Menopausal hormone therapy and menopausal symptoms

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A majority of women will experience bothersome symptoms related to declining and/or fluctuating levels of estrogen during their menopausal transition. Vasomotor symptoms, vaginal dryness, poor sleep, and depressed mood have all been found to worsen during the menopausal transition. While vasomotor symptoms gradually improve after menopause, the time course can be many years. Vaginal dryness does not improve without treatment, while the long-term course of sleep and mood deterioration is not clearly defined at this time. A small minority of women have vasomotor symptoms that persist throughout the remainder of their lives. These common menopausal symptoms all improve with estrogen treatment. Over the last 10 years, we have witnessed a dramatic reduction in enthusiasm for menopausal hormone therapy, despite its high efficacy relative to other treatments. We have also seen the emergence of sound, evidence-based clinical trials of non-hormonal alternatives that can control the common menopausal symptoms. Understanding the natural history of menopausal symptoms, and the risks and benefits of both hormonal and non-hormonal alternatives, helps the clinician individualize management plans to improve quality of life. (Fertil Steril® 2014;101:905–15. ©2014 by American Society for Reproductive Medicine.)

Key Words: Menopause, hormone therapy, vasomotor symptoms, vulvovaginal atrophy

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Women nowadays spend more than a third of their lifetime beyond the menopausal transition (1). With the progressive aging of the population, the proportion of women who are menopausal is expected to continue to rise (2). Thus, reducing the burden of menopause-related health conditions and improving overall quality of life become increasingly important. Declining and/or fluctuating levels of estrogen are associated with the menopausal transition and may result in bothersome symptoms. Those menopausal symptoms that have been shown to be associated with the onset of the menopausal transition and to improve with hormones are vasomotor symptoms, vulvovaginal atrophy/dyspareunia, sleep disturbance, and adverse mood (3–6). This review will focus on the common menopausal symptoms, along with hormonal and non-hormonal treatments targeting these conditions.

Throughout this review, we will be referring to the Stages of Reproductive Aging Workshop +10 staging system (7) for various stages of reproductive aging (Fig. 1).

VASOMOTOR SYMPTOMS

Vasomotor symptoms (VMS), commonly known as hot flashes/flushes and night sweats, are sudden episodes of intense heat that usually begin in the face or chest and spread throughout the body, accompanied by sweating and flushing that typically last 1 minute to 5 minutes (8). Although night sweats are sometimes considered unusually intense hot flashes that occur at night, it is not clear that they differ in their pathophysiology or treatment from less intense hot flashes. It is believed that hot flashes and night sweats interrupt sleep, as women frequently subjectively cite VMS at night as the source of this sleep disturbance (8), however, some laboratory studies do not support this notion (9).

Between 60% to 80% of women will experience VMS at some point during their menopausal transition (3). The frequency and severity of VMS peak in the late perimenopause and early postmenopausal years, with large ethnic and racial variation in prevalence, frequency, and severity of symptoms (3). African-American women are most likely to report VMS and are also more likely to describe them as bothersome (10), whereas women of Asian background (Japanese and Chinese-American) are least likely to report VMS, and are less likely to describe them as bothersome (3, 10). These racial/ethnic differences in VMS in the Study of Women's Health Across the

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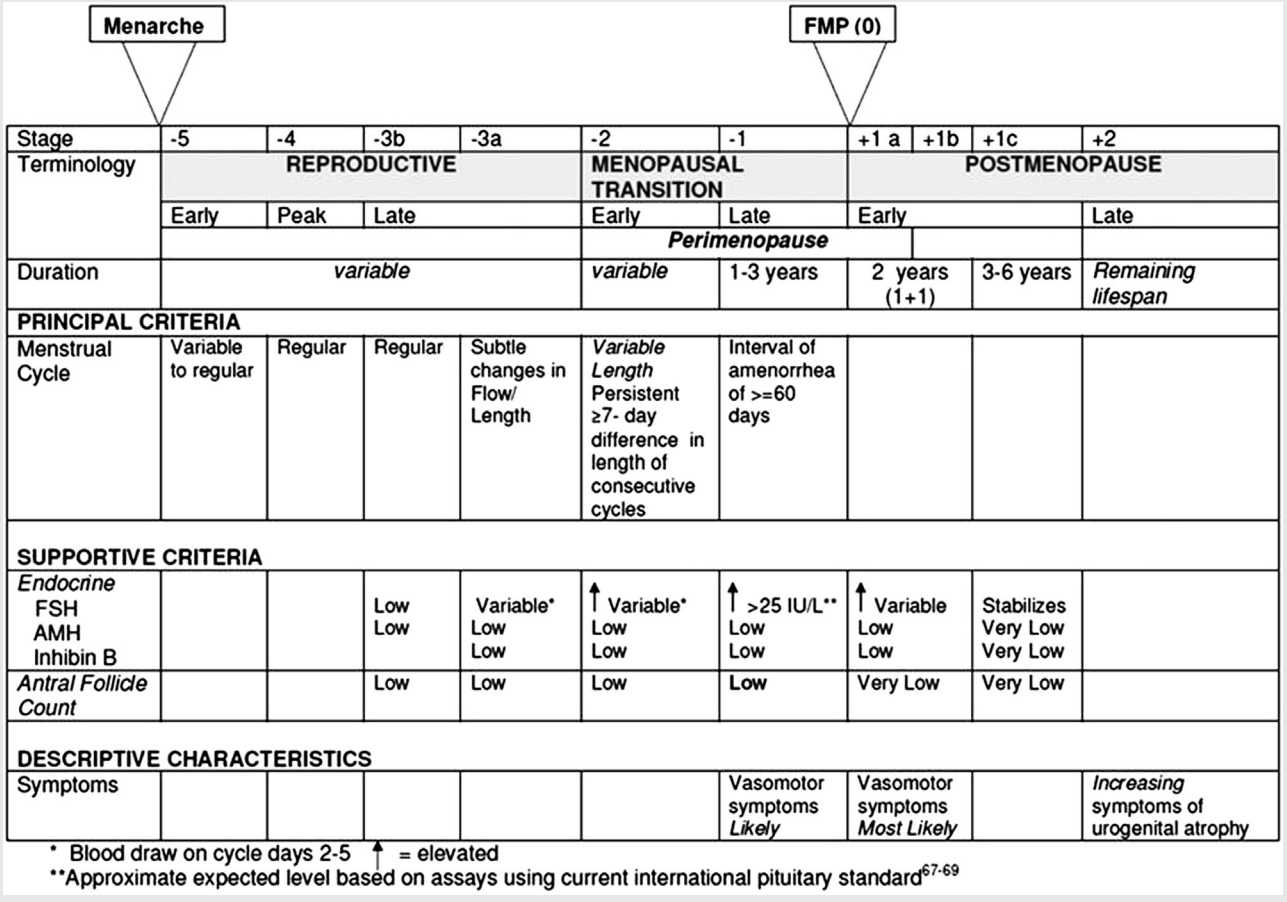
FIGURE 1



The Stages of Reproductive Aging Workshop + 10 staging system for reproductive aging in women. (Taken from Harlow. STRAW + 10: staging reproductive aging. Fertil Steril 2012.)

Al-Safi. Menopausal symptoms and hormone therapy. Fertil Steril 2014.

Nation (SWAN) persisted even after controlling for key factors like body mass index, estradiol level, hormone use, smoking, education and economic strain (difficulty paying for basic necessities) (3).

Obesity has been found to be a key risk factor for perimenopausal, but not postmenopausal, VMS. Women with higher abdominal adiposity, particularly subcutaneous adiposity, are more likely to report VMS in the early and late perimenopause (11). Smoking has also been associated with VMS, while other health behaviors such as dietary composition, has weaker and less consistent associations (3). While unadjusted data from SWAN showed association of VMS with lower physical activity scores, no such association existed after adjustment for other factors (3).

Women who experience premenstrual symptoms are at a higher risk for VMS when they traverse the menopause (3).

VMS have been associated with all aspects of perceived sleep disturbance that contribute to the subjective complaint of poor sleep. These include falling asleep, staying asleep, and early morning awakening (5).

Quality of life can be negatively affected by VMS, yet remarkably little is known about their pathophysiology (12).

The main factors thought to influence VMS occurrence and severity include reproductive hormones, particularly estradiol, inherent thermoregulatory process within the individual, and genetics (13–18). Reproductive hormones are believed to play an integral role as evidenced by the onset of VMS occurring in the context of the dramatic reproductive hormone changes of the menopausal transition and by the therapeutic role of exogenous estrogen in their treatment. Data from Penn Ovarian Aging Study showed that fluctuations of estradiol, decreased levels of inhibin B, and increased FSH levels, were significantly and independently associated with menopausal symptoms (13). VMS are believed to be thermoregulatory heat dissipation events, although the exact mechanisms underlying VMS are not entirely known. The thermoneutral zone in the hypothalamus is narrowed in women with VMS (14). This is believed to be the area of the brain in which core body temperature is maintained without triggering thermoregulatory homeostatic mechanisms such as sweating or shivering. In symptomatic women, small fluctuations in core body temperature can exceed this zone and trigger heat dissipation mechanism, such as sweating