Menopause

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Contents

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T. Falcone, W. W. Hurd (eds.), *Clinical Reproductive Medicine and Surgery*,
https://doi.org/10.1007/978-3-030-99596-6_9

Key Points

- Natural menopause, or the permanent cessation of menstruation in women due to the senescent loss of ovarian follicular activity, is typically clinically diagnosed retrospectively 12 months after the last menstrual period (LMP) has occurred, and often causes significant physical and mental health, social, and economic burdens.
- The loss of estrogen that occurs with menopause has myriad physiologic consequences throughout the body. The most common clinical signs and symptoms of menopause include vasomotor symptoms (VMS), such as hot flashes and night sweats, and the genitourinary syndrome of menopause (GSM), encompassing vaginal dryness, dyspareunia, and urinary symptoms.
- The gold standard of treatment for menopausal symptoms is hormone therapy (HT), which when initiated in low-risk women under the age of 60 years old or within 10 years of menopause is associated with improved cardiovascular, metabolic, neurological, and mortality outcomes.
- Hormone replacement therapy (HRT) is the recommended standard of care in women who experience menopause younger than 45 years old to mitigate the consequences of early estrogen loss and should be continued at least until the median age of menopause (52 years old).

9.1 Introduction

The loss of endogenous ovarian hormone production that occurs at the menopause transition (MT) is perhaps the most consequential physiologic event experienced by women in midlife. While often overlooked as a risk factor for health consequences, menopause can have serious pathological, psychological, social, and economic ramifications for women who live long enough to experience it.

The average age of menopause ranges from 40 to 60 years old, with a median age of 52 years old [1]. As female life expectancy steadily increases, women may find themselves spending up to 40% of their lives in the postmenopausal phase.

Given the significant morbidity that menopause and menopausal symptoms may cause for women, it is important for healthcare providers to adequately understand and counsel women about the associated health risks, appropriate preventive care, and available treatment options.

Case Vignette

A 48-year-old G3P2 white woman with an unremarkable past medical history presents to your clinic with concern about her menopausal symptoms of hot flashes and night sweats, vaginal dryness, and dyspareunia. She has not had any fractures after turning 40. She has a bone density scan done, which is normal. Obstetric history is remarkable for two spontaneous vaginal deliveries with no pregnancy complications. She had her menarche at age 13. She has a history of regular menses without a uterine bleeding disorder. She was on oral contraceptives for about 10 years and was well tolerated without developing venous thromboembolism or gallbladder problems. Her paternal grandmother was diagnosed with breast cancer in her 60s and a paternal aunt deceased in her 40s from breast cancer. She has no known genetic mutations. She has a personal history of abnormal mammograms remarkable for fibrocystic breast but never had breast biopsy. She had a recent normal mammogram. She has no history of hypertension, diabetes mellitus, stroke, or myocardial infarction. She is a nonsmoker. She has no personal or familial history of venous thromboembolism or prothrombotic mutations.

9.2 Impact of Menopause

Menopause significantly impacts the prevalence of chronic disease and mortality among the female population. Several longitudinal studies have demonstrated that menopause leads to pronounced cardiometabolic changes, making it an independent risk factor for cardiovascular disease (CVD) and mortality [2–6]. The loss of estrogen that occurs with menopause has also been associated with increased risk of dementia [7]. Several population-based studies have found that the use of estrogen therapy results in reduced prevalence and incidence of dementia and Alzheimer's disease [7–10]. Additionally, menopause is a known risk factor for osteoporosis and has been associated with declining pulmonary function and worsening of chronic lung disease [11, 12].

Perhaps more consequential than the physiologic impact of menopause are the psychosocial ramifications, which are often overlooked. Several studies have demonstrated a negative association with menopause and quality of life (QOL) [13–15]. In addition to the health-related burden experienced by women, menopause may also significantly impact mental health, social life, relationships, and career.

The US Bureau of Labor Statistics projects that the percentage of women in the workforce from 2014 to 2024 is expected to grow by 5.8%, with the largest increase occurring in postmenopausal women [16]. The number of women in the civilian labor force aged 65–74 and aged 75+ is expected to increase by 59.2% (~1,846,000) and 94.5% (~618,000), respectively [16].

Research has shown that menopausal symptoms negatively impact work performance and may increase absence from work [17, 18]. Hot flashes, mood swings, and "brain fog" (difficulties with memory and concentration) are all commonly reported symptoms in postmenopausal women that may interrupt work ability. Working may be correlated with improved self-esteem and decreased psychological stress in some women [19]. Menopause may also pose significant financial burdens to women and families, as severe symptoms and subsequent poor work performance may make it difficult for women to advance in their careers or in some severe cases even remain employed at all.

Many postmenopausal women also experience female sexual dysfunction (FSD) and changes in mood, which may have a negative impact on relationship satisfaction in both men and women [13]. The changes in appearance that occur due to estrogen loss may also provoke lower self-esteem and body image issues in women, leading to lower confidence levels. It is not uncommon for women and their spouses or partners to endorse relationship problems as a consequence of their menopausal symptoms.

9.3 Terminology

The stages of menopause have been classified and defined by a group of menopause experts in a model known as STRAW+10 (Stages of Reproductive Aging Workshop), which breaks down reproductive aging into seven stages throughout a woman's life [20]. This is generally accepted as the gold standard for the characterization of reproductive aging in women.

There are several different terms used both in STRAW+10 and, generally, to describe the different types and phases of menopause (see below):

- *Menarche*: The first occurrence of menstruation.
- *Premenopause*: The period of time in a woman's life prior to menopause.
- *Premature menopause/premature ovarian insufficiency (POI)*: The permanent or transient cessation of ovarian function before age 40. Premature ovarian failure (POF) is to be avoided as it implies no chance of ovulation (which cannot be ruled out), so POI is a more helpful diagnostic construct.
- *Perimenopause*: The highly symptomatic time frame that exists from the first occurrence of menopause-related symptoms to one full year after the final menstrual period (FMP).

- *Menopause transition (MT)*: This term is often interchanged with perimenopause, though the MT by definition ends at the time of the FMP.
- *Climacteric*: This term is the period of physiologic and psychologic changes that occurs during the menopausal transition.
- *Menopause:*
  - *Natural menopause:* The cessation of menstruation due to complete or near-complete follicular exhaustion, resulting in the end of ovarian hormone production.
  - *Early menopause*: Menopause occurring before the age of 45.
  - *Late menopause*: Menopause occurring after the age of 55.
- *Induced menopause*:
  - *Surgical menopause*: Cessation of ovarian function due to gynecologic surgical intervention.
  - *Iatrogenic menopause*: Cessation of ovarian function due to an iatrogenic cause, such as chemotherapy or pelvic radiation.
- *Postmenopause*: The period of time following menopause, starting 1 year after the final menstrual period and lasting through the end of life. Early postmenopause is typically a more symptomatic period than late postmenopause:
  - *Early postmenopause:* Period of time when women are 5–10 years or less from FMP.
  - *Late postmenopause:* Period of time when women are greater than 10 years from FMP.

9.4 Time to Natural Menopause

There are several factors that have been consistently identified as influencing the age at which natural menopause occurs (see Table 9.1). Race/ethnicity, dietary habits, and physical activity have been inconsistently associated with influencing menopause onset [1].

Table 9.1 Factors associated with earlier or later onset of menopause [1]

Factors associated with earlier onset of menopause	Factors associated with later onset of menopause
Active smoking	Increased body mass index (BMI)
Nulliparity/low parity	Multiparity
Medically treated depression/seizure disorder	Higher cognitive scores in childhood
Hereditary/familial influence	Hereditary/familial influence
Chemotherapy	
Pelvic radiation	
Gynecologic surgery	
Lower socioeconomic status	
No previous use of oral contraceptive pills	

9.5 The Physiology of Menopause

Menopause occurs as a result of the progressive depletion of a woman's ovarian reserve, leading to complete or near-complete follicular exhaustion, which is accompanied by a reduction in quality and capability of the aging oocytes. The subsequent disruption in ovarian steroid hormone production results in the cessation of ovulation and menstruation, as well as several physiologic consequences throughout the body that lead to increased risk of chronic disease and significant symptom burden in many women.

9.5.1 Premenopause

At 20 weeks of gestation, a female fetus possesses approximately 6–7 million eggs, the most ovarian follicles of its reproductive life

[21]. In utero, a female fetus begins to lose follicles through granulosa cell-mediated apoptosis in a process known as follicular atresia. At birth a female has about 1–2 million oocytes, and follicular loss continues, but at a slower pace [21].

In reproductive-aged women, follicle-stimulating hormone (FSH) stimulates ovarian folliculogenesis. Anti-Mullerian hormone (AMH) and inhibin B, peptide hormones primarily produced by granulosa cells in growing antral follicles, act in a negative feedback loop with FSH, functioning to restrain follicular growth. This negative feedback is necessary to moderate FSH and ensure only one dominant follicle reaches the preovulatory stage. As levels of inhibin B rise, negative feedback is provided to the pituitary gland to indicate the maturation of oocytes has started to occur, which signals the pituitary gland to stop producing FSH. The FSH negative feedback loop is also influenced by the ovarian steroid hormone estradiol (E2) and corpus luteum-secreted progesterone. Developing follicles secrete E2, which acts on the hypothalamic-pituitary-ovarian (HPO) axis to suppress FSH secretion. Each time ovulation occurs, several antral follicles are recruited, though typically only one follicle undergoes ovulation, while the rest undergo apoptosis.

E2 secretion from developing follicles also causes proliferation of the endometrium. Following ovulation, the corpus luteum secretes progesterone which, in combination with estradiol, causes the endometrial secretory changes necessary for implantation to occur. If fertilization does not occur, the corpus luteum regresses and progesterone secretion ceases, resulting in menstruation.

Throughout a female's reproductive life, she continues to experience a progressive loss of ovarian follicles through the natural processes of ovulation and follicular atresia. Ovarian reserve most sharply declines in the late reproductive period. As a woman ages, there is also a concurrent reduction in the quality and function of the remaining oocytes.

In the late reproductive phase, menstrual cycles remain predominantly ovulatory. However, the follicular phase shortens due to hastened follicular growth, resulting in increased time spent in the luteal phase of the menstrual cycle. Luteal phase progesterone levels also decline. This leads to increased menstrual frequency and subsequently more premenstrual symptoms.

9.5.2 The Menopause Transition

Follicular depletion continues into the early stages of the menopause transition, where there is a period of compensated failure of the HPO axis. The growing pool of oocytes decreases, leading to less granulosa cell production of inhibin B and AMH. As inhibin B and AMH secretion declines, there is less restraint of ovarian negative feedback on FSH, resulting in increasing FSH levels [22, 23]. Elevated FSH levels prompt the recruitment and maturation of a new cohort of follicles at the beginning of each cycle, maintaining the drive necessary for continued ovulation. While there are more follicles available for recruitment, there is also accelerated follicular atresia [21]. Levels of estradiol and regular menstrual cyclicity typically remain preserved throughout this time [22, 23].

There are often fluctuating patterns of hormones as the menopausal transition continues. While FSH elevations accompanied by low inhibin B and estradiol levels are common, they may be followed by subsequent elevations in estradiol and declining FSH levels [22, 23]. A woman may experience elevated estrogen levels through increasing androgen aromatization incurred as a result of increasing age and body weight or by increased estradiol production by an enlarged oocyte cohort [22, 23]. These intermittently high levels of estradiol lead to endometrial proliferation with subsequent heavier periods. These expansive hormonal fluctuations account for why this period is so highly symptomatic.

The significant loss in ovarian follicles that occurs in this period due to accelerated follicular atresia also leads to a decreased amount of receptors available to respond to FSH [21]. This decreased sensitivity to FSH can in turn lead to inhibition of the typical luteinizing hormone (LH) surge required for ovulation to occur [22, 23]. As a result, there is increased anovulation

with subsequent menstrual irregularity and a reduction in estrogen secretion and circulation throughout the body. The decline in estrogen levels that occur lead to a disruption of HPO axis and a subsequent failure of endometrial development, causing further menstrual irregularities [22, 23]. Anovulation may occur due to LH surge failure secondary to HPO axis dysfunction or an absence of corpus luteum formation despite the occurrence of an LH surge [22, 23]. Decreased corpus luteum production due to anovulation leads to decreased progesterone secretion. Consequently, estrogen is often unopposed leading to endometrial proliferation and thus a possible increased risk for endometrial hyperplasia and endometrial cancer. The endometrium often outgrows its own blood supply in this case, provoking tissue necrosis and shedding, which contributes to irregular bleeding patterns [22, 23]. Oocyte quality and capability also decline during this time, leading to further increasing anovulatory cycles, decreased rates of conception, and increased risk of spontaneous abortion. The decreased oocyte quality and proficiency may be due to several mechanisms, including impaired dominant follicle recruitment and the age-dependent decrease in integrity and function of granulosa cells and meiotic spindles [24].

The late menopause transition is marked by increasing hormone fluctuation, decreasing frequency of ovulatory cycles, and an increasing number of days of consecutive amenorrhea. At this point in the MT, the persistently diminishing ovarian follicle quantity decreases to a level which can no longer be compensated for. When follicular growth and recruitment does occur, ovulation is more likely to fail. However, given the intermittent ovulatory cycles that may occur throughout the late menopause transition, it is important to note that women can experience pregnancy at any point up to their final menstrual period (FMP). Eventually, the follicular numbers reach a nadir at which folliculogenesis can no longer occur and E2 and progesterone production effectively cease, leading to persistent amenorrhea. This near-complete follicular exhaustion results in the characteristic hormone profile of postmenopausal women, consisting of high FSH, low E2, low inhibin B, and low AMH [22, 23]. The menopausal ovary no longer produces sufficient E2. The resulting low level of endogenous estrogen is what causes menopausal symptoms, though severity varies between each individual woman. Some postmenopausal women may still produce small amounts of estrogen through the aromatization of adrenally secreted testosterone, which may lessen symptoms.

9.6 Premature Ovarian Insufficiency

Premature ovarian insufficiency (POI) occurs when there is a loss of ovarian function prior to the age of 40 years old. There are several possible etiologies of POI, the most common of which is idiopathic, which accounts for more than 90% of cases [25] (► Box 9.1).

Box 9.1 Etiologies of primary ovarian insufficiency (POI) [25, 115]

Genetic
Autoimmune
Metabolic
Iatrogenic
- Surgery
- Chemotherapy
- Radiation

Infectious
Idiopathic

Surgical menopause has the most significant physiologic consequences among the causes of premature menopause. When the ovaries are removed, women experience a sudden loss of estrogen, testosterone, and progesterone, resulting in significant disruption of the HPO axis [26]. Subsequently, menopausal symptoms typically occur more acutely and more severely than with the gradual hormonal loss that occurs with natural menopause. Gynecologic malignancies, such as cervical cancer, endometrial cancer, ovarian cancer, and borderline ovarian tumors, may necessitate bilateral salpingo-oophorectomies (BSO). If there is a significant disruption in ovarian

blood flow as a result of surgery, it is possible for early or premature menopause to occur in some women with a history of unilateral oophorectomy, or even hysterectomy alone. Nonmalignant gynecologic disorders, such as endometriosis, chronic pelvic pain, bilateral or recurrent ovarian cysts, tubo-ovarian abscesses, ovarian torsions, and prophylactic or risk-reducing salpingo-oophorectomy, are other possible causes of surgical menopause. There is an accelerated aging curve that occurs with premature and early menopause, whether from surgery or other causes, which leads to associated increases in coronary heart disease, early bone loss, dementia, Parkinson's disease, mental health disorders, cancer admissions, cancer deaths, and all-cause mortality [27, 28].

9.7 Physiological Effects of Estrogen

There are three naturally occurring estrogens in the human body, estrone (E1), 17β-estradiol or estradiol (E2), and estriol (E3). E2 is the strongest biologically active form of natural estrogen. E2 is predominantly produced by the dominant ovarian follicle and is the most potent and prevalent form of natural estrogen during a woman's reproductive years [29]. E1 is primarily synthesized in the skin and adipose tissue through the peripheral conversion of androstenedione [29]. Following the cessation of ovarian steroid hormone production that occurs with menopause, estrone becomes the predominant form of endogenous estrogen in the postmenopausal woman [29]. In postmenopausal women, serum estradiol is formed by the extragonadal aromatization of testosterone. It is not uncommon for levels of estradiol in postmenopausal women to be less than 20 pg/mL, which is lower than a normal male level of estradiol (~40 pg/mL). Extragonadal estradiol synthesis may increase with age and an increasing amount of adipose tissue.

Estrogens are cholesterol-derived steroid hormones that exert both genomic and nongenomic effects. They bind to estrogen receptors (ERs), ER-α and ER-β, throughout the body to perform myriad biochemical processes, such as the induction of nitric oxide, the modulation of catecholamine release, and the regulation of intracellular calcium [30]. While it is widely known that estrogen plays an important role in the female reproductive system, estrogen is also responsible for several critical physiologic processes throughout the body. Both ER-α and ER-β are concentrated in the central nervous system (CNS) and cardiovascular (CV) system. ER-α predominates in the uterus, mammary glands, bone, vagina, cervix, liver, and adipose tissue [31–34]. ER-β is primarily located in the lung, skin, thyroid, spleen, thymus, bladder, and colon [31–34].

9.7.1 Breast Tissue

Estrogens stimulate blood flow to breast tissue through vascular-mediated mechanisms [30]. They play a pivotal role in the growth of ductal epithelium and connective tissue within the breast [35]. Research has also demonstrated that estrogen can advance the production of breast cancer cells [36]. Later age to natural menopause, specifically greater than 55 years old, has been associated with increased risk of breast cancer.

9.7.2 Central Nervous System

Estrogen has myriad functions in the brain. It is known to play a role in the regulation of mood, memory, and cognition. It may also exert neuroprotective and neurotrophic effects [37, 38]. The loss of ovarian hormones that occurs during menopause is associated with mitochondrial dysfunction, oxidative stress, neuroinflammation, synaptic deficits, cognitive impairment, and an increased risk of age-related disorders, such as dementia [37, 38]. Postmenopausal women often experience new or worsening mood symptoms, cognition difficulties, and/or memory problems.

9.7.3 Cardiovascular System

Estrogen mediates a myriad of important regulatory functions in the cardiovascular system. The activation of estrogen receptors, ER-α and

ER-β, throughout the CV system positively affects vascular function, insulin sensitivity, metabolic processes, lipid and lipoprotein levels, body fat distribution, inflammation, and cardiac myocyte structure and activity [39].

Estrogens exhibit vasoprotective effects. The estrogen-mediated vasodilation and inhibition of platelet activation through the synthesis of nitric oxide, as well as estrogen's role in the suppression of inflammation and vasoconstrictive mechanisms, improve overall arterial function [30].

Estrogen plays an important role in the functional activity of cardiac myocytes through the regulation of ion channels. Through this mechanism, estrogen can influence cardiac contractility and modulate cardiac repolarization [40]. Estrogen may also play a part in delaying cardiac hypertrophy and creating more favorable myocardial remodeling, thus positively influencing the structure of cardiac myocytes [40]. Additionally, animal models have suggested that in vivo estrogen delivery immediately prior to ischemia can reduce the size of myocardial infarct [40].

The loss of estrogen that occurs during the MT not only increases CV risk directly through the loss of estrogen's cardioprotective mechanisms but indirectly as well. Hot flashes have been associated with a multitude of pathologic CV markers, including an increase in carotid intimal thickness, increased carotid and aortic calcifications, increased heart rate variability, increased sympathetic tone, endothelial dysfunction, and insulin resistance [41]. Furthermore, many women going through the MT experience novel or worsening mood symptoms, especially of depression and sleep disturbance, which have been associated with greater risk of CVD [42].

The American Heart Association (AHA) released a scientific statement in 2020 acknowledging menopause as an independent risk factor for cardiovascular disease [39]. This statement stands in agreement with the guidelines and recommendations of several other prominent specialist organizations, such as the North American Menopause Society (NAMS), the American College of Obstetricians and Gynecologists (ACOG), and the American Association of Clinical Endocrinologists (AACE).

9.7.4 Bone

Estrogen plays a critical role in the regulation of bone metabolism. Estrogen exhibits an antiresorptive effect through the inhibition of osteoclasts by suppressing the expression of receptor activator of NF-kB ligand (RANKL), a cytokine essential for osteoclast stimulation, differentiation, and longevity [43]. The bone loss that occurs after menopause due to the loss of estrogen may be most pronounced in the first 2 years after the FMP.

9.7.5 Adipose Tissue

The MT is associated with increases in both total and visceral adiposity. Estrogen regulates metabolism and deposition of adipose tissue in the female body [44]. Estrogens work directly on adipocytes to inhibit lipogenesis, and play a pivotal role in adipogenesis and adipocyte proliferation [44]. The accumulation of central body fat, a known risk factor for type 2 diabetes (T2DM), can be attenuated with the use of estrogen therapy in postmenopausal women [45]. Studies have shown that the early loss of estrogen in women who experience premature menopause is associated with a clear increased risk of T2DM [46]. Coinciding with these findings, large randomized controlled trials (RCTs) have suggested that the use of HT in postmenopausal women can reduce the risk of developing T2DM [46]. While the exact mechanisms are not completely clear, HT has been shown to decrease visceral adiposity and improve β-cell insulin secretion, insulin sensitivity, and glucose efficacy [46].

9.7.6 Liver

Within the liver, estrogen inhibits fibrogenesis and cellular senescence, promotes innate immunity and antioxidant effects, and protects mitochondrial function [47]. Estrogen also increases hemostasis through the activation of gene transcription of clotting factors (VII, VIII, X, fibrinogen) and plasminogen, decreasing antithrombin III and protein S lev-

els, and modifying activated protein C (APC) resistance [48].

Estrogen affects levels of circulating lipids. Estrogens lead to increased production of hepatic lipoprotein receptors leading to a decrease in serum LDL [49]. Premenopausal women have a more favorable lipid profile, with higher serum HDL levels and lower serum LDL levels, compared to age-matched men and postmenopausal women [49]. Following the MT, plasma LDL levels increase, and HDL levels decrease [49].

Following menopause, there is also a reduction in liver volume, blood flow, function, and capacity for regeneration [47].

9.7.7 Bowel

Estrogen is known to affect bowel motility. It also plays a protective role in cancer prevention in the colonic mucosa through the modulation of apoptotic signaling, tumor microenvironment, and immune mechanisms, and the inhibition of inflammatory markers [50].

9.7.8 Pulmonary System

Estrogen plays a role in the development and maintenance of healthy lung tissue. It has been suggested that estrogen is involved in lung tissue elastic recoil and in the production of alveoli, extracellular matrix, and surfactant [51].

Menopause is associated with lower lung function and increasing respiratory symptoms in midlife women [52, 53]. This is an especially important consideration in women with pre-existing respiratory disease, such as asthma, COPD, or restrictive lung disease.

9.7.9 Skin

Estrogen also appears to play a significant role in the maintenance of skin elasticity and the prevention of skin aging. It regulates elastic fiber and collagen content in the skin, helping to maintain its thickness [54]. Estrogen also increases hyaluronic acid and other acid mucopolysaccharides in the skin, aiding in the preservation of skin moisture [54]. Estrogen may also play a role in promoting cutaneous wound healing through the regulation of cellular growth factors and repair enzymes [55].

The loss of estrogen that occurs during the MT causes several significant changes in skin quality and function. The disruption of elastin, cellular growth factor, and repair enzyme production leads to decreased skin elasticity and increased skin fragility [55]. Changes in blood flow and cellular oxygenation effects on keratinocytes lead to epidermal thinning [55]. Women can experience impaired wound healing as a result of these changes.

Many women find the changes to their skin distressing. It is not uncommon for women to complain of their appearance, often in vague terms. Accelerated lipoatrophy, fat distribution changes, and increased bone resorption can lead to facial hollowing, eyelid sagging, jowling, contour deformities, and shadow creation. The decreased fibroblast activity and glycosaminoglycan production cause decreased skin hydration, increasing skin dullness, and more pronounced appearance of lines and wrinkles [54]. Estrogen loss may also lead to a testosterone imbalance that can cause or worsen acne.

9.7.10 Hair

Many women in midlife experience hair thinning or loss on the scalp and eyebrows and/or increased growth of facial hair, and accurately associate these changes with menopause. Estrogen increases levels of sex hormone-binding globulin (SHBG), which is responsible for binding and carrying testosterone in its inactive state [56]. When estrogen levels drop during menopause, levels of SHBG also decrease, which increases the amount of free testosterone available in the circulation [56]. This increase in active testosterone may lead to symptoms such as hirsutism and female pattern hair loss in women.

It is also important to note, however, that there are many other factors which may influence the thinning or loss of hair in midlife women, including genetic predisposition, stress, other hormones, medications, vitamin deficiencies, and chronic illness.

9.7.11 Eyes

Estrogen may affect corneal elasticity, which in turn affects clarity of vision [57]. Estrogen also functions to reduce intraocular pressure [57]. Hormone therapy has been associated with decreased incidence of glaucoma, age-related macular degeneration, and cataracts [58].

9.7.12 Vulvovaginal Tissue

There are an abundance of estrogen receptors throughout the vagina and vulva [59]. Estrogen has several functions in the vulvovaginal tissue, including preserving adequate blood supply, maintaining the integrity and moisture of the tissue, and supporting the local microbiome [59–63]. Androgens have also been shown to help support nerve fibers and maintain moisture and tissue integrity [60]. Premenopausal women typically have well-estrogenized, multilayered vaginal tissue with substantial blood supply and glycogen-rich superficial cell layers [62]. In contrast, postmenopausal women typically have atrophic vulvovaginal tissue with marked epithelial thinning and reduced blood supply [59–61]. The tissue atrophy and reduction of tissue collagen can lead to narrowing of the vaginal canal and loss of elasticity, which may contribute to the dyspareunia experienced by some postmenopausal women [59–61].

Estrogen also functions to help maintain an acidic intraluminal vaginal pH by supporting the growth of lactic acid-secreting lactobacillus [64]. Glycogen acts as a substrate facilitating lactobacillus production of lactic acid [64]. The reduction in the glycogen content of the postmenopausal epithelium leads to decreased lactic acid production and resulting increased intraluminal vaginal pH [63, 64]. The change in local microbiome and more basic pH leads to unfavorable changes in the concentration of protective inflammatory cells, leaving the vulvovaginal tissue more vulnerable to infectious pathogens [63, 64] (Fig. 9.1).

9.7.13 Pelvic Floor

Estrogen receptors are located throughout the pelvic floor, and have been found in the uterosacral ligaments, pubocervical fascia, and pelvic floor musculature [65, 66]. Through the regulation of collagen metabolism, estrogen functions to support the strength of the pelvic floor [65, 66]. The loss of these supportive mechanisms in postmenopausal women may contribute to increasing the risk of pelvic organ prolapse [66].

9.7.14 Urinary Tract

Estrogen and androgen receptors in the urethra and the bladder contribute to numerous important functions, including protection against infection and aiding in the prevention of urogenital prolapse [60, 67]. Estrogen receptors located in the urethra and bladder also directly affect urethral smooth muscle, detrusor muscle contraction, and urethral pressure to help maintain urinary continence [67]. The loss of estrogen and androgen support in the urogenital tissue of postmenopausal women leads to reduced collagen and epithelial thinning with subsequent tissue atrophy (Fig. 9.2). This atrophy increases the risk of urogenital prolapse [67]. Interestingly, despite the function of estrogen in these tissues, data has shown that there is no association between low serum estradiol levels and increased risk of urinary incontinence [68].

Menopause additionally puts women at risk for recurrent urinary tract infections (UTIs). The atrophy and shriveling of urogenital tissue also leaves the urethra more prominent and brings it closer to the introitus, leading to higher rates of UTIs. The change in vaginal microflora and decreased production of urogenital antimicrobial substances also increase the risk of urinary infections [69].

9.8 Symptoms of Menopause

9.8.1 Vasomotor Symptoms (VMS)

Vasomotor symptoms (i.e., hot flashes and night sweats) are experienced by up to 80% of women during the menopause [70]. Hot flashes are typically described as a sudden intense feeling of warmth throughout

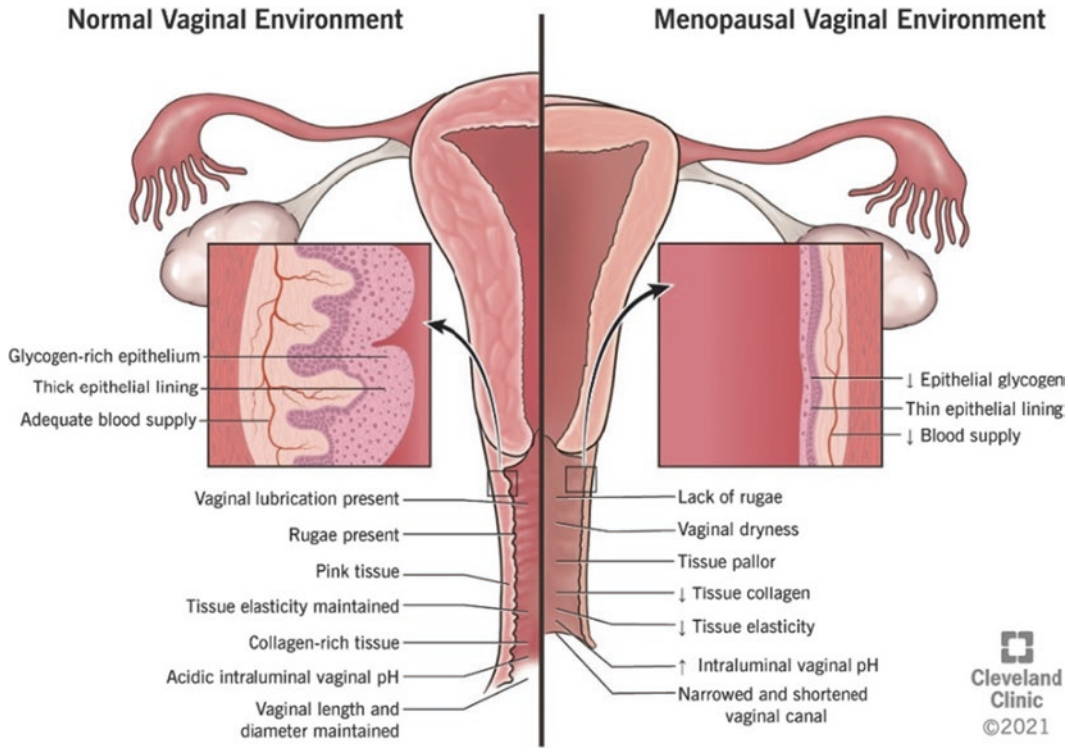

Fig. 9.1 Normal vs. postmenopausal vaginal environments. From left to right, the left half of the figure demonstrates the ideal vaginal environment typically found in a healthy, premenopausal woman of reproductive age [59–64]. The right half of the figure demonstrates the pathological changes that may occur in the vaginal environment of an untreated postmenopausal woman [59–64]

the upper body, typically most severe over the chest, neck, and face. If redness can be seen on the skin, these episodes are typically termed hot flushes. This feeling may be accompanied by several symptoms women find bothersome or even concerning, such as diaphoresis (this may range from mild to severe perspiration), flushing or reddening of the skin, chills, anxiety, and/or heart palpitations [71]. When a hot flash occurs during sleep, it is termed a night sweat. Night sweats can cause significant sleeping disruption for some women.

A single hot flash episode typically lasts between 1 and 6 minutes [70–72]. The frequency and severity of hot flashes vary from woman to woman, though typical triggers that can provoke or worsen an episode include stress, heat, caffeine, alcohol, cigarette smoke, spicy foods, and tight clothing.

Estrogen is known to play an important role in the regulation of body temperature. Estrogen deficiency results in a disruption of the thermoregulatory center of the hypothalamus, triggering the occurrence of hot flashes [73]. During a hot flash, blood flows to the periphery leading to a decrease in core body temperature and cutaneous vasodilation with the associated sensation of extreme warmth [71].

Research has increasingly shown that hot flashes are not physiologically benign symptoms. Hot flashes have been associated with increased carotid intima thickness, increased carotid and aortic calcifications, increased endothelial dysfunction, decreased nitric oxide production, increased insulin resistance/elevated blood glucose levels, increased sympathetic tone, increased heart rate variability, white matter hyperintensity, and increase in

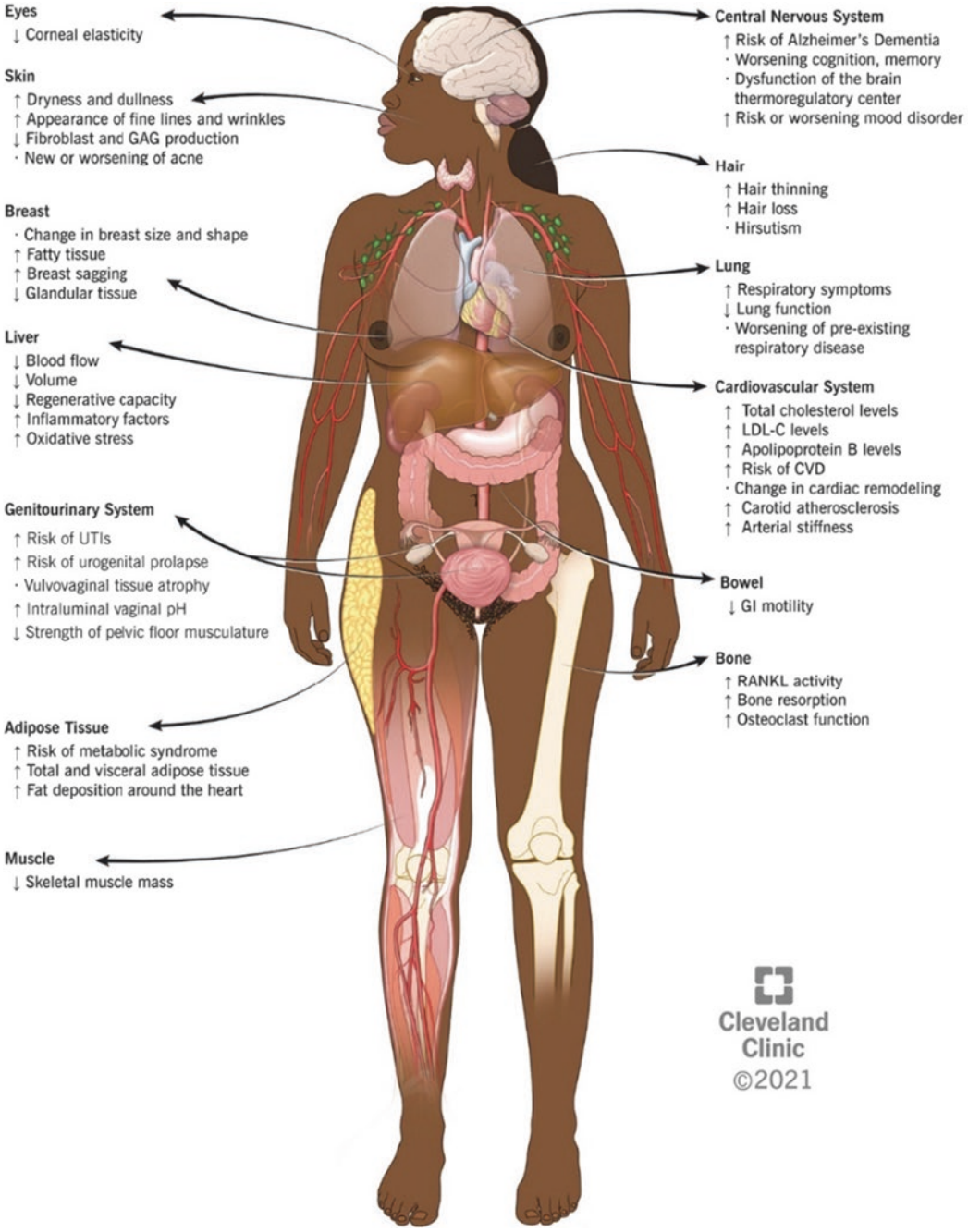

Fig. 9.2 Physiologic changes with menopause. The physiological changes of various organs and organ systems that occur due to the estrogen deficiency associated with menopause [30–69]. Abbreviations: GAG glucosaminoglycans, LDL-C low-density lipoprotein cholesterol, UTI urinary tract infection, RANKL receptor activator of NF-kB ligand, GI gastrointestinal, CVD cardiovascular disease

N-telopeptide (NTx), which is a marker of bone turnover (increased bone loss) [74–84].

9.8.2 Genitourinary Syndrome of Menopause (GSM)

Genitourinary syndrome of menopause describes the signs and symptoms resulting from estrogen deficiency of the female genitourinary system. There has been a change in vocabulary from the previous term vulvovaginal atrophy (VVA). This change was made to create more accurate and all-encompassing terminology, as vulvovaginal atrophy is only a component of GSM and does not encapsulate the entire syndrome.

GSM symptoms will affect at least 50–70% of postmenopausal women at some point in their lives [85]. The most bothersome symptoms of GSM as recognized by the US Food and Drug Administration (FDA) are vaginal dryness, dyspareunia (painful intercourse), vulvovaginal irritation, vaginal soreness, dysuria, and bleeding associated with sexual activity [86]. Many women may also experience vulvovaginal burning and/or abnormal vaginal discharge. These symptoms are chronic and progressive, and will not improve without treatment. Women with surgical menopause tend to have more severe symptoms than those who go through menopause naturally [87]. Many postmenopausal women are unaware of or embarrassed by the vulvar, vaginal, and urinary changes that result from estrogen loss. Additionally, symptoms do not always correlate to physical exam findings. As a result, GSM is typically underdiagnosed and/or treated with significant delay. The goals of GSM treatment are to relieve symptoms, reverse any anatomic changes that may have occurred, improve sexual dysfunction, and prevent infection.

9.8.3 Other Peri- and Menopausal Symptoms

There are myriad recognized symptoms of the menopause transition. While VMS, GSM, sleep disturbances, and mood changes are commonly thought of as menopausal, there are also many symptoms that are often overlooked. Joint aches, palpitations, formications (tactile hallucinations), and hair thinning, for example, are often missed or misdiagnosed (Table 9.2).

9.9 Evaluation

9.9.1 Diagnosis

Menopause is typically diagnosed retrospectively following 12 months of amenorrhea after the last menstrual period in a woman over the age of 45, though there remains a small possibility of continued cycles even after these characteristics are met. In women under 45 years old without any other known cause of early or premature menopause, an evaluation for underlying causes of secondary amenorrhea and premature ovarian insufficiency should be pursued. The European Society of Human Reproduction and Embryology (ESHRE) guidelines suggest that POI may be diagnosed in women with absence of menstruation for at least 4 months, and elevated FSH levels on two separate occasions, at least 4 weeks apart, in a women under the age of 40 years old [88]. While this guideline allows for diagnosis to be reached at 4 months after LMP, 12 months of amenorrhea is preferable for a more accurate diagnosis.

While obtaining FSH levels is not necessary for diagnosis, they can be clinically useful in some patients. A clinician can be more confident in the diagnosis of menopause when it is supported by two elevated FSH levels (>30 mIU/mL) 12 months apart, especially in women with concurrent menopausal symptoms. In women with abnormal or absent menstrual cycles, such as women with PCOS, women with a hormonal levonorgestrel intrauterine system (IUS) in place or on continuous combined hormonal contraceptive (CHC) therapy, and women with a history of hysterectomy or endometrial ablation, the menstrual cycle criteria cannot accurately be applied. Endocrinological evaluation with FSH and 17β-estradiol levels can be especially helpful in the diagnosis of these patients. FSH should always be interpreted with a simultaneous serum estradiol level, as elevated estra-

Table 9.2 Peri- and menopausal symptoms [91]

Body system	Symptom
Genitourinary	Irregular periods/bleeding Vaginal dryness Changes in libido Urinary urgency and incontinence Recurrent UTIs
CNS	Headaches Paresthesias/electric shocks Difficulty with concentration Memory lapse Dizziness Formications (tactile hallucinations)
Gastrointestinal	Digestive issues (constipation, flatulence, cramps, abdominal bloating)
Psychological	Mood swings Sleeping difficulty New-onset or worsening anxiety/depression Panic disorder Formications
Breast	Breast tenderness or soreness Loss of breast fullness Breast sagging
Musculoskeletal	Joint aches and pains Muscle tightness/soreness Decreased skeletal muscle mass
Oral	Burning tongue Gum health issues
Integumentary	Dry, itchy skin Brittle nails Hair thinning or loss Change in body odor
Bone	Osteoporosis/bone loss
Cardiovascular	Hot flashes and hot flushes (redness seen) Night sweats Palpitations
Immunologic	Worsening allergies
General	Fatigue Weight gain Bloating/water retention

diol levels may suppress FSH, allowing for the momentary appearance of a normal FSH value. Of note, endocrine evaluation should not be completed until at least 3 months following hysterectomy or ablation, as FSH levels may be transiently elevated immediately after gynecologic surgery [89].

In 2018, the FDA approved an AMH enzyme-linked immunosorbent assay (ELISA) test, known as the pico AMH diagnostic ELISA test, for the determination of menopausal status. Research in the last few decades has shown that serum AMH levels may be the most accurate blood test reflecting ovarian follicular reserve [90]. Given that AMH is not affected by the menstrual cycle, it may be a more useful test than FSH and 17β-estradiol. However, given that this test remains expensive and is relatively new, it is not commonly used in practice to diagnose menopause (Table 9.3).

9.9.2 Clinical History

Full obstetric and gynecological history should be taken of all women who present with menopausal concerns. Women should also be assessed for full family history and past medical history, with special attention toward cancer history, neurological history, cardiovascular history, mental health history, and bone health history (Table 9.4).

9.9.3 Physical Exam

Clinical exam of the perimenopausal and menopausal patient should be focused on the possible physical changes that can occur during menopause. Vital signs should be taken at each office visit. Heart rate and cardiac exam should be recorded, as women undergoing hot flashes may experience tachycardia or palpitations. Weight, BMI, and blood pressure should also be trended, as these levels increase in the postmenopausal woman. While often overlooked, height is a valuable measurement

Table 9.3 Hormone changes in menopause [21–24, 90]

Hormone	Source	Change in menopause	Notes
Estrogen	Ovaries, adrenal glands, peripheral conversion by adipose tissue	↓	E1 (estrone) is the dominant estrogen during menopause
Progesterone	Corpus luteum	↓	Often co-administered with estrogen for endometrial protection in the treatment of menopausal women with an intact uterus
Testosterone	Ovaries, adrenal glands, peripheral tissues	↓	White ethnicity, lower BMI, oral estrogen, and corticosteroid use are each associated with lower testosterone in women 65 and older Surgical menopause often results in lower testosterone than other types of menopause
Follicle-stimulating hormone (FSH)	Anterior pituitary gland	↑	FSH should be interpreted with estradiol because elevated estradiol can suppress FSH leading to "falsely" normal FSH levels Cycle day 3 FSH is commonly used as a test of ovarian reserve
Anti-Mullerian hormone (AMH)	Antral follicle granulosa cells	↓	AMH levels are reflective with ovarian follicular reserve

in postmenopausal women, as decreasing height may be indicative of osteoporotic vertebral fractures, especially more than or equal to 1.5 inches of height loss from maximum adult height in women (and 2 inches in men).

Physical appearance may display increased visceral adiposity. Women should also be evaluated for signs of testosterone excess, such as hirsutism, hair thinning or sparseness, adult acne, and deepening of the voice (especially important to evaluate if changes are career significant for women, as with Opera singers).

Mental status should be assessed for clinical signs of mental health issues and abnormalities in memory and cognition. A mini cognitive evaluation or mini-mental status exam (MMSE) may be appropriate in some patients.

Pelvic examination should be completed to assess for signs of estrogen deficiency, such as vulvovaginal atrophy, vaginal dryness, pallor, lack of rugae, and narrowing of the vaginal canal. Bimanual pelvic and rectal exam should also be performed to assess for adequate pelvic floor tonicity (▶ Box 9.2).

Box 9.2 Possible pelvic exam findings [85–87]

Labial atrophy
Vaginal dryness
Introital stenosis
Clitoral atrophy
Phimosis of the prepuce
Reduced mons pubis and labia majora bulk
Reduced labia minora tissue and pigmentation
Prominence and erythema of the urethral meatus
Urethral caruncle
Vaginal pallor
Lack of vaginal rugae

Table 9.4 Important history points in menopausal evaluation

History	Specific questions
Gynecologic history	Age at menarche Menstrual history Last menstrual period Total number of years of oral contraceptive use
Obstetrics history	Gravidity and parity Breastfeeding history Age at first full-term pregnancy Pregnancy and postpartum-associated medical conditions
Breast history	Personal history of breast cancer Family history of breast cancer Personal history of breast biopsy or surgery
Menopausal history	Age at menopause onset Date of last menstrual period Menopausal symptom assessment Vasomotor symptoms. GSM symptoms Sexual function
Cardiovascular history	Tobacco use history History of hypertension History of hyperlipidemia History of diabetes History of myocardial infarction History of: Deep vein thrombosis (DVT) Pulmonary embolism (PE) Cerebrovascular accident (CVA) Family history of early CAD
Other medical history	History of gallbladder disease or surgery History of autoimmune disorder
Bone history	History of previous bone mineral density/DXA scan History of fractures over the age of 40 Family history of osteoporosis and/or hip fracture History of disorders that affect calcium absorption or regulation Vitamin D status

Patients should have annual vision and hearing screening after the age of 65. It should also be recommended that patients stay up to date with regular dental care, which is a reflection of bone status.

9.10 Treatment

9.10.1 General Counseling and Recommendations

Women should be educated about the health risks associated with menopause due to the deleterious effects of estrogen loss. Midlife women should be routinely counseled on lifestyle interventions aimed at reducing triglycerides, weight gain, blood pressure, insulin resistance, and atherosclerosis. There is also a need for individualized counseling on the indications and benefits of hormone therapy for treatment among menopausal women. When discussing treatment options, it is important to counsel that the beneficial effects of HT often supersede the risks when initiated within 10 years from LMP in symptomatic women under the age of 60 and that HT is the standard of care in women with menopause prior to age 45 and should be continued until at least 52 years old. There is no time limit to HT; rather, there should be yearly re-evaluation of the woman's medical status, her preferences, and shared treatment goals.

9.10.2 Hormone Therapy: Treatment of Vasomotor Symptoms and Systemic Menopausal Symptoms

9.10.2.1 Treatment of Perimenopause

Women in perimenopause often experience more severe symptoms than postmenopausal women, due to the extreme fluctuation in

estrogen levels that can occur. Hormone therapy is the most effective medication currently available to treat menopausal symptoms. Combined hormonal contraceptives are often utilized to achieve symptom relief in women who are still ovulating, as these medications will relieve symptoms and are potent enough to prevent pregnancy. The greatest major health risk associated with the use of CHCs in midlife-aged women is the risk of blood clot/stroke. It is important to assess women for contraindications and other vascular risk factors prior to initiation of therapy.

Another option for treatment of women in perimenopause is cycled or continuous progesterone, with or without concurrent estrogen therapy. Many women in perimenopause may experience periods of high levels of unopposed estrogen due to lack of corpus luteum formation and subsequent lack of progesterone production. Progesterone treatment can offset this balance and help to regulate bleeding patterns. Low-dose estradiol therapy can be added in women with continued symptoms of estrogen deficiency. Some women in perimenopause, especially if in late perimenopause, may achieve symptom relief with menopausal estrogen therapy, which contains a much lower dose of estrogen than found in CHCs. It is important to note that menopausal hormone therapy (MHT) is not potent enough to suppress ovulation and thus does not prevent ovulation or resultant pregnancy from a fertilized egg. Therefore, if using MHT in a perimenopausal woman who is still ovulating, it is of paramount importance that clinicians counsel patients on using some form of contraception if a pregnancy is not desired, as women can become pregnant up until the time of their final menstrual period.

9.10.2.2 Treatment of Menopause: Menopausal Hormone Therapy

Hormone therapy treatment for 5–10 years when used in appropriate candidates within 10 years of menopause and under the age of 60 years old can shift the aging curve of women and provide significant cardiovascular, neurological, and mortality benefits. This is the gold standard of therapy for treatment for vasomotor symptoms. Hormone replacement therapy (HRT) is also the gold standard of treatment for women who experience early or premature menopause and should be continued at least until the median age of menopause (52 years old) to mitigate the consequences of early estrogen loss. Estrogen monotherapy may be used in hysterectomized women. In women who possess an intact uterus, a progestogen (bioidentical or synthetic progesterone) must be co-administered with estrogen for endometrial protection. Co-administration of estrogen and progestogen may also be necessary in women who have a history of endometriosis, even when hysterectomized, if there is any concern for remnant endometrial tissue. Certain selective estrogen receptor modulators (SERMs), such as bazedoxifene, also offer sufficient endometrial protection when administered with estrogen.

9.10.2.3 Indications for Treatment with Hormone Therapy

Treatment of menopausal symptoms is indicated in any woman for symptom relief (VMS or GSM) and/or to improve or maintain quality of life. For patients who undergo premature or early menopause without contraindications (including surgical/radiation-induced menopausal patients and POI patients), HRT is the gold standard of treatment and should be continued at least until the age of natural menopause. Hormone therapy is also indicated and FDA-approved for the prevention of osteoporosis in postmenopausal women. While there are no absolute contraindications to hormone therapy use, there are several relative contraindications that necessitate further risk stratification. The decision to use HT for treatment should occur on an individualized basis, through shared decision-making between patient and

medical provider after appropriate counseling has occurred (▶ Box 9.3).

Box 9.3 Relative contraindications to hormone therapy [91]

Severe active liver disease
History of endometrial cancer
History of estrogen-sensitive malignancy
Porphyria cutanea tarda
History of deep vein thrombosis
History of pulmonary embolism
History of stroke
Dementia
Coronary heart disease
Unexplained vaginal bleeding that has not been evaluated

9.10.2.4 Selecting a Route of Therapy

While conjugated and synthetic estrogen formulations are only available for oral administration, bioidentical estradiol can be administered orally, transdermally, or vaginally [92, 93]. Oral estrogens undergo first-pass metabolism through the liver, a process which is avoided through transdermal or vaginal estrogen delivery [92, 93]. Subsequently, oral estrogens need to be given in higher dosages and have a more pronounced effect on liver protein production [93]. Oral estrogen therapy only has also been associated with increased triglycerides, slightly increased risk of VTE, gallbladder disease, and stroke [94]. Stroke risk with oral estrogen is increased 1 extra case per 1000 women in women over age 65, not under age 65 [94, 95]. These risks are not seen with transdermal or vaginal hormone therapy [91]. The advantages of oral HT include ease of use, and typically improved symptomatic control on skin, hair, and mood. Additionally, some women may have issues with skin adherence and skin irritability with the transdermal patch that can be avoided with oral therapy. Cost and insurance coverage, which may vary among treatment options between patients, are also considerations that clinicians must keep in mind when deciding between medication routes (◘ Fig. 9.3).

Points to consider when prescribing hormone therapy:

- Is she menopausal? Yes or no
- Does she have a uterus? Yes or no
- Does she have indications for HT? Yes or no (VMS, GU, bone, QOL)
- Is she within 10 years of menopause and/or under 65? Yes or no
- What type of therapy is indicated: oral, transdermal, topical, or vaginal ring?

If patients are postmenopausal and do not report systemic symptoms, providers must be sure to also assess for silent changes, such as bone loss and any genitourinary symptoms.

9.10.2.5 Estrogen (E) Therapy Formulations (◘ Tables 9.5, 9.6, and 9.7)

9.10.2.6 Equivalencies of Estrogen Formulations

0.625 mg CEE/esterified estrogen = 5 ug ethinyl estradiol = 1 mg 17β-estradiol = 50 ug transdermal estradiol [93].

9.10.2.7 Progestogen (P) Therapy (◘ Table 9.8)

9.10.2.8 Estrogen + Progestogen (E+P) Therapy (◘ Tables 9.9, 9.10, and 9.11)

9.10.3 Clinical Data

9.10.3.1 Women's Health Initiative

The confusion over the safety of hormone therapy first arose in July 2002, when the Women's Health Initiative (WHI) published its initial results suggesting hormone therapy posed significant health risks to menopausal women while offering insufficient benefits [96]. The WHI was a National Institutes of Health (NIH)-sponsored multi-outcome study conducted in part to evaluate the risks and benefits of the use of HT for primary prevention of heart disease [96]. Postmenopausal women (average age 63 years old) were stratified to conjugated estrogen (CE) alone in hysterec-

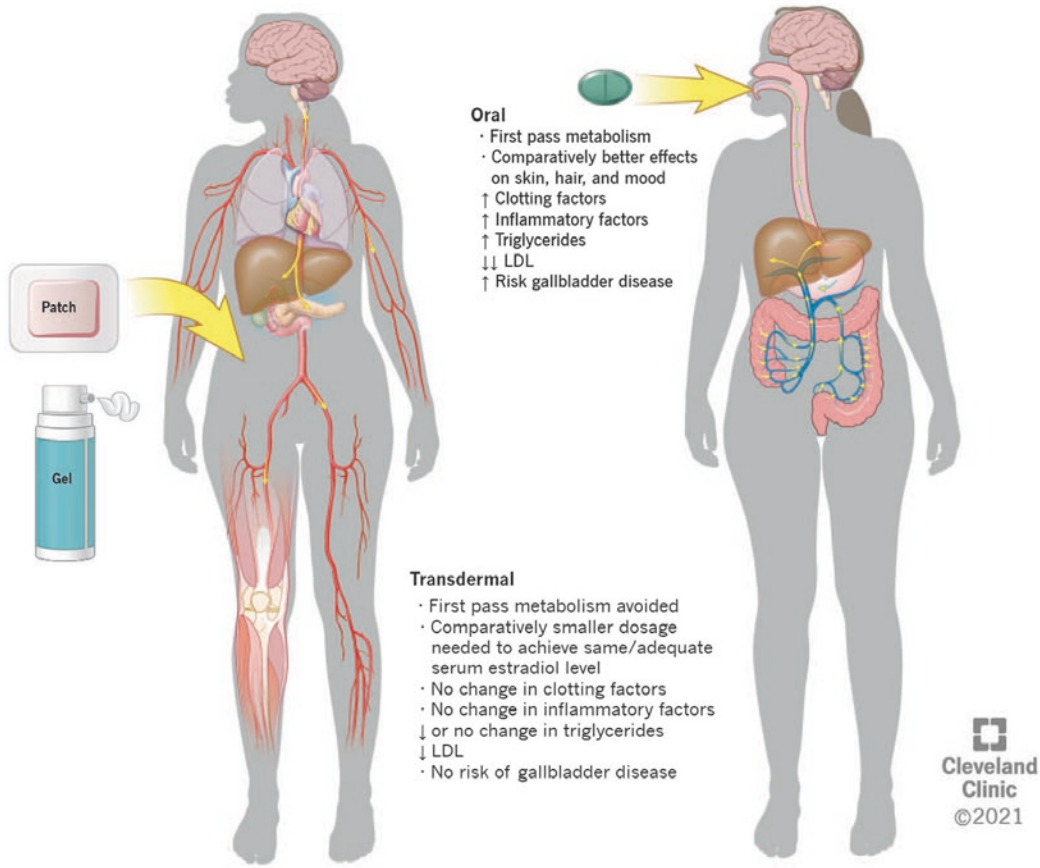

Fig. 9.3 Oral vs. transdermal hormone therapy. Distinctions in the pharmacology and result physiological effects of oral vs. transdermal hormone therapy administration [92, 93]

Table 9.5 Oral estrogens [93, 116, 117]

Estrogen	Brand name	Dosage	Notes
17β-Estradiol (bioidentical)	Generic available Estrace	0.5 mg total daily 1 mg total daily 2 mg total daily	Total daily dose divided into two doses for BID (every 12 hours) dosing
Esterified estrogen	Generic available Menest	0.3 mg daily 0.625 mg daily 1.25 mg daily 2.5 mg daily	
Conjugated equine estrogen (CEE)	Premarin	0.3 mg daily 0.45 mg daily 0.625 mg daily 0.9 mg daily 1.25 mg daily	Composed of ten different types of sulfated estrogens extracted from the urine of mares (female horses)

Table 9.6 Transdermal estrogens [93, 116, 117]

Generic	Route	Brand name	Dosages	Notes
17β-Estradiol (bioidentical)	Transdermal patch/film	Climara Menostar Alora Estraderm Minivelle Vivelle-Dot now generic available	0.025, 0.0375, 0.05, 0.06, 0.075 mg 1×/week 0.014 weekly only for bone protection 0.025, 0.05, 0.075, 0.1 mg 2×/week (every 84h) 0.05, 0.1 mg 2x/week 0.025, 0.0375, 0.05, 0.075, 0.1 mg 2x/week 0.025, 0.0375, 0.05, 0.075, 0.1 mg 2x/week 0.025, 0.0375, 0.05, 0.075, 0.1 mg 2x/week	Sufficient skin permeability required for adequate absorption Typically applied to buttocks, lower abdomen, lower back, or groin
	Gel	Divigel EstroGel Elestrin	0.25, 0.5, 0.75, 1.0, 1.25 mg E/g gel 0.75 mg E in 1.25 g gel/pump actuation 0.52 mg E in 0.87g gel/pump actuation	
	Spray	Evamist	1.53 mg E/spray (1–3 sprays per day)	

Table 9.7 Other formulations [93, 116, 117]

Generic	Brand name	Dosage	Administration
Estradiol acetate	Femring	0.05 mg/d, 0.10 mg/d	Replace ring every 90 days

Table 9.8 Oral progestogens [93, 116, 117]

Generic	Brand name	Dosage	Administration notes
Medroxyprogesterone acetate	Provera	2.5, 5, 10 mg/d	Cyclic administration 12–14 days/month with 200 mg or 100 mg nightly
Micronized progesterone (bioidentical)	Prometrium	200 mg P or 100 mg P	Cyclic administration 12 days/month Use at night given relaxing properties Bioidentical

tomized women and conjugated estrogen plus medroxyprogesterone acetate (CE + MPA) in women with an intact uterus [96]. The CE + MPA arm was terminated after 5.6 years due to concern over increased risk of invasive breast cancer and no apparent coronary benefit [96]. Less than 2 years later, the CE-alone arm was terminated due to concern over increased stroke risk [97]. Post hoc analysis of the data subsequently showed a reduction in CV risk in women using HT when initiated at or before the age of 60, or within 10 years of their last menstrual period (LMP) [97, 98]. Two subsequent landmark studies, the Kronos

Table 9.9 Oral estrogen + progestogen therapy [93, 116, 117]

Generic	Brand name	Dosage
Conjugated estrogens + medroxyprogesterone acetate	Prem-phase	0.625 mg CE + 5.0 mg MPA (2 tablets: E daily and MPA days 15–28)
Conjugated estrogens + medroxyprogesterone acetate	Prempro	0.3, 0.45 mg CE + 1.5 mg MPA daily 0.625 mg CE + 2.5, 5 mg MPA daily
Ethinyl estradiol + norethindrone acetate	FemHRT Generic	0.025 mg EE + 0.5 mg NA daily 0.05 mg EE + 1 mg NA daily
17β-Estradiol + norethindrone acetate	Activella Mimvey Lo Mimvey (generic)	0.5 mg E + 0.1 mg NA daily 1 mg E + 0.5 mg NA daily
17β-Estradiol + drospirenone	Angelic	0.5 mg E + 0.25 mg DRSP daily 1 mg E + 0.5 mg DRSP daily In Europe 1 mg E/2 mg DRSP daily
17β-Estradiol + progesterone (bioidentical)	Bijuva	1 mg E + 100 mg P daily

Table 9.10 Transdermal estrogen + progestogen therapy [93, 116, 117]

Generic	Brand name	Dosage	Administration
17β-Estradiol + norethindrone acetate	Combi-Patch	0.05 mg E + 0.14 mg NA 0.05 mg + 0.25 mg NA	Replace patch every 84 h (2×/week patch)
17β-estradiol + levonorgestrel	Climara-Pro	0.045 mg E + 0.015 mg L	Replace patch weekly

Table 9.11 Other formulations [93, 116, 117]

Generic	Brand name	Dosage	Notes
Conjugated estrogens + bazedoxifene	Duavee	0.045 mg CE + 20 mg Bazedoxifene daily	Previously produced by Pfizer, currently post COVID not in production
Esterified estrogens + methyltestosterone	Previously Estratest Previously Covaryx	0.625 mg EE + 1.25 mg MT daily 1.25 mg EE + 2.5 mg MT daily	

Early Estrogen Prevention Study (KEEPS) and the Early Versus Late Intervention Trial with Estradiol (ELITE), supported these findings in women who started HT less than 10 years after their LMP [99, 100]. Despite these critical trials and many others, the confusion around the safety of HT has remained prevalent throughout the medical community,

resulting in a sharp decline in the number of HT prescriptions written since 2003 [101]. Presently, the FDA continues to mandate a package insert boxed warning indicating increased risk of endometrial cancer, breast cancer, CVD, and dementia to appear on all estrogen-containing MHT products.

9.10.3.2 Breast Cancer

Breast cancer risk associated with the use of hormone therapy has been a source of confusion for decades. The CE + MPA arm of the WHI initially demonstrated an increased risk of breast cancer diagnosis [96–98, 102]. Later review of the data, however, suggested that this increased risk was more likely due to the unexpectedly lower incidence of breast cancer in a subgroup of women with a history of HT use who were randomized to the comparative placebo arm, rather than a true increase in breast cancer risk [103]. The CE-alone arm of the WHI initially demonstrated a nonsignificant reduction in breast cancer risk, with the 18-year follow-up results showing a statistically significant decrease in breast cancer mortality compared to placebo [102].

Since the WHI, there have been several other studies examining the association between hormone therapy use and breast cancer. It is important to note that these studies are often plagued by confounders and biases and that they do not provide cause and effect conclusions. Several decades of observational studies suggest that HT does not increase breast cancer death. The data also appears to demonstrate that hormone therapy does not increase breast cancer risk in women with high risk of breast cancer (i.e., genetic mutations, family history, etc.). The Danish Osteoporosis Study (DOPS) was a prospective study that did not show any increase in breast cancer or mortality with prolonged HT treatment, rather a reduction in all-cause mortality [104].

9.10.3.3 Venous Thromboembolism (VTE)

Several decades of research have shown an association between oral hormone therapy and rare increased risk of venous thromboembolism. Among specific oral estrogen formulations, conjugated equine estrogen seems to have a higher risk of VTE than bioidentical 17β-estradiol. The WHI demonstrated a slightly increased risk of VTE with both CE and CE + MPA oral therapy compared to placebo [96–98]. A subsequent two-nested case-control study that looked at the use of HT and VTE risk in the UK found that over 80,000 women aged 40–79 years old who had a primary diagnosis of VTE over the span of 19 years and who were matched by age, index date to almost 400,000 female controls, had a dose-dependent increased risk of VTE for all oral hormone therapy agents (E + P > E alone) [105]. Importantly, this study also found that transdermal hormone therapy was not associated with any increased risk of VTE [105].

9.10.3.4 Alzheimer's Disease (AD) or Senile Dementia of the Alzheimer's Type (SDAT)

There has been increasing research in the influence of hormone therapy on dementia outcomes. In one multi-institutional case control study, women aged 50–63 years old who used hormone therapy were found to have a reduced risk for AD (odds ratio [OR] 0.35, 95% CI 0.2–0.7) [7]. In this study, no significant associations were found in women older than 63 using hormone therapy and Alzheimer's risk [7]. There have been several other observational studies that support this notion that HT, when initiated in younger postmenopausal women, is associated with a reduced risk of AD [8–10]. When menopausal symptoms of VMS and sleep disturbance are treated, many women report resolution of their "brain fog." The effects of endogenous hormones, menopause, and hormone therapy remain critical areas in need of further research, as there are still many unanswered questions.

9.10.3.5 Cardiovascular Disease

The ELITE trial showed less progression of atherosclerosis, as measured by carotid intima thickness levels, in women treated with oral estradiol within 6 years of menopause [100]. Oral estrogen therapy has been shown to reduce LDL levels, increase HDL levels, and increase VLDL levels in postmenopausal

women [49]. HT has been shown to decrease serum levels of lipoprotein (a), which is considered an independent risk factor for developing cardiovascular disease due to its athero-thrombogenic properties [106].

Oral, not transdermal or vaginal, estrogen has been associated with 1 additional case of stroke per 1000 women over the age of 65 [94, 95]. However, after 10 years of randomized treatment, younger women on HT had a significantly reduced risk of heart failure, MI, VTE, and stroke, as well as reduced risk of mortality [107]. In women less than 10 years from menopause and under the age of 60 years old, the data consistently shows statistically significant reductions in cardiovascular mortality, coronary heart disease, and all-cause mortality, which strongly affects the risk benefit equation for younger and symptomatic menopausal women.

9.10.3.6 Mortality Data

A historical perspective shows that in the USA, female mortality rates from 1992 to 1996 vs. 2002 to 2006 increased in 42.8% of counties, while male mortality rates in comparison increased in only 3.4% of counties [108]. Menopause experts postulate one of the reasons for this dramatic change was the publication of the 2002 WHI study, which resulted in the decline of prescriptions for HT nationally [101]. A nationwide study in Finland examining mortality in postmenopausal women (average age 52.2 years old) showed a 12–38% reduction in the risk of all-cause mortality, an 18–54% reduction in cardiovascular mortality, and an 18–39% reduction in stroke mortality in HT users vs. age-matched controls [109]. Research has also shown that women who have undergone bilateral oophorectomy have an increased risk of cardiovascular mortality when not treated with E + P or estrogen-alone therapy [110].

9.10.4 Unregulated Hormone Therapy

Women should be counseled about the dangers of unregulated hormonal therapies, such as testosterone pellets or unchecked compounded hormone regimens. If patients present on this type of therapy, detailed history of medication use and symptoms should be assessed. Serum hormone levels for 17β-estradiol, free and total testosterone, and dehydroepiandrosterone (DHEA) should be assessed if indicated. Progesterone levels are more accurately assessed through evaluation of the endometrial lining than through hormonal blood levels. If women have been on estrogen therapy with unregulated compounded progesterone creams, which may not absorb adequately enough to protect the uterus sufficiently, they may have been receiving unopposed estrogen which puts them at risk for endometrial cancer. If postmenopausal women have had any vaginal bleeding or spotting, they should undergo pelvic ultrasound to assess the endometrial stripe or thickness, which should be 4 mm or less, and ideally also undergo an endometrial biopsy.

9.10.5 Non-hormonal Therapy Options

Non-hormonal therapeutic options should be considered based on patient preference or if a woman has contraindications to hormone therapy. While lifestyle modification and non-hormonal medications exist for the treatment of vasomotor symptoms, women should be counseled that they are not as effective as hormone therapy.

Non-pharmacologic treatment strategies should focus on patient education and lifestyle modification. Women should dress in layers, keep a lower temperature in the bedroom, and use fans/cooling devices, as needed. Women should be advised to avoid triggers and limit caffeine and alcohol intake. Smoking cessation should be encouraged in any tobacco users. Weight loss, meditation, deep breathing exercises, and yoga can be helpful in controlling symptoms. There is limited evidence that cognitive behavioral therapy (CBT), hypnosis, and acupuncture can also be helpful in the treatment of hot flashes.

9.10.5.1 Non-hormonal Pharmacologic Therapy Options (◘ Table 9.12)

9.10.5.2 Herbal Remedies

There is insufficient evidence to support the use of any herbal remedies for the treatment of menopausal symptoms. Women should especially be counseled about the commonly used supplement black cohosh. There is not sufficient evidence that black cohosh improves menopausal symptoms and persistent use may lead to hepatotoxicity.

9.10.6 Neurokinin 3 Receptor (NK3R) Antagonists

Emerging research regarding the physiology behind hot flashes has demonstrated that the thermoregulatory center in the brain is affected by several neuroendocrine influences, including the HPO axis and the hypothalamic expression of kisspeptin and neurokinin B (NKB) [111]. The loss of estrogen that occurs with menopause has been found to disrupt the thermoregulatory center in the hypothalamus through removal of negative feedback of neurokinin 3 receptor (NK3R) activation [111].

Fezolinetant, a novel neurokinin 3 receptor antagonist, is currently in phase 3 trials with promising results [112, 113]. Several clinical trials have demonstrated that use of NK3R antagonists is not only safe but associated with improved hot flash severity and frequency [112, 113]. This groundbreaking medication will likely become the treatment of choice for relief of vasomotor symptoms in women with contraindications to hormone therapy, who previously had very limited options for relief.

9.10.7 Treatment for Genitourinary Syndrome of Menopause

9.10.7.1 Hormone Therapy for GSM Treatment

Treatment of GSM can be most effectively achieved through both systemic and local hormone therapies. Local hormone therapy can provide sufficient hormonal supplementation to relieve GSM with minimal systemic absorption. When systemic HT is needed, women may have resolution of GSM, though some may require additional low-dose vaginal hormone therapy to achieve adequate symptom relief (◘ Fig. 9.4).

◘ **Table 9.12** Non-hormonal medication options [118]

Generic	Brand names	Dosage	Notes
SSRI/SNRI Paroxetine Venlafaxine Desvenlafaxine Escitalopram Citalopram	Brisdelle Effexor Pristiq Lexapro Celexa	7.5 mg po daily 37.5, 75 mg po daily 50 mg po daily 5, 10 mg po daily 10, 20 mg po daily	Brisdelle is the only FDA-approved non-hormonal treatment for VMS Cannot use paroxetine in patients using tamoxifen because of cross-reaction between the drugs Lower dosages are more effective for hot flashes; higher doses may worsen VMS Fluoxetine and sertraline have not been shown to be as effective as the other SSRIs
Antihypertensive Clonidine	Catapres	0.1 mg daily po or patch	Can be useful in patients with high BP; however, use caution as these patients can get rebound HTN
Anticonvulsants Gabapentin Pregabalin	Neurontin Lyrica	300–900 mg total daily dose po 75–300 mg po daily	Can cause significant drowsiness in some women
Anticholinergic Oxybutynin	Ditropan	5 mg BID po	Can cause dry mouth, constipation, and worsening of acute angle glaucoma

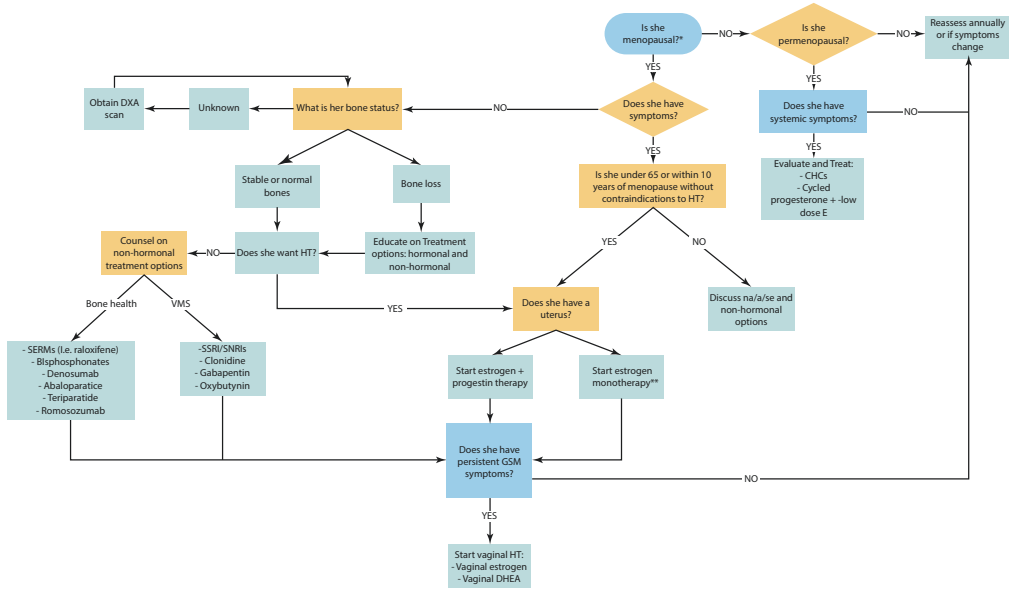

Fig. 9.4 Treatment of menopause. CHCs combined hormonal contraceptives, DHEA dehydroepiandrosterone, DXA dual-energy X-ray absorptiometry, E estrogen, HT hormone therapy, GSM genitourinary syndrome of menopause, r/b/a/se risks, benefits, alternatives, side effects, SERM selective estrogen receptor modulator, SSRI selective serotonin reuptake inhibitor, SNRI serotonin-norepinephrine reuptake inhibitor. *Defined clinically as ≥12 months since LMP (see 10.9.1 Diagnosis for further details). **Consider estrogen+progestogen therapy in hysterectomized patient with a history of endometriosis if concerned for any remnant endometrial tissue

There are two main types of local hormone therapy currently available, vaginal estrogen and vaginal DHEA. Vaginal estrogen comes in several forms, including creams, rings, tablets, and inserts [87]. Vaginal DHEA comes in suppository form, though a ring formulation is currently in development. All of these FDA-approved products have proven efficacy in placebo-controlled trials to alleviate symptoms of vaginal dryness and dyspareunia [87]. Additionally, research has shown that with the use of both vaginal estrogen and vaginal DHEA, serum estradiol levels remain within postmenopausal range [87].

It is important for clinicians to know that the package insert boxed warning regarding risk of endometrial cancer, breast cancer, CVD, and dementia that appears on systemic estrogen products is also seen in vaginal estrogen productions. Women must be educated about the differences between vaginal ET and systemic ET and should be informed about this box warning before they use the product so they are prepared (Table 9.13).

9.10.7.2 Non-hormonal Treatment for GSM

Non-hormonal options may be sufficient to relieve symptoms in some women, and would be an appropriate choice for those who do not wish to use local hormone therapy (Table 9.14).

Table 9.13 Hormone therapy for the treatment of GSM [87, 116, 117]

Generic	Brand name	Dosage	Notes
17β-Estradiol (bioidentical)	Estrace vaginal cream Generic	0.1 mg E/g 2–4 g/d × 1–2 weeks 1 g 1–3×/week	
Conjugated equine estrogen	Premarin vaginal cream	0.625 mg CE/g 0.5–2 g/d for 2 weeks then then 0.5 g 2×/weekly	
Estradiol hemihydrate	Vagifem vaginal tablet Generic Yuvafem vaginal tablet	0.01 mg Initial: 1 tablet/d × 2 weeks Maintenance: 1 tablet 2×/week	
Estradiol vaginal	Imvexxy vaginal insert	4mcg, 10 mcg Daily for 2 weeks then 2×/week	FDA-approved
Vaginal DHEA (prasterone)	Intrarosa vaginal suppository	6.5 mg insert daily	Through intracrinological processes, genitourinary tissue takes up DHEA and processes it into androgens and estrogens, leading to improved dryness, urinary symptoms, and sexual function
Ospemifene (SERM)	Osphena	60 mg pill daily with food	FDA-approved for dyspareunia and dryness Not recommended for breast cancer survivors Can worsen VMS.

Table 9.14 Non-hormonal treatment options for GSM [87, 114]

Type of therapy	Description	Mechanism of action	Duration of action	Notes
Moisturizers	Gel or cream Use regularly	Hydrophilic agents that coat the vagina and bring moisture to vaginal epithelial surface to maintain hydration and relieve dryness	Longer duration of action	
Lubricants	Gel or cream (water vs. silicone vs. oil vs. hybrid) Use only prior to vaginal penetration	Moistens vaginal epithelium to improve dryness and alleviate dyspareunia prior to intercourse or medical examinations	Shorter duration of action	Silicone lubricants are more expensive, but typically last longer Water lubricants are easier to wash off Not all lubricants are condom compatible
MonaLisa Laser Therapy (experimental with FDA warnings issued)	Vaginal fractional carbon dioxide (CO2) laser	Produces new collagen and elastic fibers to remodel atrophic vaginal connective tissue	Longer duration of action	While women may experience improved symptoms with this treatment, there are no current well-powered studies that are sham procedure-controlled to confirm efficacy

Conclusion

Menopause, whether premature, early, natural, or surgical, offers a key opportunity to clinicians and patients to chart the second half of female adult life with a focus on symptom control, risk assessment, and disease prevention. There are a multitude of hormonal and non-hormonal treatment options available. Women under age 65 and within 10 years of menopause are in the best situation to obtain both symptom control and increased longevity with the use of hormone therapy. However, regardless of time since menopause, vasomotor symptoms, bone tissue, and the genitourinary systems are responsive to HT. For maximal prevention and reduced risk, starting HT within 6–10 years of hormonal menopause is optimal, noting one cannot just rely on age and/or menstrual history to make the diagnosis of menopause.

9.11 Learning Assessment

9.11.1 Review Questions

1. Which of the following etiologies of POI causes the most significant physiological consequences and the most severe symptoms in women?
   A. Iatrogenic
   B. Infectious
   C. Surgical
   D. Autoimmune

2. Estrogen has a multitude of functions in the body, including:
   A. Neuroprotective and neurotrophic effects on the brain
   B. Preserving blood supply, maintaining integrity, and supporting the microbiome of the vagina
   C. Bone protection through RANKL-mediated antiresorptive effects
   D. All of the above

3. Which of the following statements about the diagnosis of menopause is not true?
   A. Menopause is typically diagnosed retrospectively 12 months after the final menstrual period.
   B. There is a rare possibility of continued cycles even after a woman meets the criteria of the classic clinical definition of menopause.
   C. FSH and 17β-estradiol, which should always be interpreted together, can be helpful in confirming the diagnosis of menopause.
   D. The pico AMH diagnostic ELISA test is the most commonly used test to confirm the diagnosis of menopause.

4. Which of the following statements regarding systemic hormone therapy is not true?
   A. Women without a uterus can use estrogen therapy by itself. Women with an intact uterus must use E + P therapy.
   B. In accordance with the FDA-mandated black box warning, vaginal hormone therapy increases the risk of endometrial cancer, breast cancer, CVD, and dementia.
   C. There is only one FDA-approved SSRI for the treatment of vasomotor symptoms, Brisdelle (paroxetine 7.5 mg).
   D. NK3R antagonists will likely become the treatment of choice for relief of vasomotor symptoms in women with contraindications to hormone therapy.

9.11.2 Answers

1. C
2. D
3. D
4. B

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