WHI clearly showed that women more than 9 years post menopause should not be started on hormone therapy or estrogen therapy for CAD prevention.

Administration routes for hormone therapy are as follows:

- Oral
- Transdermal
- Topical
- Vaginal route cream, ring, or tablet for vaginal symptoms

Contraindications for estrogen therapy include the following:

- Undiagnosed vaginal bleeding
- Severe liver disease
- Pregnancy
- Venous thrombosis
- Personal history of breast cancer

Well-differentiated and early endometrial cancer, once treatment for the malignancy is complete, is no longer an absolute contraindication. Progestins alone may relieve symptoms if the patient is unable to tolerate estrogens.

### Nonhormonal therapy

In June 2013, the FDA approved paroxetine mesylate (Brisdelle) as the first nonhormonal therapy for vasomotor symptoms (VMS) (hot flashes) associated with menopause.[8, 9]

## Overview

Menopause, by definition, is the final menstrual period. It is a universal and irreversible part of the overall aging process as it involves a woman's reproductive system. Menopause is diagnosed after 12 months of amenorrhea and is characterized by a myriad of symptoms that include, but are not limited to, changes from regular, predictable menses; vasomotor and urogenital symptoms such as vaginal dryness and dyspareunia; and sleep and mood dysfunction.[1, 2]

Hormonal changes and clinical symptoms occur over a period leading up to and immediately following menopause. This period is frequently termed the climacteric or perimenopause but is increasingly referred to by a more recently coined name, the menopausal transition (MT).[1, 2] The MT characteristically begins years before menopause.

Along with the increase in the number of middle-aged and older individuals, there is a concomitant and continuing rise in the number of women who live most of their lives in a hypoestrogenic state. More and more women can expect to live approximately 79 years and to experience the consequences of gonadal steroid hormone loss.

Although the time spent in menopause (now up to one third of the life cycle) has increased, the average age at which menopause occurs, approximately 50-51 years, has not changed since antiquity. Women from ancient Greece experienced menopause at the same age as modern women do, with the symptomatic transition to menopause usually commencing at approximately age 45.5-47.5 years.[4, 10] Factors that can lower the age of physiologic menopause include the following:

- Smoking[10, 11]
- Hysterectomy
- Oophorectomy
- Fragile X carrier
- Autoimmune disorders
- Living at high altitude
- History of receiving certain chemotherapy medications or undergoing radiotherapy

For related information, see Menopause Resource Center. For patient education resources, see the Women's Health Center and the Bone Health Center, as well as Menopause, Female Sexual Problems, and Hormone Replacement and Osteoporosis.

## Physiology

Menopause results from loss of ovarian sensitivity to gonadotropin stimulation, which is directly related to follicular attrition. The oocytes in the ovaries undergo atresia throughout a woman's life cycle, resulting in a decline in both the quantity and the quality of follicles. Thus, the variable menstrual cycle length during the menopausal transition (MT) is due more to a shrinking follicle cohort size than to follicle failure.

Anovulatory cycles and absence of cyclicity become common, with a highly variable pattern of gonadotropin and steroid hormone production, estrogen insensitivity, failure of the luteinizing hormone (LH) surge, the occurrence of the final menstrual period, and permanent amenorrhea.[1, 2]

Hormonal fluctuation may not be responsible for all irregular bleeding during this period; therefore, pelvic pathology (eg, uterine fibroids, uterine polyps, endometrial hyperplasia, or endometrial cancer), which becomes more prevalent during this time, must be excluded through endometrial sampling (eg, with endometrial biopsy [EMB] or dilatation and curettage [D&C]).

During the fifth decade of life, many women are lulled into a false sense of security, thinking that they are

no longer fertile because they are so close to menopause. Although fertility declines, pregnancy can still occur, as demonstrated by a relatively high rate of unintended pregnancies in women aged 40-44 years. In fact, the number of unintended pregnancies in this age group has increased over the past decade,[12] which underscores the need for continued contraceptive practice in heterosexual couples.

A shorter menstrual cycle (< 25 days) is the most common change in menstrual cyclicity that occurs during the MT in women who have no pelvic pathology and who continue to be ovulatory.[13] Because functional follicles, which are stimulated by follicle-stimulating hormone (FSH) during the first part of the menstrual cycle, have declined in number, less recruitment of oocytes occurs, and the follicular phase shortens accordingly. However, once ovulation occurs, the luteal phase remains fairly constant, at 14 days.

Over time, as aging follicles become more resistant to gonadotropin stimulation, circulating FSH and LH levels increase. Elevated FSH and LH levels lead to stromal stimulation of the ovary, with a resultant increase in estrone levels and a decrease in estradiol levels. Inhibins are peptides of the transforming growth factor (TGF)-β superfamily and are produced by the granulosa cells of the ovarian follicles in the terminal stages of development. Inhibin levels also drop during this time because of the negative feedback of elevated FSH levels.[1, 2, 14]

With the commencement of menopause and a loss of functioning follicles, the most significant change in the hormonal profile is the dramatic decrease in circulating estradiol, which rapidly declines over a period of 4 years (starting 2 years before the final menstrual period and stabilizing approximately 2 years after the final period). Without a follicular source, the larger proportion of postmenopausal estrogen is derived from ovarian stromal and adrenal secretion of androstenedione, which is aromatized to estrone in the peripheral circulation.

Total serum testosterone levels do not change during the MT. Dehydroepiandrosterone (DHEAS) levels do decline with age. A trend toward higher total cholesterol, low-density lipoprotein (LDL), and apolipoprotein B levels, in conjunction with loss of the protective effect of high-density lipoprotein (HDL), is characteristic in menopause.[1, 2, 15]

With cessation of ovulation, estrogen production by the aromatization of androgens in the ovarian stroma and estrogen production in extragonadal sites (adipose tissue, muscle, liver, bone, bone marrow, fibroblasts, and hair roots)[15] continue, unopposed by progesterone production by a corpus luteum. Consequently, perimenopausal and menopausal women are often exposed to unopposed estrogen for long periods, and this exposure can lead to endometrial hyperplasia, a precursor of endometrial cancer.

Although estradiol levels decrease significantly because of the loss of follicular production with menopause and postmenopause, estrone, which is aromatized from androstenedione from nonfollicular sources, is still produced and is the major source of circulating estrogen in the postmenopausal female.

Because most conversion of androgens to estrogens occurs in adipose tissue, it is frequently assumed that obese women, who have more circulating estrogen, should have fewer complaints of vasomotor symptoms. However, this is not always the case, and vasomotor symptoms of menopause can be as frequent and severe in heavier women as they are in thinner women.

The clinical indication that menopause has occurred is a rise in the measured FSH level. The FSH level rises more than the LH level because of the reduced renal clearance of FSH in comparison with LH. A slightly elevated or borderline menopausal FSH level in the MT may not be a reliable indicator of menopause, because of the wide variation of FSH and LH levels in response to increased release of gonadotropin-releasing hormone (GnRH) by the hypothalamus and increased pituitary sensitivity to GnRH.

Repeated measurement of FSH and LH levels at 2- to 3-month intervals is helpful for establishing whether the woman is progressing through menopause. Women with elevated, but not postmenopausal, FSH levels are still at risk for pregnancy, and contraception should continue to be used until FSH levels remain in the postmenopausal range.

## Clinical Effects

The menopausal transition (MT) is a time when physiologic changes in responsiveness to gonadotropins and their secretions occur, and it is characterized by wide variations in hormonal levels. Women often experience a range of symptoms, including the following:

- Hot flashes or flushes
- Insomnia
- Weight gain and bloating
- Mood changes
- Irregular menses
- Mastodynia
- Depression
- Headache

As noted, the length of time over which these symptoms occurs is widely variable; symptoms may begin up to 6 years before the final menstrual period and continue for a variable number of years after the final menstrual period.[1, 2, 4] As the postmenopause years progress, with an accompanying loss of ovarian response to gonadotropins, associated affective symptoms of menopause also decline.

The effects of gonadal hormone depletion can be obvious on pelvic examination, with changes noted before menopause in some women. The reproductive organs of a woman who is of reproductive age greatly differ in appearance from the organs of a woman who is menopausal. With loss of estrogen, the vaginal epithelium becomes redder as the epithelial layer thins and the small capillaries below the surface become more visible. Later, as the vaginal epithelium further atrophies, the surface becomes pale because of a reduced number of capillaries.

A decrease in urine pH leading to a change in bacterial flora may result in pruritus and a malodorous discharge. Rugation also diminishes, and the vaginal wall becomes smooth. Such changes often result in insertional dyspareunia and, for many women, eventually lead to sexual abstinence if left untreated.

Inside the pelvis, the uterus becomes smaller. Fibroids, if present, become less symptomatic, sometimes shrinking to the point where they can no longer be palpated on manual pelvic examination. Endometriosis and adenomyosis are also alleviated with the onset of menopause, and many patients with pelvic pain finally achieve permanent pain relief.

The menopausal ovary diminishes in size and is no longer palpable during gynecologic examination. A palpable ovary on pelvic examination warrants a full evaluation in all women who are menopausal or postmenopausal.

For older women, a general loss of pelvic muscle tone also occurs, sometimes manifested as prolapse of reproductive or urinary tract organs (see Uterine Prolapse and Pelvic Organ Prolapse). Vaginal pressure, lower back pressure, or bulging at the vaginal introitus is common in women with prolapse. On examination, cystocele, rectocele, and uterine prolapse are obvious as causes of these symptoms.

In September 2013, the North American Menopause Society (NAMS) updated and expanded its recommendations regarding symptomatic vulvovaginal atrophy (VVA) in postmenopausal women.[16, 17] Among the recommendations are the following[17] :

- Discuss with patients how VVA is diagnosed and treated
- For mild symptoms, use over-the-counter products such as vaginal lubricants and moisturizers
- Depending on symptom severity, use prescription therapies, such as vaginal estrogen, hormone therapy, and ospemifene (a selective estrogen-receptor modulator that is indicated for dyspareunia),
- Do not use progesterone with local administration of low-dose estrogen in women without a uterus and, generally, in those with an intact uterus

NAMS also noted the following[17] :

- Vaginal microflora affect VVA symptoms
- Therapy is based on the patient’s symptom severity and preference, as well as the clinical efficacy

and safety of the treatment
- Estrogen remains the most effective therapy for moderate to severe symptomatic VVA, but there are no head-to-head studies between estrogen and ospemifene
- Long-term studies regarding endometrial safety and use of local estrogen and ospemifene are still needed

Atrophic cystitis, when present, can mimic a urinary tract infection (UTI). Women report symptoms of urinary frequency, urgency, and incontinence. However, atrophic cystitis renders women more prone to UTI during this time, and a urine culture should be obtained in all symptomatic women.

In addition to alterations in the pelvic organs, marked changes occur throughout the body. Skin loses elasticity, bone mineral density (BMD) declines, and dense breast tissue is replaced by adipose tissue, making mammographic evaluation easier.

The most common presenting complaint in the MT is symptomatic hot flashes. Flashes (or flushes), which are unpredictable in onset and sometimes occur over many years, are reported in about 75% of women who are perimenopausal or postmenopausal. Hot flashes often cause embarrassment and discomfort, as well as sleep disturbances and emotional lability, especially if they are intense and occur frequently. Vasomotor episodes usually last a few minutes. Their frequency ranges from hourly to every few days.

A woman whose flushes are severe enough to cause major sleep disturbances may also complain of cognitive or affective disorders resulting from sleep deprivation. The vasomotor flush is described as a feeling of warmth or heat that begins from the umbilical area and moves upward toward the head, followed by sweating of the head and upper body.

Other cardiovascular or neurologic symptoms (eg, palpitations, dizziness, light-headedness, and vertigo) can also occur, with or without flushing, making the episode more difficult to classify as simply a climacteric symptom. Because of the wide range of symptoms, symptomatic women who have risk factors for a condition other than menopause should undergo thorough evaluation.

A study by Kim et al suggests menopause does not increase the risk of diabetes.[18]

## Osteoporosis and Menopause

Although osteoporosis is one of the most pervasive conditions in older women, it often is not taken seriously enough by menopausal women. With proper intervention, osteopenia is a largely preventable sequela of menopause. Osteoporosis is defined as a bone mineral density (BMD) equal to or greater than 2.5 standard deviations (SDs) below the peak bone mass, or T score. Osteopenia is defined as a BMD that is 1.0-2.49 SDs below the T score.[19]

In a 2001 meta-analysis of data from 22 trials involving a total of 8800 women, Grady and Cummings found a 27% reduction in risk of nonvertebral fractures in older women who received hormone therapy.[20] For hip and wrist fractures, the risk reduction was 40%, increasing to 55% in women younger than 60 years. The data from the Women's Health Initiative (WHI) also demonstrated decreased bone fractures in women on hormone therapy.

After the findings of the WHI were released, millions of women in the United States discontinued hormone therapy. Karim et al evaluated the impact of this cessation and found that women who discontinued hormone therapy were at higher risk for hip fracture and lower BMD than women who continued hormone therapy; they also found that the protective effect of hormone therapy against hip fracture disappeared within 2 years of cessation.[21]

The onset of menopause leads to rapid loss of BMD because bone resorption, uncoupled from bone formation, is accelerated while formation continues at the premenopausal rate. Trabecular bone is affected more than cortical bone; thus, bone loss is more commonly observed at vertebral, coaxial, and radial sites. The normal bone loss associated with senescence is different from the accelerated loss observed after menopause. Bone loss in just the few years after onset of menopause may be as high as 20% of lifetime

bone loss.[20]

The overall effect of menopausal bone loss is reduction of bone strength, leading to an increased risk of fracture. The younger the woman is when ovarian function ceases, the more severe bone loss is likely to be. Similarly, the lower the woman's bone mass is when she enters menopause, the more severe the osteoporosis will be.

The severity of osteoporosis is also related to race, being worse in whites than in Asians and least severe in women with dark complexions. Other risk factors are smoking and slender build. Osteoclasts have been shown to have estrogen receptors, and these are hypothesized to be the mechanism by which estrogen replacement protects against osteoporosis.

Bone densitometry is the most accurate clinical predictor of osteoporosis. If bone mass is more than 1 SD below average for the specific bone measured, the risk of fracture is much higher. Other risk factors for osteopenia and osteoporosis include low serum estrogen, female sex, low serum androgen, smoking, physical inactivity, low body weight, and little exposure to sunlight. Bone densitometry testing is recommended for all postmenopausal women. Neither the age of initial BMD screening nor the optimal frequency of screening has been determined.

Assessment of bone density by means of dual-energy x-ray absorptiometry (DXA) is the standard for diagnosing osteoporosis. However, the cost of this test is high, and the test is not universally available. The Australian Primary Care Evaluation of Clinical Tests (PROSPECT) suggests that a better prescreening protocol can reduce the need for unnecessary radiologic tests at the primary care level.[22] Assessment of risk factors such as age, prior fracture, risk of falling, and BMD is valuable in predicting fracture risk.[23]

Currently, there are many treatment options for preventing fractures among postmenopausal women with osteoporosis, including the following:

- Bisphosphonates
- Selective estrogen receptor modulators (SERMs)
- Calcium
- Vitamin D
- Calcitonin
- Monoclonal antibodies
- Hormonal medications
- Estrogen therapy (considered a second-line therapy for osteoporosis[6] )

Variations in osteoporosis care are common among physicians. Whereas the majority of patients receive bisphosphonates, younger patients who have fewer comorbidities or are cared for by physicians with greater experience have a greater chance of receiving SERMs, hormone replacement therapy, or calcium and vitamin D.[24] Oral and transdermal estrogen preparations have been approved for osteoporosis prevention in postmenopausal women who are considered at risk.

Bone loss accelerates in the late menopausal transition and continues for the first few years after menopause.[5] Postmenopausal women and elderly women should be treated early and on a long-term basis unless a contraindication to such treatment exists.

Bisphosphonates (alendronate, etidronate, ibandronate, risedronate, and zoledronic acid), are the most useful pharmacologic intervention. Most of them prevent vertebral fractures, as do raloxifene, calcitonin, and estrogen. Some bisphosphonates (alendronate, risedronate, and zoledronic acid) and estrogen prevent hip and other nonvertebral fractures. Whether bisphosphonates prevent fractures more effectively than the other therapies is unknown.[6] Bisphosphonates increase BMD more than raloxifene and calcitonin do.[25, 26, 27]

Alendronate, risedronate, and ibandronate are all both widely used and effective. In the Vertebral Efficacy With Risedronate Therapy (VERT) study, which included 2458 postmenopausal women with vertebral

fractures from 110 centers, administration of risedronate at a dose of 5 mg for 36 months yielded a statistically significant reduction in the relative risk of new vertebral fractures.[27] The cumulative incidence of nonvertebral fractures was also reduced.

In May 2010, the *Journal of the American Medical Association* reported a possible association between bisphosphonates and atypical femoral fractures.[28] Further data on this possibility should be forthcoming, but a letter to the editor in the *New England Journal of Medicine* presented data disputing the extent of these atypical fractures and emphasized that overall, fracture rates are much lower in patients who take bisphosphonates than in those who do not.[29]

A population-based nationwide analysis of atypical fractures in bisphosphonate users in Sweden concluded that for individual patients with a high risk of osteoporotic fractures, the absolute risk of osteoporotic fractures is small in comparison with the beneficial effects of the medication.[30]

Initially, both alendronate and risedronate were introduced with daily dosing for treatment of osteoporosis. Currently, patients can be prescribed a weekly dose of either alendronate or risedronate, which increases the tolerability of these agents and reduces side effects. Ibandronate is approved for monthly use, and zoledronic acid is approved for once-yearly use.

The main adverse effects of bisphosphonates continue to be gastrointestinal upset and reflux. Patients with significant gastroesophageal reflux disease (GERD) should be discouraged from bisphosphonate use unless it is approved by a gastroenterologist. Supplementation with calcium 1000-1500 mg/day remains a mainstay of prevention, as does vitamin D supplementation and regular weight-bearing exercise. Excessive salt, animal protein, alcohol, and caffeine offset these benefits.

Raloxifene is an SERM that acts directly on estrogen receptors in the bone to decrease resorption. In clinical trials with up to 8 years of follow-up, raloxifene significantly reduced the risk of vertebral, but not nonvertebral, fracture.[31] Raloxifene, tamoxifen, and estrogen all were shown to increase the risk of thromboembolic events.[6]

The combination product of bazedoxifene, a SERM, and conjugated estrogens (CEs) was approved by the FDA in October 2013. Combining a SERM with CEs lowers the risk of uterine hyperplasia caused by estrogens. This eliminates the need for a progestin and its associated risks (eg, breast cancer, MI, VTE). In clinical trials, this combination decreased bone turnover and bone loss in postmenopausal women at risk for osteoporosis. Bone mineral density increased significantly more with all bazedoxifene/CE doses compared with placebo at the lumbar spine and total hip and with most bazedoxifene/CE doses compared with raloxifene at the lumbar spine.[32] Bazedoxifene/CE is FDA-approved for prevention of osteoporosis and treatment of vasomotor symptoms in postmenopausal women.

Calcitonin is a peptide hormone that acts by inhibiting osteoclasts, which are involved in bone resorption activity. A decreased vertebral fracture rate has been demonstrated with this therapy, as has a small increase in BMD in older women. Serum calcium levels must be monitored in patients taking this drug.

## Cardiovascular Issues and Menopause

Coronary artery disease (CAD) is the leading cause of morbidity and mortality in men and postmenopausal women. Menopause increases the risk for women still further, independent of age. Before menopause, the risk of CAD for women lags behind the risk for men by approximately 10 years; after menopause, it catches up. As a result, mortality from CAD is increasing in women. The Framingham study was pivotal in showing the relation between menopause and increased cardiovascular mortality.[33]

The Women's Health Initiative (WHI) was a randomized, controlled trial that addressed the issue of whether postmenopausal women should take hormone therapy or estrogen therapy for prevention of CAD[34, 35] ; more than 27,000 healthy women participated in the trial. The investigators concluded that hormone therapy and estrogen therapy are not indicated for the prevention of CAD.

Emerging analyses of WHI data from the Estrogen-Alone Trial—a double-blind, placebo-controlled, randomized clinical trial evaluating the effects of conjugated equine estrogens (CEE) on chronic disease incidence among postmenopausal women with prior hysterectomy and after a mean of 7.1 years of follow-up—suggested that treatment effects differ by age.[7] Compared with older women, younger women receiving CEE had a lower risk of CAD.

Greater safety and possible benefit for women in their 50s, with potential harm for older women, were observed with respect to coronary heart disease, total myocardial infarction, colorectal cancer, total mortality, and the global index of chronic diseases.[7] Although immediate use of hormone or estrogen therapy in the early postmenopausal time may reduce the risk of CAD, the WHI clearly shows that women more than 9 years post menopause should not be started on hormone therapy or estrogen therapy for CAD prevention.

Initiating hormone therapy or estrogen therapy in the immediate perimenopausal or postmenopausal period is believed to be beneficial because significant atherosclerotic changes have not yet occurred. Once 9 years have passed since menopause, the arterial damage seems to have commenced.

Studies are ongoing to prove these theories in humans and primate models. Studies of hormones and atherosclerotic arterial plaques in ovariectomized monkeys show promise in this regard.[36, 37] Further evidence in support of estrogen's protective effects when it is used within a few years of menopause came from the subanalysis by Manson et al in 2007, which showed that there was less coronary artery calcification in women taking oral CEE than in those taking placebo.[38]

Data from the National Heart, Lung, and Blood Institute (NHLBI)-sponsored Women's Ischemia Syndrome Evaluation suggested that by using the quantitative measurements of the timing and type of menopause and hormone therapy use, earlier initiation was associated with less angiographic CAD in women with natural, but not surgical, menopause.[39]

The beneficial effect of estrogen on cardiovascular mortality is due to many factors. One mechanism appears to be estrogen's effects on lipid metabolism, which includes reducing low-density lipoprotein (LDL) and increasing high-density lipoprotein (HDL). Studies have suggested that the best predictors of CAD in men and women are different[40] and that triglycerides, HDL, and lipoprotein(a) may be more significant in women.[41]

Women with elevated lipoprotein(a) levels should be treated more aggressively, and the treatment considered should include estrogen therapy, as well as a statin. A positive relation between estrogen therapy and reduction of primary cardiovascular risk has been demonstrated in several studies, and the risk reduction in women who are taking estrogen therapy may be similar to the risk reduction in those who are receiving specific lipid-lowering therapy.[42]

In view of the WHI data, however, neither hormone therapy nor estrogen therapy should be given for CAD at this time. The primary indication for hormone therapy or estrogen therapy is symptomatic relief of vasomotor symptoms.

The Heart and Estrogen/Progestin Replacement (HERS) Study,[43, 44, 45] a study of 2763 postmenopausal women with known CAD, compared the effect of continuous combined hormone therapy versus that of placebo over an average of 4.2 years; no beneficial reduction of CAD event rates was initially observed in the hormone therapy groups.

In fact, the initial adverse event rate was higher in the treatment arm than in the placebo arm, offsetting a later reduction in risk in the hormone therapy group.[43, 44, 45] An 11% reduction in LDL and a 10% increase in HDL were apparent in the treatment group. These observations together suggest that the protective effects of estrogen on cardiovascular morbidity result from many mechanisms and not solely from lowering of lipids and that estrogen alone is inadequate for secondary prevention of CAD.

The Postmenopausal Estrogen/Progestin Interventions (PEPI) Trial, compared various CAD risk factors as

predictors of outcomes in 875 healthy postmenopausal women who received various hormone therapy regimens by randomizing the participants to receive either placebo or 1 of 5 estrogen/progestin regimens.[46]

All treatment groups showed an overall improvement in HDL and LDL levels in comparison with the placebo group.[46] The improvement in HDL level was better in the group that received unopposed estrogen than in the other treatment groups; however, individuals using unopposed estrogen also had the highest rate of endometrial hyperplasia.

The Nurses' Health Study demonstrated an approximately 11% risk reduction for primary cardiovascular disease in postmenopausal women who used hormone therapy compared with women who had never used hormone therapy, irrespective of the duration of use.[47] The risk reduction did not appear to be dose-dependent. However, these data have been eclipsed by those reported by the WHI.

The greatest beneficial effect of estrogen appears to be on endothelial function. Women undergoing angioplasty appear to be protected against restenosis by estrogen therapy.[48] Progression of early atherosclerosis, as measured by carotid intimal thickness, was greater over time in postmenopausal women who smoked than in women who smoked and were on estrogen therapy.[49]

Monkey studies have shown that coronary vasculature has a favorable response to CEEs.[50, 51] These findings continue to be investigated in further human studies, in the breakdown of age groups in the WHI data, and in animal studies.[37, 50, 52]

## Breast Cancer and Menopause

Estrogen therapy is known to benefit postmenopausal women in a multitude of ways, mostly through the relief of vasomotor symptoms associated with postmenopause. Estrogen is also beneficial for the prevention and treatment of osteoporosis.

Much controversy exists about the use of estrogen and breast cancer. Some studies show an increased risk of breast cancer with postmenopausal estrogen use; others show a decrease. A possible link to cancer is also suggested by the finding that breast cancer risk is increased in women with an earlier age at menarche and a later age at menopause. However, a reduction in risk is observed with early age at pregnancy and the interruption of menstrual hormonal changes. The role of estrogen in the development of breast cancer continues to be studied.

In the Women's Health Initiative (WHI), the incidence of breast cancer increased in the estrogen-plus-progestin versus placebo arm of the study (38 vs 30 per 10,000 person years); however, the incidence of breast cancer decreased in the estrogen-only versus placebo arm of the study (26 vs 33 per 10,000 person years).[34, 35]

Additional follow-up in patients from the WHI suggested similar results: Breast cancer incidence and mortality were increased in the estrogen-plus-progestin group as compared with the placebo group.[53] The role of combined estrogen-plus-progesterone therapy (associated with most of the breast cancer risk) continues to be puzzling in the development of breast cancer.

Data suggest a slightly increased relative risk with estrogen use, approximately 1.1-1.3,[54, 55] but not all of the evidence supports this finding.[56] The risk appears to be related to duration of use, with longer-term users being more affected.[57]

Data suggest that the addition of sequential progestin to the regime increases the RR of subsequently developing breast cancer beyond the risk associated with estrogen alone, though some believe that continuous combined hormone therapy using much smaller doses of progestin may attenuate this risk.[58] Most earlier studies evaluating breast cancer risk and estrogen therapy were conducted at a time when the progestin in hormone therapy was administered on a cyclical basis.

Notably, women with a history of using hormone therapy have more localized tumors, as well as better survival rates. That is, women receiving hormone therapy who are diagnosed with breast cancer are found to have more favorable staging at the time of diagnosis,[55] including smaller tumor size, negative lymph node involvement, and better-differentiated tumor histology.[59, 60, 61, 62, 63, 64, 65, 66, 67]

A beneficial effect on breast cancer mortality has been documented in postmenopausal women who have received hormone therapy as compared with controls who have no prior history of hormone therapy use.[54] Study findings do not agree on whether the benefit is due to earlier detection or to effects of the therapy itself on breast tissue.

The general belief is that any increase in risk is small and that each patient should be evaluated as a candidate for estrogen therapy or hormone therapy on an individual basis, with the overall balance of risks and benefits taken into account. An essential precept in the management of menopause is that each individual is unique and that therapy should be tailored accordingly. AT present, the main indication for hormone therapy and estrogen therapy remains the relief of vasomotor symptoms.

## Central Nervous System and Menopause

The association between estrogen and memory function is an intriguing area of research. Normal aging itself induces a decline in certain cognitive capabilities, and a lack of estrogen may contribute to this process. If this is the case, postmenopausal estrogen therapy may be able to preserve this function and slow or even prevent decline in certain cognitive functions.

An inherent difficulty in this area involves the limitations of objective cognitive testing for functions such as memory. Postmenopausal women receiving estrogen therapy have shown better performance on memory testing than postmenopausal control subjects not receiving estrogen therapy.[68, 69] The effect of estrogen is to slow the decline of preserved memory function. Women's Health Initiative (WHI) data do not show improved cognitive function in women taking either hormone therapy or estrogen therapy.[34, 35]

Current data suggest that Alzheimer disease (AD) is more common in women than in men, even when the longer average lifespan of women is taken into account, because AD is primarily an age-related condition.[70] In earlier studies, estrogen therapy appeared to reduce the relative risk of AD or to delay its onset.[71, 72] Estrogen therapy has not been shown to improve cognitive function in patients with AD; it cannot reverse previous cognitive decline and therefore has no role as a sole treatment modality in AD. WHI data support this view.

The menopausal transition (MT) is frequently a time of depressive symptoms arising from direct hormonal effects and changes in life circumstances and occurring secondary to effects such as estrogen-related sleep disturbance and vasomotor symptoms. However, major depression is associated with the female sex at all ages. Objective demonstration of a cluster of cases around menopause has been difficult, though there is some anecdotal evidence for such clustering.

Regardless of whether the criteria for a definitive diagnosis of major depression are met, depressive symptoms should always be considered in the context of level of functioning; any functional impairment warrants consideration of intervention.

In all but a very few cases, symptoms caused by menopause may not be distinguishable from symptoms caused by primary depression. Treatment of depressive symptoms with estrogen in perimenopause, the postpartum period,[73] and premenstrual syndrome is common, with observed resultant improvement in functioning and mood, both subjective and objective, in many clinical instances.

Clinical depression, however, warrants treatment with antidepressants, with estrogen showing benefit as adjuvant therapy in this scenario. Short-term use of estrogen during times of estrogen fluctuation seems to be of some benefit.[74]

The microcellular effects of estrogen in the central nervous system (CNS) have yet to be clearly outlined,

but further research may reveal intricate processes by which estrogen exerts a direct effect on CNS function. One of these processes may turn out to be a reduction in free radical damage by estrogen therapy.

## Menopause Markers

Gonadotropin secretion increases dramatically after menopause. Follicle-stimulating hormone (FSH) levels are higher than luteinizing hormone (LH) levels, and both rise to even higher values than those seen in the surge during the menstrual cycle. The FSH rise precedes the LH rise. FSH is the diagnostic marker for ovarian failure. LH is not necessary to make the diagnosis.

The large cyclical variation of estradiol and estrone observed during the menstrual years ceases, and fluctuation in levels is small and inconsequential, with the mean value being considerably lower. The levels of circulating estradiol have very different ranges before and after menopause, and these levels are obviously much lower in menopause. Smears of the vaginal epithelium provide a composite picture of endogenous and exogenous estrogen stimulation over time; the more estrogen present, the greater the number of superficial cells.

No specific changes in thyroid function related to menopause have been found.

Other markers of ovarian aging include anti-Müllerian hormone (AMH) and Müllerian-inhibiting substance (MIS), which are produced by granulosa cells of all follicles. Assessment of these markers may be the earliest and most effective way of measuring progress toward menopause. At present, however, testing is not sufficiently developed to be considered a standard of care. Consequently, an increase in serum FSH and decreases in estradiol and inhibin are the major endocrine changes that occur during the transition to menopause.[1, 2]

*Endometrial assessment*

Endometrial biopsy can show a range of endometrial appearances, from mildly proliferate to atrophic. No secretory changes are observed after menopause, because no ovulation occurs and therefore no corpus luteum forms to produce progesterone.

Endometrial hyperplasia is a sign of hyperstimulation by estrogen from either endogenous sources or replacement therapy and may be a precursor of endometrial cancer. Endometrial hyperplasia can also be suggested by ultrasonographic findings (ie, endometrial thickness > 5 mm), which are useful for excluding hyperplasia and cancer of the endometrium in postmenopausal women.

The European Menopause and Andropause Society (EMAS) released a new clinical guide that provides recommendations on endometrial assessment in perimenopausal and postmenopausal women. The recommendations also address how to deal with inconclusive evaluations and persistent symptoms, as well as testing in women who use tamoxifen and unopposed estrogen.[75, 76]

The EMAS recommendations include the following:

- Speculum examination and palpation should always be done first to exclude non-endometrial gynecologic pathology
- Once speculum examination and cervical cytology have been assessed, transvaginal ultrasound scanning should be performed initially because it is noninvasive and will measure endometrial thickness, as well as detect other pelvic pathology (eg, leiomyomas, ovarian tumors)
- The primary indication for invasive methods should be to obtain endometrial tissue to diagnose or exclude endometrial cancer or premalignancies
- Hysteroscopy allows visually guided biopsies and the identification and removal of focal lesions, including endometrial polyps or submucous fibroids in the uterine cavity
- No single method is perfect, and a combination of methods may be necessary

## Hormonal Replacement Therapy

The main reasons for treating symptoms of the menopausal transition (MT) and actual menopause are as follows:

- To provide relief of vasomotor symptoms
- To reduce the risk of unwanted pregnancy
- To avoid the irregularity of menstrual cycles
- To preserve bone
- To lower the risk of disease
- To improve quality of life

The time at which therapy should be begun depends on the patient's presenting complaints (if any) and medical history. It is the opportune time to conduct a health evaluation, identify risk for osteoporosis and other specific diseases, and assess for alterable behavioral risk factors.

Whether a woman is in the MT or in actual menopause affects the choice of the most suitable type of therapy. Counseling regarding hormone therapy differs, depending on the patient's age and hysterectomy status. Many factors, including personal history, family history, smoking, peer and commercial influences, culture, need for contraception, ethnicity, and economics, also play roles in the final decision, and all must be carefully weighed by the clinician and patient together.

In May 2013, the British Menopause Society and Women's Health Concern issued updated guidelines on the use, benefits, and risks of hormone replacement therapy (HRT).[77, 78] Key recommendations include individualization of HRT, annual risk/benefit assessment, use of HRT in women with premature ovarian insufficiency, an exploration of pharmacologic alternatives to HRT, and a discussion of the benefits of phytoestrogens.

In January 2014, the American College of Obstetricians and Gynecologists released an updated Practice Bulletin on the treatment of vasomotor symptoms of menopause and vaginal atrophy.[79] Recommendations include the following:

- Systemic hormone therapy with estrogen or estrogen plus progestin is the most effective treatment for vasomotor symptoms.
- Low-dose estrogen and ultra-low systemic doses of estrogen have a better adverse effect profile than standard doses.
- Alternatives to hormone therapy for vasomotor symptoms include selective serotonin reuptake inhibitors, selective serotonin and norepinephrine reuptake inhibitors, clonidine, and gabapentin.
- Use of progestin alone, testosterone, compounded bioidentical hormones, phytoestrogens, herbal supplements, and lifestyle modifications are not supported by the data.

Adverse effects of replacement therapy may include bloating, mastodynia, vaginal bleeding, and headaches. Selective estrogen receptor modulators (SERMs) and estrogen increase the risk of thromboembolic events.[6] Unexplained adverse effects are often the reason for discontinuance of therapy, and reassuring counseling as well as different options and dose combinations should be tried before therapy is stopped.

The use of hormone replacement therapy (HRT) also appears to be associated with an increased risk of acute pancreatitis.[80, 81] In a study of 31,494 women, researchers found that woman who never used HRT had an incidence of acute pancreatitis of 52 cases per 100,000 person-years, compared with an incidence of 71 cases per 100,000 person-years in woman who had used HRT. This translates to a 57% increased risk.[80, 81]

Controlling for waist circumference, the factors of alcohol consumption, age at menarche, parity, use of oral contraceptives, and history of diabetes did not significantly change these results.[80, 81] The increased risk did not differ by current or past HRT use, but the risk was higher in women who used systemic therapy.

Hormone therapy can be administered either systemically via the oral, transdermal, or topical routes or

locally via the vaginal route in a cream, ring, or tablet. Topical preparations are used solely to treat vaginal symptoms.

Contraindications for estrogen therapy include undiagnosed vaginal bleeding, severe liver disease, pregnancy, venous thrombosis, and personal history of breast cancer. Well-differentiated and early endometrial cancer, once treatment for the malignancy is complete, is no longer an absolute contraindication. Progestins alone may relieve symptoms if the patient is unable to tolerate estrogens.

It has been suggested that oral estrogens are associated with a higher risk of recurrent venous thromboembolism among postmenopausal women.[82] However, transdermal estrogens may be safe with respect to venous thromboembolism risk.

The combination product of bazedoxifene, a SERM, and conjugated estrogens (CEs) was approved by the FDA in October 2013. Combining a SERM with CEs lowers the risk of uterine hyperplasia caused by estrogens. This eliminates the need for a progestin and its associated risks (eg, breast cancer, MI, VTE). This combination significantly reduced the number and severity of hot flashes at weeks 4 and 12 ($P < 0.001$). At week 12, bazedoxifene/CE reduced hot flashes from baseline by 74% (10.3 hot flashes [baseline] vs 2.8) compared with 51% (10.5 vs 5.4) for placebo.[83] Bazedoxifene/CE is FDA-approved for prevention of osteoporosis and treatment of vasomotor symptoms in postmenopausal women.

Alternative products (eg, herbal preparations and dietary supplements containing phytoestrogens), are reputed to ease the transition from perimenopause to postmenopause and are widely available. However, unlike pharmaceutical products, they have not been scrutinized in randomized, controlled trials. These over-the-counter products are assumed to act in the same manner as their pharmaceutical counterparts, but the herbal and vitamin industry is not regulated by the US Food and Drug Administration (FDA).

In a double-blind, randomized controlled trial, Lui et al observed a mild but significant favorable effect on body composition (eg, weight, body mass index [BMI], and fat percentage) in postmenopausal women who received 6 months of soy protein supplementation as compared with similar women who received milk protein. Each group also received isoflavones.[84]

However, in another randomized, double-blind trial that compared 200 mg of soy isoflavone supplementation with placebo, no difference was seen between the 2 groups with respect to bone mineral density (BMD) or menopausal symptoms.[85, 86]

In women who either cannot undergo estrogen or hormone therapy (because of a history of breast cancer) or choose not to do so and who suffer from hot flashes or flushes, the selective serotonin reuptake inhibitors (SSRIs) and serotonin-norepinephrine reuptake inhibitors (SNRIs—in particular, venlafaxine) have been shown to alleviate vasomotor symptoms. A study by Freeman et al found that the use of the SSRI escitalopram in a dosage of 10-20 mg/day can help reduce and alleviate more severe hot flashes.[87]

Japanese traditional medicines such as keishibukuryogan and kamishoyosan have also shown to reduce the circulating interleukin (IL)-8 level in perimenopausal women and to decrease the circulating monocyte chemotactic protein (MCP)-1 level in postmenopausal women.[88]

A study by Freeman et al suggested that the median duration of hot flashes actually exceeds the timeframe generally accepted in clinical practice.[89] Clinicians should consider identifiable risk factors such as menopausal stage, race, and BMI when creating individualized treatment plans and evaluating the risk-to-benefit ratios of hormone replacement and other therapies.

Estrogens and progestins are prescribed for both prevention and therapy, and the expectations for the 2 uses are very different. Relief of vasomotor and vaginal symptoms is the primary indication for hormone therapy. Hormones are the most effective agents available for vasomotor-related symptoms and remain the standard of care. Efficacy can be achieved with lower doses than are traditionally used. Frequent nighttime sleep disruption due to hot flashes may be relieved by synthetic conjugated estrogens-B in dosages as low as 0.3 mg/day.[90]

The duration of use should be dictated by individual symptoms and related risks. The benefits of hormone therapy are clear for women who initiate therapy close to menopausal age, but such therapy is considered riskier with continuing use and advancing age. Additional and ongoing studies will help determine the risks and potential benefits of longer-term therapy.

## Nonhormonal Therapy

In June 2013, the FDA approved paroxetine mesylate (Brisdelle) as the first nonhormonal therapy for vasomotor symptoms (VMS) (hot flashes) associated with menopause.[8, 9]

Despite the FDA's Advisory Committee for Reproductive Health Drugs vote against recommending approval (noting that paroxetine's minimal superiority to a placebo did not outweigh the increased risks of suicidal ideation and osteoporosis), approval was based on 2 clinical trials involving 1,175 postmenopausal women with moderate to severe hot flashes.[8, 9, 91]

Results of both studies showed paroxetine 7.5 mg reduced the frequency of VMS significantly more than placebo.[91] However, labeling for paroxetine will include a boxed warning about the increased risk for suicidality and a warning that paroxetine mesylate can reduce the effectiveness of the breast cancer drug tamoxifen, increase bleeding risk, and increase the risk for serotonin syndrome.[8, 9]

Antidepressants and gabapentin have been widely used off-label for VMS.


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Disclosure: Wyeth Grant/research funds PI on research; Bayer Grant/research funds PI on research; GSK Grant/research funds PI on research; Duramed Grant/research funds PI on research; Novartis Grant/research funds PI on research; Pfizer Grant/research funds PI on research; Boehringer-Ingelheim Grant/research funds PI on research; Johnson and Johnson Grant/research funds PI on research; Roche Grant/research funds PI on research; Boston Scientific Grant/research funds PI on research; Novo Nordisk Grant/research funds PI on research; Proctor and Gamble Grant/research funds PI on research; Merck Grant/research funds PI on research; Xanodyne Grant/research funds PI on research; Hormos Grant/research funds PI on research

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Disclosure: Johnson and Johnson Honoraria Speaking and teaching; Conceptus Honoraria Speaking and teaching; ConMed Consulting fee Consulting

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