Onset of the Menopause Transition
The Earliest Signs and Symptoms

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INTRODUCTION
Four of 5 women experience psychological or physical symptoms around menopause, with varying degrees of severity and disruption in their lives. Clinicians and women normally identify the transition to menopause by the onset of irregular menstrual cycles or the experience of vasomotor symptoms that commonly occur at this time. However, in addition to vasomotor symptoms that are readily recognized, other common menopausal symptoms, such as mood changes, sleep difficulties, and changes...
in sexual functioning, may increase early in the menopause transition. This transition period, termed perimenopause, is highly variable but can extend for 5 to 10 years before menopause (marked by the final menstrual period [FMP], which is identified by the absence of menstrual bleeding for at least 12 months).

Information on the normal process of reproductive aging and its acute consequences has been limited by many factors. Research has been dominated by cross-sectional study designs, small clinical samples, suboptimal assessment, and lack of adjustment for confounding factors. However, in recent years, several large population-based, longitudinal cohort studies have been conducted that more fully characterize changes during this transition period. This article focuses on current evidence, primarily from large, population-based studies, for symptoms that increase during the menopausal transition. Specifically, we address vasomotor symptoms, mood changes, sleep problems, and changes in sexual functioning.

VASOMOTOR SYMPTOMS

Characteristic Symptoms

The sudden sensation of extreme heat in the upper body, particularly the face, neck, and chest is referred to as a “hot flush.” Flushing, chills, clamminess, sweating, anxiety, and occasionally palpitations can occur lasting 1 to 5 minutes. These episodes vary in frequency and duration and include night sweats. Some studies show that up to 87% of women reporting hot flushes experience daily symptoms, with one-third experiencing more than 10 per day. Sleep disruption has been demonstrated with physiologic measures of hot flushes.

Prevalence and Duration

Vasomotor symptoms are the most common symptom of menopause experienced by up to 80% of women. In the United States, the prevalence of vasomotor symptoms among naturally menopausal women is approximately 40% in the early menopause transition, with the peak prevalence of 60% to 80% in the first 2 years after the FMP.

On average, hot flushes commence before the FMP and continue for several years after the FMP. More than one-third of women who experience moderate/severe hot flushes will continue to have them for more than 10 years after the FMP.

Pathophysiology

The pathophysiology of the hot flush is not clearly understood. A current hypothesis is that the thermoregulatory mechanisms change during the transition so that the thermoregulatory zone is narrowed and becomes more sensitive to subtle changes in core body temperature. Small increases in temperature lead to what we know as a hot flush (vasodilatation, sweating, and decreased skin resistance). Freedman postulates that noradrenergic stimulation in conjunction with estrogen may trigger thermoregulatory changes resulting in hot flushes.

Although there is little doubt that estrogen is important in the pathophysiology of hot flushes, changes in estrogen alone do not account for vasomotor symptoms. Instead, the mechanism of action appears to be centrally mediated. Some evidence indicates that hot flushes are temporally related to luteinizing hormone (LH) pulses, but other findings showed that LH is not the direct cause. In another study, cortisol dysregulation was related to more frequent, severe, and bothersome hot flushes, which supports a potential role of the hypothalamic pituitary adrenal axis in the etiology of the symptoms.
The relationship of genetic variation and hot flushes was recently evaluated using data from the Women’s Health Initiative and found that genetic variation in tachykinin receptor 3 (TACR3) might contribute to the risk of hot flushes.\(^{15}\) The hypothalamic neuron neurokinin B (NKB) and its receptor NK3R (which is encoded by TACR3) may also be involved in the pathophysiology of hot flushes.\(^{16,17}\)

### Risk Factors

Epidemiologic studies have identified numerous risk factors for vasomotor symptoms, including racial/ethnicity and body weight (body mass index [BMI]). In the Study of Women’s Health Across the Nation (SWAN), African American women reported significantly more vasomotor symptoms, white women reported more psychosomatic symptoms, and Asian women reported the fewest symptoms compared with other groups in a cross-sectional survey of 14,906 multiethnic women aged 40 to 55 years in the United States.\(^{18}\) In the Penn Ovarian Again Study (POAS), African American women reported more physiologic symptoms (hot flushes, dizziness, clumsiness, urine leaks, and vaginal dryness) compared with white women even when adjusting for age, BMI, and demographic factors.\(^{4,12}\) Such racial and cross-cultural variability in the prevalence of self-reported hot flushes is substantiated by other studies.\(^{19–21}\) Although physiologic or dietary differences may account for variable symptomatology, it is also possible that ethnic variations are largely due to differences in cross-cultural perceptions and reporting.\(^{2,22,23}\) (see the article by Nancy E. Avis and colleagues’ article, “Vasomotor Symptoms Across the Menopause Transition: Differences Among Women,” elsewhere in this issue for more details).

POAS, SWAN, and other studies have reported that obese women have more frequent vasomotor symptoms than nonobese women independent of race, age, and smoking.\(^{4,24–27}\)

Smoking is a strong risk factor for hot flushes. Smokers in SWAN had a more than 60% greater likelihood of reporting vasomotor symptoms overall and moderate to severe hot flushes compared with nonsmokers.\(^{28,29}\)

Physical activity has not significantly reduced vasomotor symptoms in a number of studies.\(^{24,30–32}\) Moreover, highly active women (ages 35–40 years) were significantly more likely to report moderate to severe hot flushes than minimally active women, which may be explained by a rise in core body temperature.\(^{33,34}\)

Many other behavioral, social, and demographic factors have been associated with hot flushes. Negative or depressed mood, a history of depression, higher anxiety levels, and greater perceived stress are associated with increased hot flushes in SWAN and POAS.\(^{2,12,24}\)

### Depressed Mood

Identifying the risk of depression is clinically important because of the significant disability that accompanies depression and conditions related to depression, including cardiovascular disease, metabolic syndrome, and osteoporosis.\(^{27,35–37}\) Although the National Institutes of Health State-of-Science Report of 2005 concluded that evidence for an association of depression and menopausal status was poor or mixed, more recent population-based, longitudinal cohort studies have challenged this conclusion.\(^{8}\)

#### Increase in Depressive Symptoms Related to Menopausal Status

Several population-based studies show that the likelihood of depressed mood is 30% to 3 times greater in the menopause transition compared with the premenopausal stage, even after adjustment for important variables, such as history of depression,
hot flushes, and poor sleep. Women with a history of depression are nearly 5 times more likely to have a depression in the menopause transition.38,43,45,46

Investigation of the longitudinal pattern of depressive symptoms around natural menopause shows that the FMP is pivotal in the overall pattern of decreasing depressive symptoms in midlife women, with higher risk before and lower risk after the FMP.12 Importantly, women who had no history of depression before the menopause transition had a low risk of depressive symptoms 2 or more years after the FMP, which suggests the transient nature of menopausal depression for some women.

Associations between perimenopausal depressed mood and changes in the hormonal milieu have been observed.38,43 An association between follicle-stimulating hormone and depressive symptoms has been demonstrated and suggests that the changing hormonal milieu may contribute to a transient dysphoric mood. However, studies suggest that psychosocial and lifestyle factors, together with health experience may have more effect on mood than endocrine changes.45,47 Indeed, there are many health and demographic factors that are associated with depression in the perimenopause, including health problems, marital problems, “empty nest” issues, financial difficulty, lack of physical exercise, and environmental stresses.27,38

**Depressive Symptoms Related to Vasomotor Symptoms**

Vasomotor symptoms are strongly correlated with depressive symptoms. It has long been postulated that the depressive symptoms are secondary to hot flushes,18 but the temporal associations and causal pathways between these symptoms in perimenopausal women are not clear.34,48 In the Massachusetts Women’s Health Study, the association between perimenopause and increased depression was explained by increased reporting of vasomotor symptoms.49 In contrast, by studying symptoms over 10 years, the POAS study demonstrated that although both hot flushes and depressive symptoms occurred early in the menopause transition, depressive symptoms were more likely to precede hot flushes in women without previous symptoms.48

Depression is episodic and multifactorial, associated with numerous health and psychosocial factors, which makes it difficult to determine causality. However, it is clinically important to identify and treat depression regardless of cause.

**Anxiety**

Anxiety manifests in many ways, ranging from symptoms to fully diagnosed disorders that include generalized anxiety disorder, panic disorder, phobias, and posttraumatic stress disorder. Anxiety syndromes or high anxiety symptoms have been shown to diminish quality of life.50–52

In the POAS cohort of midlife women, the likelihood of anxiety was similar to that of depression in the menopause transition, and together with irritability and mood swings, anxiety peaked early in the transition.53 Reports from SWAN similarly indicated that “psychological distress” (combination of irritability, depression, and tension) was greatest in early perimenopausal women and was highest among whites compared with other ethnicities.42 A follow-up study confirmed these associations even when the analysis was adjusted for vasomotor and sleep symptoms, factors thought to mediate the relationship between emotional symptoms and menopause.41 Additional studies have suggested that women with low anxiety levels premenopausally are more likely to report high anxiety levels in the transition, whereas those with high anxiety before menopause continue to experience these symptoms throughout the transition.54,55

There are many reports of anxiety as a risk factor for hot flushes and many conflicting findings, which are in part due to the varied manifestations of anxiety
disorders and to the similarity of the somatic symptoms of anxiety and the somatic complaints of hot flushes.\textsuperscript{12,54,56–61} A recent POAS study showed that somatic anxiety, but not affective anxiety, was a strong predictor of menopausal hot flushes.\textsuperscript{62} Therefore, somatic anxiety may be a potential target for treatments of menopausal hot flushes.

**Poor Sleep**

The prevalence of sleep problems in women increases dramatically during middle age. Among women between the ages of 45 and 49, 23.6\% report sleep difficulties, and by the early 50s, 39.7\% complain of such trouble.\textsuperscript{63} Reported problems include trouble falling asleep, disturbed sleep, and frequent awakenings. Midlife sleep difficulties are often attributed to symptoms of menopause. Poor sleep is clearly associated with hot flushes, but evidence indicating that biological decline in ovarian function has direct effects on sleep is limited and controversial.\textsuperscript{64,65}

**Sleep and Menopausal Status**

Many studies have reported an association between self-reported sleep problems and menopausal status, with more sleep problems reported in the menopause transition.\textsuperscript{66,67} Findings from SWAN indicate that perimenopausal and postmenopausal women are more likely to report “difficulty sleeping over the past 2 weeks” compared with premenopausal women,\textsuperscript{58} and that symptoms are more prevalent in late perimenopause.\textsuperscript{69} Although the POAS study also reported a high prevalence of moderate/severe poor sleep in midlife, only a small subgroup had worse sleep in relation to the FMP.\textsuperscript{70} Premenopausal poor sleep is an important predictor of poor sleep during the transition.\textsuperscript{71}

Although hot flushes appear to contribute to poor sleep during the menopause transition, physiologic studies have not found a direct link.\textsuperscript{7,68,72–74} In addition, a variety of other factors during menopause may contribute to poor sleep, including poor health, chronic illness or pain, anxiety, depression, and medications.

**Objective Sleep Measures**

Objective measures of sleep during the menopause have recently been conducted using polysomnography. Shaver and Zenk\textsuperscript{75,76} assessed 17 sleep-quality parameters with polysomnography in 3 groups of women of different menopausal status and could not demonstrate a significant difference in sleep quality. In the Wisconsin Sleep Cohort Study, which is an ongoing population-based longitudinal study of sleep disorders, a cross-sectional study examined 589 women who underwent extensive interview and overnight polysomnography. Based on self-report questionnaires, both perimenopausal and postmenopausal women were twice as likely to report that they were never or not usually satisfied with sleep compared with premenopausal women.\textsuperscript{64} Although perimenopausal women were more likely to complain of difficulty initiating sleep, polysomnographic measures of sleep quality did not differ by menopausal stage. In fact, postmenopausal women had the best sleep architecture, with less stage 1 sleep and more stage 3 to 4 sleep compared with premenopausal women. In addition, even though women with sleep-related hot flushes were more likely to report dissatisfaction with sleep, no differences in objective sleep quality were noted.\textsuperscript{64} This study challenges the hypothesis that menopause diminishes sleep quality and suggests that other factors likely explain the sleep difficulties. Therefore, sleep problems during the transition should not be attributed to hormonal changes alone, and should prompt further investigation of other sleep-related conditions.
Sleep-Disordered Breathing

A report from the Wisconsin Sleep Cohort Study demonstrated that the menopausal transition is associated with an increased likelihood of sleep-disordered breathing.\textsuperscript{77} Postmenopausal women were 3.5 times more likely to have 15 or more apnea and hypopnea events per hour compared with premenopausal women. Although disordered breathing was associated with worse sleep architecture in all women, postmenopausal women overall had better sleep architecture than premenopausal women. Evidence suggests that this disordered breathing is not related to vasomotor symptoms or estradiol levels.

The subjective nature of sleep quality makes it difficult to assess. Unfortunately, current objective measures of sleep quality from polysomnography do not necessarily reflect subjective sleep quality. Although it is clear that the prevalence of poor sleep clearly increases in the transition to menopause, only a small proportion of this problem can be attributed to menopausal status. Many other health, lifestyle, and relationship factors are associated with poor sleep, and these require careful evaluation for women who seek treatment.

Sexual Functioning

Female sexual dysfunction is extremely prevalent in the United States, affecting more than 40\% of women ages 18 to 59.\textsuperscript{78} There is substantial evidence that sexual dysfunction increases through the menopausal transition.\textsuperscript{79,80} Estimates of sexual dysfunction during the transition are as high as 88\%.\textsuperscript{81}

There is relatively little research on the sexual problems of women in relation to reproductive aging. This may in part be due to the complexity of female sexuality, which is influenced by a variety of emotional, social, and physiologic factors.\textsuperscript{79–83} It may also be due to the complexities of the menopausal transition, when other significant psychosocial and physiologic changes occur and concomitant illnesses arise.\textsuperscript{83} Studies differ dramatically with respect to patient population, research design, the assessment of female sexuality and other potential determinants of sexual function, making it difficult to come to clear conclusions regarding sexuality during the menopausal transition.

Characteristics

Several investigators have attempted to characterize the types of sexual problems affecting women during the transition. In a longitudinal study of 438 middle-aged Australian women using a validated questionnaire of sexual function, a significant overall decline in sexual functioning during the menopause transition was observed.\textsuperscript{79} This decline was particularly dramatic from early to late perimenopause. This and other studies suggest that sexual responsivity, libido, sexual frequency, and positive feelings for the partner decrease while vaginal dyspareunia increase over the transition.\textsuperscript{79,84}

The SWAN study showed that sexual function did not change until 20 months before the FMP, after which sexual function scores decreased annually and continued to decline more than 1 year after the FMP but at a slower rate.\textsuperscript{85} Vaginal dryness, depressive symptoms, or anxiety did not explain the decline in sexual function. The decline was smaller in African American than in white women.

Pathophysiology

Until recently, the decline in sexual function has largely been attributed to physical changes that occur in the genitourinary system after menopause. For instance, there is evidence that after menopause, the physiologic sexual response is altered by...
decreased skin flushing, muscle tension, Bartholin gland secretion, vaginal lubrication, clitoral reactivity, vaginal expansion and congestion, and uterine contractions with orgasm.86 Community-based studies of self-reported sexual function in postmenopausal women appear consistent with the physiologic findings. For example, menopausal women reported decreased desire, vaginal dryness, decreased clitoral sensitivity, orgasmic intensity, and orgasmic frequency.87 However, physiologic studies of sexual responsiveness during the menopausal transition are lacking, and further studies are needed to confirm or refute these self-reported findings.

Hormone links
Although some of the physiologic changes that occur with sexual functioning are related to the decline in estrogen that follows menopause, sexual changes that occur early in the transition cannot be attributed to estrogen-related genitourinary atrophy. Indeed, circulating estrogen levels do not fall to their low postmenopausal levels until after the FMP.88 Nonetheless, a longitudinal study of 438 middle-aged women indicated that decreasing scores for self-reported sexual functioning correlated with decreasing estradiol levels.81 In contrast, in the Massachusetts Women’s Health Study, estradiol levels were related only to pain, not other aspects of sexual functioning.89 In the POAS, estradiol levels were similar between women with and without a self-reported decline in libido in the early menopausal transition.82

Androgens
The relationship between androgens and sexuality during the menopausal transition remains elusive. Coincident with decreasing sexual interest, circulating androgens decline during the late reproductive years with levels of circulating androgens at age 45 approximately one-half that of women in their 20s.90 It has been presumed that the age-related decline in androgens contributes to the decline in sexual function well before menopause because androgen insufficiency has been associated with decreased sexual functioning in many domains.83 However, studies have not consistently been able to demonstrate that sexual dysfunction is related to decreased androgen levels in women during the menopausal transition.81,91 In POAS, preliminary data suggest that the variability in total testosterone levels is associated with decreased libido during the late reproductive years.82 Of 326 women, 87 (27%) reported a decreased libido, whereas 239 (73%) did not. Although hormone levels were similar between groups, women with the greatest fluctuation in total testosterone over the study were more likely to report decreased libido (odds ratio 4.0 [95% confidence interval 1.6–10.0]). Possibly the variability in testosterone, rather than absolute level, relates to sexual problems in women during this period, but further investigation is needed.

Although evidence suggests that testosterone supplementation to supraphysiologic levels may improve sexual satisfaction in menopausal women,92–95 the benefits and risks of testosterone supplementation are not clear, and further research is needed.

Other factors affecting sexual functioning
Epidemiologic studies have highlighted numerous factors affecting women’s sexuality during the menopausal transition, including health, marital status, mental health, and smoking89; depression and children living at home82; feelings for partner, and the partner’s sexual problems47; and social variables, such as paid work, interpersonal stress, daily hassles, and educational level.47

In summary, many women suffer from a decline in sexual function during the menopausal transition. Numerous factors appear to be involved in the sexual changes that occur during this time. Hormone changes may contribute to sexual problems, but...
stronger contributors are likely to be relationship issues, mental health, sociocultural influences, and medical illnesses. Current studies are limited by lack of validated measures of sexual functioning, small sample sizes, and insufficiently sensitive hormone assays. The International Consensus Development Conference on Female Sexual Dysfunctions classified sexual dysfunction into 4 major categories: desire disorders, arousal disorders, orgasmic disorders, and sexual pain disorders. Validated measures of sexual functioning that correspond with this new classification system exist and should be used to investigate specific areas of dysfunction to identify potential areas for therapeutic interventions.

SUMMARY

The transition to menopause marks a time of profound change in a woman’s life. Hormonal, physiologic, and psychosocial factors are in flux. Acute symptoms of hot flushes, sleep disruption, psychological symptoms, and decreased sexual functioning may accompany these biological and psychosocial changes. Contrary to common beliefs, these symptoms can begin early in the menopausal transition during the late reproductive years, well before menstrual irregularities occur. Importantly, studies show that these acute symptoms are multifactorial in nature, with biological changes interacting with other psychological, cultural, and socioeconomic characteristics of women. Indeed, inasmuch as women’s experience of menopause varies widely, it is obvious that the severity of menopausal symptoms cannot be attributed solely to the changing reproductive hormonal milieu that defines the transition to menopause.

It is important for clinicians to understand the complexity of acute menopausal symptoms. It is not sufficient to attribute these complaints to menopause, or to dismiss them as not related to menopause, but rather to provide treatment options for relief of the symptoms and recognize when further investigation is warranted. Most importantly, one must determine whether these symptoms are primarily associated with the menopausal transition, and are thus likely to be time-limited, or whether the symptoms are a continuum of medical or psychiatric illnesses. In addition, this is an ideal time to reevaluate a woman’s psychosocial history to determine whether she has an adequate support system to deal with life stressors. The clinician should have a wide understanding of changes that occur during the transition to maximize women’s health and well-being.

Finally, continued epidemiologic and basic research is needed to better understand the symptoms and changes of the menopause transition. Longitudinal studies with sample sizes sufficient for statistical validity, appropriate hormone measurement, and validated instruments to assess menopausal symptoms and potential confounders are essential to disentangle the complex relationships between hormones and symptoms and other factors that mediate these relationships.

REFERENCES


