

confirm the diagnosis. A distinction between the late perimenopause transition, marked by episodes of > 60 days of amenorrhea and increasing severity of VMS (15), and early postmenopause cannot be made on the sole basis of hormone measurements. With radiotherapy- or chemotherapy-induced menopause, it is important to recognize that ovarian function may resume after 12 months of amenorrhea (22), depending on the age of the woman and the dose and duration of treatment (22). For POI, persistent FSH elevation in women < age 40 provides a tentative diagnosis (Table 1).

Signs and symptoms

Vasomotor symptoms

Prevalence. Hot flashes (also called hot flushes) occur in approximately 75% of postmenopausal women in the United States (23). In the Study of Women Across the Nation (SWAN), after controlling for age, education, health, and economic strain, researchers found that US Caucasian women report more psychosomatic symptoms, African American and Hispanic women report more VMS, and Asian women report more somatic complaints (16, 24). Notably, across countries and ethnic backgrounds, the percentage of women reporting hot flashes varies (25–27). In a cross-sectional study of premenopausal women (mean age, 48 y), one-third reported “ever” experiencing hot flashes (28). A comparison between VMS experienced during the premenopause vs the postmenopause may be informative when counseling a postmenopausal woman regarding symptom relief, although to our knowledge, the presence and frequency of premenopausal hot flashes have not been studied as being predictive of response to therapy in the postmenopause. Persistence of hot flashes may also vary depending upon when in the menopausal transition VMS were first noted. In SWAN, earlier onset of VMS was associated with longer postmenopausal duration (16).

Clinical manifestations. Hot flashes typically begin as the sudden sensation of heat centered on the upper chest and face. When moderate or severe, the hot flash rapidly becomes generalized, lasts from 2 to 4 minutes, and can be associated with profuse perspiration, palpitations, or anxiety. Triggers include spicy food or alcohol. At night, vasomotor instability manifests as hot flashes or night sweats, which may represent different physiological mechanisms. The differential diagnosis includes several entities distinguishable by clinical features (Table 2). New-onset VMS in older (age, $\geq$ 65 y) postmenopausal women may be associated with, but not necessarily causally related to, increased risk of major CHD and all-cause mortality (29).

Table 2. Conditions That May Cause or Mimic Vasomotor Events and That Can Be Distinguished From Menopausal Symptoms by History, Examination, and Investigations, as Indicated

Hormone excess
Thyroid hormone excess
Carcinoid syndrome (flushing without sweating)
Pheochromocytoma (hypertension, flushing, and profuse sweating)
Dietary factors
Alcohol
Spicy food
Food additives (eg, monosodium glutamate, sulfites)
Pharmaceuticals
Chronic opioid use
Opiate withdrawal
SSRIs (may cause sweats)
Nicotinic acid (intense warmth, itching lasting up to 30 min)
Calcium channel blockers
Medications that block estrogen action or biosynthesis
Chronic infection (increased body temperature)
Other medical conditions
Postgastric surgery dumping syndrome
Mastocytosis and mast cell disorders (usually with gastrointestinal symptoms)
Some cancers: medullary carcinoma of the thyroid, pancreatic islet-cell tumors, renal cell carcinoma, lymphoma
Anxiety disorders

Association with sleep. In polysomnography studies, nocturnal hot flashes are more common during the first 4 hours of sleep, whereas subsequent rapid eye movement sleep suppresses hot flashes, arousals, and awakenings (30). A recent study that induced estrogen deficiency in healthy premenopausal women with a GnRH agonist directly demonstrated that hot flashes are associated with three factors: 1) an increase in episodes of waking after sleep-onset; 2) a decrease in perceived sleep efficiency; and 3) a statistically significant correlation between nocturnal VMS and sleep disruption (31). Although these data are informative, it has not been substantiated whether they apply in naturally postmenopausal women with continuously high gonadotropins. An important contributing factor is aging, which likely is also involved in sleep disturbances in menopausal women.

Mechanisms. VMS appear to involve the central nervous system (32) because: 1) hot flashes occur simultaneously with, but are not caused by, LH pulses (33, 34); and 2) research has shown an association with the neuroregulators kisspeptin, neurokinin B, and dynorphin (35). Alterations of thermoregulatory systems are mechanistically involved because women with hot flashes exhibit a narrowing of the thermoregulatory-neutral zone (32). Whereas premenopausal women initiate mechanisms to dissipate heat when the core body temperature increases