Menopause
The Best Chapter of Our Lives

Elyse Watkins, DHSc, PA-C

KEYWORDS

• Menopause • Menopausal transition • Perimenopause • Estrogen
• Vasomotor symptoms • Genitourinary syndrome of menopause

KEY POINTS

- Clinical practice guidelines advise against the use of estrogen solely for the prevention of chronic diseases, such as cardiovascular disease, Alzheimer dementia, and colon cancer.
- Current guidelines advise using the lowest dose of systemic estrogen, if within 10 years of a woman's last menstrual period or before age 60 years, to treat vasomotor symptoms.
- For patients in whom estrogen is not an option, paroxetine is currently the only FDA-approved SSRI for the treatment of vasomotor symptoms; evidence does not support the use of black cohosh, red clover, or soy.
- New pharmacologic treatment options for the genitourinary syndrome of menopause include a DHEA vaginal insert and an oral SERM.
- Patients with a uterus who wish to use estrogen must also take a progestin to help prevent endometrial hyperplasia and uterine cancer, but the addition of a progestin increases the risk of thromboembolic events, dementia, breast cancer, and CVD.

INTRODUCTION

Menopause is clinically defined as the unintentional absence of menses for 1 year because of ovarian senescence resulting in a state of hypoestrogenism. The average age of menopause has remained constant globally at 51 years of age; in contrast, the average age of menarche has declined. Perimenopause is defined as the period of time occurring before a woman's last menstrual period (LMP) where she experiences alterations in sex hormone pulsatility, resulting in menstrual changes.[1] Early perimenopause has a variable duration, but is described as a persistent change in the length of the menstrual cycle of 7 days or more. Pituitary follicle-stimulating hormone (FSH) levels fluctuate during this phase, therefore FSH testing is not recommended to diagnose or stage perimenopause. Late perimenopause is defined as intervals of missed menses equal to or greater than 60 days. Typically, late perimenopause lasts from 1 to

The author has no relationships to disclose.
Department of Physician Assistant Studies, High Point University, One University Parkway, High Point, NC 27268, USA
E-mail address: ewatkins@highpoint.edu

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3 years. Menses during late perimenopause are characteristically variable, and sex hormone levels fluctuate considerably.

During early and late perimenopause, anti-Müellerial hormone and inhibin B, both produced by ovarian follicular granulosa cells, remain low. In early postmenopause, FSH levels can again be variable, but at about 6 years after the final LMP, the FSH remains persistently elevated. Transvaginal ultrasounds reveal low antral follicle counts throughout all phases of the menopause transition.

Early postmenopause is divided into three stages (stages +1a, +1b, +1c) based on symptomatology and hormone levels.[1]

- Stage +1a: lasts about 1 year after the final menstrual period; vasomotor symptoms (VMS); FSH variability
- Stage +1b: lasts about 1 year; VMS; FSH variability
- Stage +1c: lasts about 3 to 6 years; variable VMS; FSH remains elevated; estradiol remains low

Late postmenopause occurs approximately 8 years after the final menstrual period. Clinically, women may experience worsening of vulvovaginal atrophy and genitourinary syndrome of menopause (GUSM).[1]

Surgical menopause occurs when the ovaries are removed from a woman premenopausally. Premature ovarian failure, also called primary ovarian insufficiency, is menopause occurring before age 40 years. Many of the somatic and neurocognitive effects of natural menopause occur in surgical menopause and premature menopause. There is evidence that bilateral oophorectomy resulting in surgical menopause is associated with an increased risk of cardiovascular disease (CVD).[2]

THE WOMEN'S HEALTH INITIATIVE

A discussion of hormone therapy must include a brief overview of the Women's Health Initiative (WHI). The WHI, started in 1991 under the auspices of the National Heart, Lung, and Blood Institute, was designed to determine if the use of conjugated equine estrogen and medroxyprogesterone acetate, a progestin, could prevent chronic diseases, such as colon cancer, dementia, and CVD. The initial trial was halted when researchers found a statistically significant increase in cardiovascular events, thrombotic events, and breast cancer. Since then, careful scrutiny of the WHI has revealed several areas of concern regarding methodology, and newer randomized control trials (RCTs) have yielded evidence that has created opportunities for managing VMS, preventing osteoporosis, and treating the GUSM (see **Table 3**).

A SUMMARY OF MANAGEMENT STRATEGIES

Estrogen

Estrogens that are naturally produced in the body are estrone (E1), estradiol (E2), and estriol (E3). Estradiol is the most potent of endogenous estrogens; estriol is found primarily during pregnancy, and estrone during menopause.

There are several synthetic estradiol preparations available in the United States for treatment of menopausal symptoms. Oral estradiol is micronized to help with absorption (**Table 1**).

Phytoestrogens, particularly those found in soy, act as selective estrogen receptor modulators (SERMs). As such, they have the ability to bind to estrogen receptors.[3] Conversion and absorption of phytoestrogens takes place in the human gut. There are vast differences between humans in regards to their gut microbiota. Thus, the bioavailability of phytoestrogens varies considerably from person to person, making