

The Menopause and Vasomotor Symptoms Manual



Table of Contents

Introduction i

1: Overview of Reproductive Aging: Focus on Menopause..... 1

2: Focus on Vasomotor Symptoms 13

Glossary 26

Acronyms 28

References 29

Introduction



This internal training is for the VEOZA™ TEAM. The objective of this training is to provide an overview of vasomotor symptoms (VMS), the most common symptoms of menopause. This training provides background information on women's health as it relates to VMS due to menopause. This training is not for external distribution or promotional use.

Menopause is a normal part of natural reproductive aging in women, and it represents the end of female reproductive function.^{1,2}

To provide a context for menopause, this module will begin by describing the stages of reproductive aging and where menopause fits in. The first part of the module will cover the phases of menopause, the changes in hormone levels that occur during menopause transition, and the signs and symptoms that women may experience.

The rest of the module will focus on vasomotor symptoms (VMS), which are the most common symptoms of menopause.³ This part of the module will discuss the definition, burden, and causes of vasomotor symptoms.

1: Overview of Reproductive Aging: Focus on Menopause



Introduction

Menopause is the end of female reproductive function, and it is a normal event that occurs during natural reproductive aging in women.^{1,2} This section will describe the stages of reproductive aging, including menopause and its phases. The changes in hormone levels that occur during menopause transition and the accompanying signs and symptoms that women may experience during menopause will be described.

Learning Objectives

By the end of this section, you should be able to:

- State the stages of reproductive aging
- Describe the prevalence of women experiencing menopause
- Explain the role of estrogens and other hormones in the onset of menopause
- Describe the signs and symptoms of menopause and the impact they may have on women

1.1: Transition to Menopause

Menopause is a normal physiological event that is experienced by women (and people assigned female at birth who currently identify as transgender or nonbinary).¹ Menopause is defined as the permanent end of menstruation, and a woman is diagnosed as having entered menopause after she has not had a menstrual cycle for 12 consecutive months.^{1,3} In a pooled analysis of over 200,000 postmenopausal women from 17 studies in 7 countries (including Australia, Denmark, France, Japan, Sweden, the United Kingdom, and the United States), the average age at natural menopause was 50.2, plus or minus 4.4 years.⁴ Some women with premature ovarian insufficiency (POI) may experience symptoms of menopause prior to the age of 40.² In approximately 3% of the

population, early menopause in women ages 40 to 45 can occur naturally, but most commonly it is due to surgical intervention.²

The number of women aged 50 years and older has been increasing over the years and is expected to grow significantly in the future:

- in 1990, 471 million women were ≥50 years of age worldwide²
- in 2015, 861 million women were ≥50 years of age, corresponding to an 82.6% increase and a 2.4% average increase per year²

The American Society for Reproductive Medicine established a reproductive aging classification system, Stages of Reproductive Aging Workshop (STRAW), in 2001 with an update in 2010 (STRAW + 10).¹ STRAW + 10 provides a comprehensive basis for assessing reproductive aging in research contexts.⁵ Application of the STRAW + 10 improves comparability of studies in midlife women.⁵ The STRAW + 10 system broadly divides the female life span into 3 phases¹:

- reproductive phase (which starts at stage -5 following menarche)¹
- menopausal transition phase (which ends at stage 0, which is the final menstrual period [FMP])¹
- postmenopausal phase¹

Each phase is divided into stages, which are defined based on menstrual cycle pattern, menopause-related symptoms, hormone levels, and **antral follicle count**, as shown in the figure below.²

Figure 1.1: STRAW + 10 Staging System for Reproductive Aging⁵

Menarche					FMP (0)					
Stage	-5	-4	-3b	-3a	-2	-1	+1a	+1b	+1c	+2
Terminology	REPRODUCTIVE				MENOPAUSE TRANSITION		POSTMENOPAUSE			
	Early	Peak	Late		Early	Late	Early		Late	
					Perimenopause					
Duration	Variable				Variable	1 to 3 years	2 (1+1) years	3 to 6 years	Remaining lifespan	
PRINCIPAL CRITERIA										
Menstrual cycle	Variable to regular	Regular	Regular	Subtle changes in flow/length	Variable length Persistent ≥7-day difference in length of consecutive cycles	Interval of amenorrhea of ≥60 days				
SUPPORTIVE CRITERIA										
Endocrine										
FSH			Low	Variable ^a	Elevated variable ^a	Elevated >25 IU/L ^b	Elevated variable ^a	Stabilizes		
AMH			Low	Low	Low	Low	Low	Very low		
Inhibin B				Low	Low	Low	Low	Very low		
Antral follicle count			Low	Low	Low	Low	Very low	Very low		
DESCRIPTIVE CHARACTERISTICS										
Symptoms						Vasomotor symptoms likely	Vasomotor symptoms most likely		Increasing symptoms of urogenital atrophy	

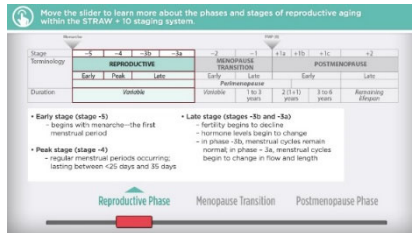
AMH = antimüllerian hormone; FMP = final menstrual period; FSH = follicle-stimulating hormone.

^a Blood draw on cycle days 2 to 5.

^b Approximate expected level based on assays using current international pituitary standard.

STRAW + 10 Staging System^{1,2}

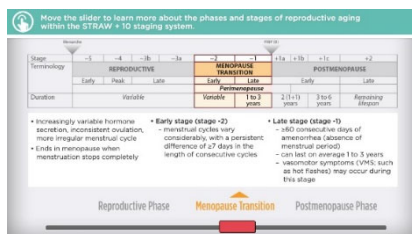
Reproductive Phase²



- Early stage (stage -5)
 - begins with menarche—the first menstrual period²
- Peak stage (stage -4)²
 - regular menstrual periods occurring; lasting between 21 and 35 days²
- Late stage (stages -3b and -3a)

- fertility begins to decline²
- hormone levels begin to change²
- in phase -3b, menstrual cycles remain regular; in phase -3a, menstrual cycles begin to change in flow and length²

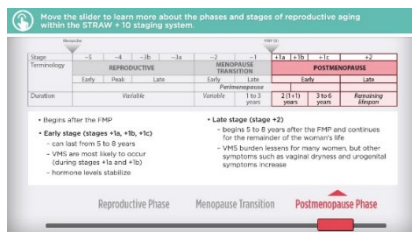
Menopause Transition²



- Increasingly variable hormone secretion, inconsistent ovulation, more irregular menstrual cycle²
- Ends in menopause when menstruation stops completely²
- Early stage (stage -2)
 - menstrual cycles vary considerably, with a persistent difference of ≥7 days in the length of consecutive cycles²

- Late stage (stage -1)
 - ≥60 consecutive days of amenorrhea (absence of menstrual period)²
 - can last on average 1 to 3 years²
- VMS; such as hot flashes may occur during this stage¹

Postmenopausal Phase²



- Begins after the FMP²
- Early stage (stages +1a, +1b, +1c)
 - can last from 5 to 8 years²
 - VMS are most likely to occur (during stages +1a and +1b)²
 - hormone levels stabilize²

- Late stage (stage +2)
 - begins 5 to 8 years after the FMP and continues for the remainder of the woman's life²
 - VMS burden lessens for many women, but other symptoms such as vaginal dryness and urogenital symptoms increase¹

Other key terms that are often used to characterize menopause are defined in the table below.

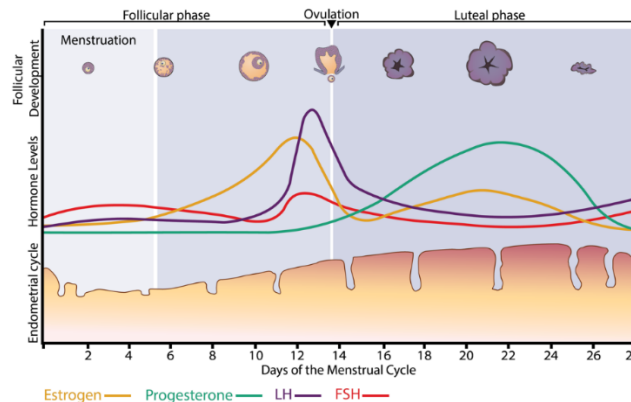
Menopause Terminology ²	
Term	Definition
Climacteric	The period of endocrinologic, somatic , and transitory psychologic changes that occur at the time of menopause; sometimes used interchangeably with “perimenopause”
Early and late menopause	Menopause that occurs earlier or later within the normal range of ages at the FMP: early if FMP occurs before age 45, late if it occurs after age 54
Early and late postmenopause	According to the STRAW + 10 system, postmenopausal women are considered to be in early postmenopause if they are within 8 years of their FMP; otherwise, they are considered to be in late postmenopause
Induced menopause	The end of menstruation after either surgical removal of both ovaries or ablation of ovarian function (e.g., due to chemotherapy)
Menopause transition	According to the STRAW + 10 system, menopause transition is the time before FMP when the menstrual cycle becomes variable or other symptoms related to menopause begin
Natural menopause	Permanent end of menstruation because of loss of ovarian follicular activity; determined retrospectively after 12 consecutive months of amenorrhea after FMP
Premenopause	The stage of life that precedes menopause
Perimenopause	Means “around menopause”; corresponds to STRAW + 10 stages -2, -1, and +1a, thus lasting 1 year longer than menopause transition; encompasses highly symptomatic years
Postmenopause	The stage of life after menopause

1.2: Hormonal Involvement in Menopause

During the reproductive years, a woman’s menstrual cycle involves an interaction of several hormones whose levels change throughout the cycle.² The cycle begins with menstruation, and in the beginning of the cycle (the follicular phase) levels of **follicle-stimulating hormone (FSH)** rise slightly to stimulate the development of several follicles in the ovaries.² As the cycle progresses, the dominant follicle is selected and levels of estradiol (a type of estrogen hormone; produced by the dominant follicle) rise until a peak in the middle of the cycle.² The peak in estradiol triggers a surge of FSH and **luteinizing hormone (LH)** in the middle of the cycle.² The surge in LH stimulates ovulation (egg release), after which (during the luteal phase) levels of FSH and LH drop and remain low for the remainder of the cycle, while progesterone levels rise dramatically.² During the second half of the cycle (luteal phase), the levels of estrogen and progesterone remain high to

thicken the lining of the uterus in preparation for possible pregnancy, and levels of both hormones drop toward the end of the cycle if pregnancy does not occur.²

The Menstrual Cycle²



The cycle begins with menstruation.² As the cycle progresses, levels of estrogen rise, followed by a rise in LH, FSH, and a slight increase in progesterone, until ovulation.² During this follicular phase, the dominant follicle is selected and it matures until its release at ovulation.² After ovulation, during the luteal phase, the levels of LH and drop and remain low for the rest of the cycle, while estrogen and progesterone levels rise to thicken the lining of the uterus in preparation for possible pregnancy.² At the end of the of the cycle, progesterone and estrogen levels drop if pregnancy does not occur.²

As a woman transitions into menopause, the levels and interplay of the hormones involved in the menstrual cycle change.²

- In early menopause (STRAW + 10 stage -2), the ovaries gradually stop producing 2 **glycoproteins**—antimüllerian hormone (AMH) and inhibin-B—both of which limit follicular growth each month in order to prevent ovulating all of the follicles over a few menstrual cycles.^{2,3}
- With a reduction and eventual loss of inhibin-B, secretion of FSH from the **pituitary gland** increases.^{2,3}
- The increase in FSH and the loss of AMH make more follicles available for ovulation and maintain cycle regularity; however, this accelerates follicle loss.²

The elevated levels of FSH increase the rate of follicular maturation, thus shortening the follicular phase and speeding up the cycles; however, cycle length may vary significantly and cycles may become irregular.³ Cycles may become irregular by 7 or more days, or menstruation may be absent for 60 days or longer.² Due to a shorter follicular phase, a woman may spend more time in the luteal phase of the cycle, which may lead her to experience more premenstrual symptoms.² Furthermore, more and more cycles become **anovulatory** (in which ovulation does not occur) during this transition period.³

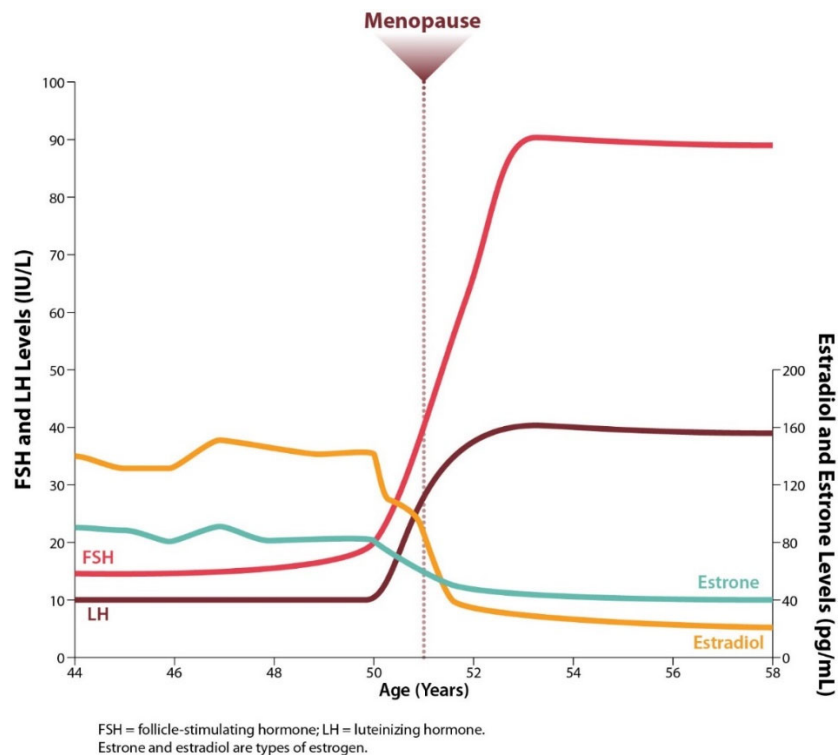
In the early menopause transition stage, levels of estradiol fluctuate.² In fact, overall estrogen level is often elevated at this stage due to higher FSH levels and thus greater number of growing follicles, which produce estrogen.¹ However, in the late transition period (STRAW + 10 stage -1):

- follicular count reaches critically low level²
- amenorrhea of 60 days or longer becomes more common²
- serum FSH level increases to 25 IU/L or higher²
- estradiol and progesterone production decreases and eventually essentially stops²

Although in the first years after FMP estrogen production may still vary, progesterone is not produced and thus menstruation does not occur.² The drop in estradiol level during menopause is steep in the first year of postmenopause, followed by a more gradual decline.¹ In postmenopause, the dominant circulating type of estrogen is estrone.³

The changes in hormone levels described above that occur during transition into menopause are summarized in the figure below.

Figure 1.2: Hormone Changes During Menopause Transition¹



1.3: Signs, Symptoms, and Consequences of Menopause

Up to 85% of women experience various symptoms associated with menopause during menopausal transition; this is the result of changes in circulating hormones, particularly a decline in estrogen levels.³ The duration of symptoms may vary from less than a year to several years.³

VMS

Many women experience VMS, also known as hot flashes, at some point during the menopause transition.⁶ Hot flashes are sudden and intense feelings of heat in the chest and face that sometimes spread to other parts of the body, and may also involve profuse sweating.³ Hot flashes may be a minor annoyance or a major problem that significantly impacts the quality of life.³

VMS will be discussed in greater detail in the next section of this module.

Besides VMS, other signs, symptoms, and consequences of menopause include:

- menstrual cycle/bleeding changes¹
- urogenital symptoms (e.g., vaginal atrophy, incontinence)¹

Many menopausal women experience sleep disturbances and changes in their mood.⁷ These symptoms may have multiple underlying causes, including VMS.⁶ Many other symptoms are reported by menopausal women, such as joint and muscle aches, changes in body shape (including abdominal weight gain), changes in sexual function, increased wrinkling of the skin, deepening of the voice, and growth of hair on chin and upper lip.^{3,7} However, it is difficult to establish a definitive relationship between menopause and some of these symptoms.⁷

The symptoms of menopause are described in more detail below.

Irregular Menstrual Cycle

During menopause transition, women increasingly experience anovulatory uterine bleeding.¹ It is estimated that even early in the menopause transition, about 20% of cycles are anovulatory.¹ In the beginning of the transition, the cycles tend to shorten, while later in the transition period they become longer.¹ In the late phase of menopause transition, intervals of amenorrhea of ≥ 60 days become common until the occurrence of the FMP.²

Urogenital Symptoms

The low levels of estrogen in women in postmenopause can make urogenital tissues fragile as these tissues are very sensitive to estrogen.⁷ Many women experience vaginal dryness, inflammation of the urethra, urinary tract infections, and incontinence.^{1,7} Vaginal atrophy, narrowing and shortening of the vagina, and uterine prolapse may occur; together, these factors lead to high rates of **dyspareunia** (painful intercourse).⁷ Even in the absence of intercourse, vaginal atrophy may cause itching, irritation, and burning.¹ Without treatment, vulvovaginal atrophy will not improve over time.⁷

Sleep Disturbances

While the quality of sleep generally worsens with aging, women entering the menopausal transition report having more trouble sleeping.⁷ Sleep quality can be compromised by the hormonal changes that are associated with the menopausal transition, and sleep disturbances may become more common over time; as such, more than 50% of postmenopausal women experience sleep difficulties.⁷

Psychological Symptoms

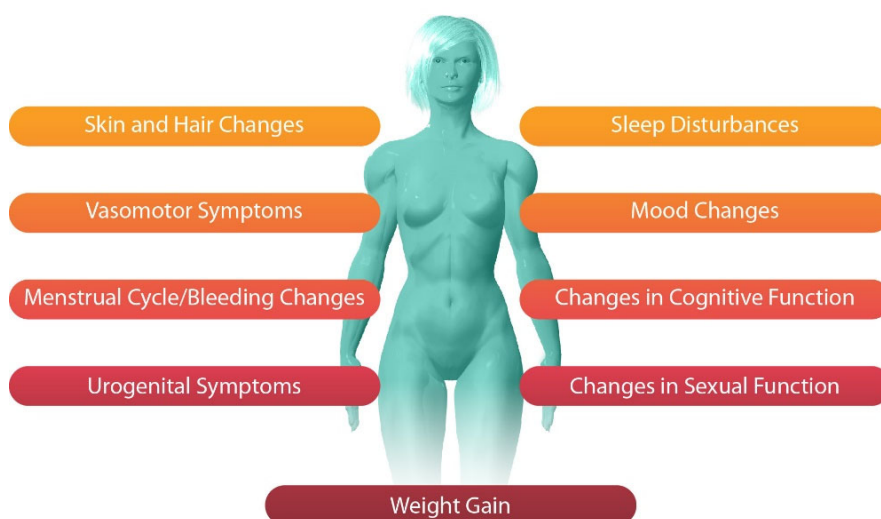
Women are up to 70% more likely to develop depression than men; the risk of depressed mood increases during the menopause transition and perimenopause compared with premenopause.^{7,8} Hormonal changes during menopause likely play a role as the following factors increase the risk for depression⁷:

- variability in estradiol levels⁷
- increasing FSH levels⁷
- surgical menopause⁷
- presence of hot flashes⁷
- history of premenstrual syndrome⁷

In addition to depression, many women report changes in cognitive function, such as worsening of memory, during menopause transition.⁷ Estrogen plays a significant role in cognitive functioning, and dementia is more common in women than in men.⁷ However, patients and their clinicians can be reassured that for most women, cognitive function is not likely to worsen in postmenopause in any pattern other than that expected with normal aging.⁷

The signs, symptoms, and consequences of menopause are summarized in the following figure.

Figure 1.3: Signs, Symptoms, and Consequences of Menopause^{1,3,7}



Knowledge Checks

- 1.1 In a pooled analysis of over 200,000 postmenopausal women from 17 studies in 7 countries, the average age at natural menopause was.⁴
- A 45.3 years
 - B 48.6 years
 - C 50.2 years
 - D 55.8 years
- 1.2 **True or False?** In postmenopause, the dominant circulating type of estrogen is estrone.³
- A True
 - B False
- 1.3 Which of the following are symptoms of menopause?^{1,6,7} (Select all that apply.)
- A Hot flashes
 - B Menstrual cycle changes
 - C Vaginal dryness
 - D Sleep disturbances

Answers

- 1.1 C (Section 1.1)
- 1.2 A (Section 1.2)
- 1.3 A, B, C, D (Section 1.3)

2: Focus on Vasomotor Symptoms



Introduction

VMS are the most commonly reported symptoms by women transitioning through menopause.^{3,6} VMS can significantly impact many aspects of a woman's life, from interpersonal relationships to professional achievements.⁹ This section will define and describe the proposed causes of VMS and discuss the burden of VMS.

Learning Objectives

By the end of this section, you should be able to:

- Define VMS
- Discuss the burden of VMS, including epidemiology, risk factors, associated physiological changes, and impact on daily functioning
- Describe the causes of VMS

2.1: Defining VMS

As mentioned in the previous section, VMS (hot flashes) are the most commonly reported symptoms of menopause.^{3,6} Hot flashes are sudden and intense feelings of heat in the upper body, especially the chest, neck, and face, with reddening of the skin.⁶ Hot flashes may occur together with other symptoms, such as sweating (which can be profuse), chills, anxiety, and sometimes even heart palpitations.^{1,6} Hot flashes may occur rarely or they may recur as frequently as every few minutes.¹ The duration of each hot flash episode varies, and typically lasts from seconds to minutes, and, rarely, can last for up to an hour.⁶ Hot flashes can occur during the day or at night; hot flashes during sleep are commonly referred to as night sweats.^{1,6}

Hot flashes are sometimes broken into 3 severity categories as described in the table below.⁶

Categories of Hot Flash Severity ⁶		
Mild	Moderate	Severe
Sensation of heat without sweating	Sensation of heat with sweating; able to continue activity	Sensation of heat with sweating; causes stopping of activity

2.2: Epidemiology of VMS

In a survey of over 2000 postmenopausal women from France, Germany, Italy, Spain, and the United Kingdom (UK) published by Nappi et al in 2023, the proportion of those experiencing hot flashes and night sweats in the previous 12 months ranged from 54% to 69%.¹⁰ The prevalence of moderate-to-severe VMS ranged from 31% to 52%.¹⁰ The proportion of women from this group who contacted a healthcare professional in the previous 12 month to discuss hot flashes/night sweats varied by country, from 27% in the UK to 64% in Italy.¹⁰

In a 2005 survey done by the European Menopause Society, 74% of the 4201 women surveyed reported experiencing hot flashes.¹¹ The prevalence ranged from 67% in Germany to 82% in the UK and Belgium.¹¹

In a survey of peri- and postmenopausal women in East Asia published by Yu et al in 2022, the prevalence of VMS associated with menopause was ~80% in each geographical location.¹² Overall, the prevalence of moderate-to-severe VMS was 55%, which included 49% who had moderate VMS and 7% who had severe VMS.¹² Furthermore, 25% of women had mild VMS.¹² More women in the Beijing sample visited hospitals or clinics to seek care for VMS compared with women in the Seoul and Taipei samples, but undertreatment was a common issue, with >50% of all women with moderate-to severe VMS remaining untreated across the 3 geographical locations.¹²

Hot flashes are the primary menopause-related reason for which women seek medical care.⁹ The median duration of VMS is 7.4 years.¹³

The predicted estimate for the number of women who will be experiencing menopause-related VMS by the year 2025 is shown below.

Value	Text
1,100,000,000	Estimated number of women around the world who will be experiencing menopause-related VMS by the year 2025 ⁶

In order to assess how menopause and the menopause transition may affect health and outcomes, the Study of Women's Health Across the Nation (SWAN) began in the United States in 1994.¹⁴ SWAN explores the physical, biological, psychological, and social changes that occur during the menopausal transition.¹⁴ The goal of SWAN is to help scientists, healthcare providers, and women learn how midlife experiences affect health and quality of life during aging.¹⁴ SWAN researchers have published over 500 manuscripts covering a wide range of topics related to menopause and women's health.¹⁵

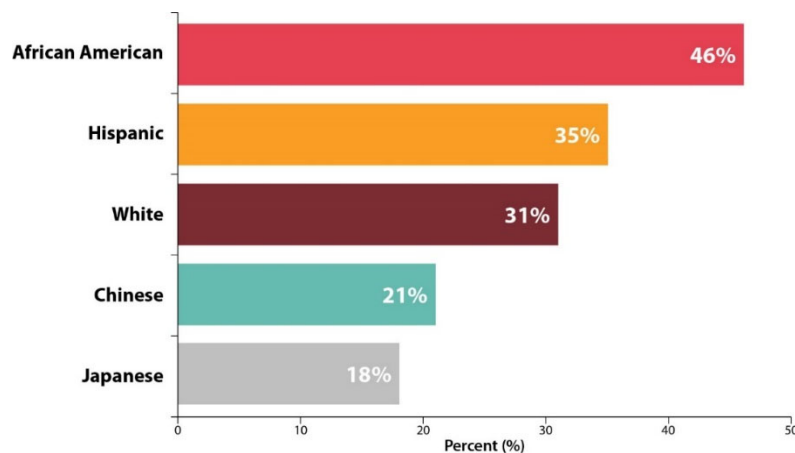
In one of the SWAN publications, the longest total duration of VMS was experienced by women who first reported frequent VMS during premenopausal or early perimenopausal stages (median >11.8 years).¹³ The shortest total VMS duration was reported by women with the onset of VMS in the postmenopausal stage (median 3.4 years).¹³ The median total VMS duration was 7.4 years, and the median VMS duration after FMP was 4.5 years.¹³

In the Penn Ovarian Aging Study, a cohort of 436 women, aged 35 to 47 years at enrollment, were monitored for 13 years (1995 to 2009).¹⁶ The overall median duration of moderate-to-severe hot flashes was 10.2 years.¹⁶ The median duration of moderate-to-severe hot flashes was more than 11.25 years when the onset was in the premenopausal or late premenopausal stage, compared with 3.84 years when the onset was in the late transition or postmenopausal stage.¹⁶

The prevalence of VMS also changes throughout the menopause transition.⁶ About 20% to 40% of premenopausal women report VMS, increasing to 60% to 80% of women in perimenopause and through to postmenopause, with variations throughout racial groups.⁶ For example, in the Yu 2022 study, perimenopausal women had a higher prevalence of VMS (94.5%) versus postmenopausal women (78.1%) in the Beijing sample, while in the Seoul sample, perimenopausal women had a lower prevalence of VMS (69.0%) versus postmenopausal women (78.5%).¹²

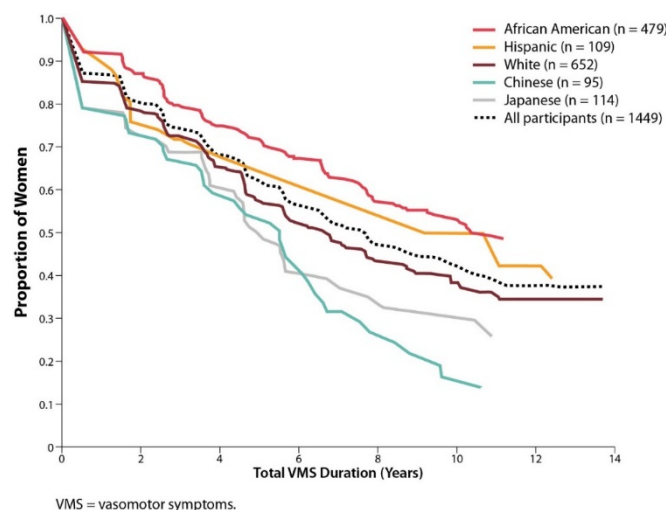
The prevalence of VMS varies by racial/ethnic group.⁶ In the initial SWAN survey of 16,065 women aged 40 to 55 years in the United States, VMS were more commonly reported by African-American and Hispanic women.¹⁷ In contrast, Japanese women were the least likely to report symptoms of VMS.¹⁷ The racial/ethnic differences in VMS prevalence persisted even when accounting for key covariates such as body weight and smoking (see figure below).¹⁷

Figure 2.1: Prevalence of VMS Among Different Racial/Ethnic Groups in the United States (1995 to 1997)¹⁷



The duration of VMS varied by race/ethnicity in the SWAN study as well.¹³ The median total VMS duration was longest in African-American women (10.1 years) and shortest in Japanese (4.8 years) and Chinese (5.4 years) women.¹³ Median total VMS duration was 6.5 years for non-Hispanic white women and 8.9 years for Hispanic women. The variation in total VMS duration by race/ethnicity in the SWAN study is illustrated in the figure below.¹³

Figure 2.2: Total VMS Duration by Race/Ethnicity in the SWAN Study in the United States¹³



In the Penn Ovarian Aging Study, African American women also reported a longer duration of hot flashes than white women.¹⁶ The physiological reasons behind the racial/ethnic differences in VMS duration are unknown at this time.¹⁶

In addition to race/ethnicity and menopausal stage at onset, various other risk factors impact the frequency, severity, or duration of VMS.⁶ These risk factors are discussed below.

Socioeconomic factors, such as lower educational attainment, lower socioeconomic position, lower income, and having difficulty paying for basics were found to be risk factors for VMS.^{6,17}

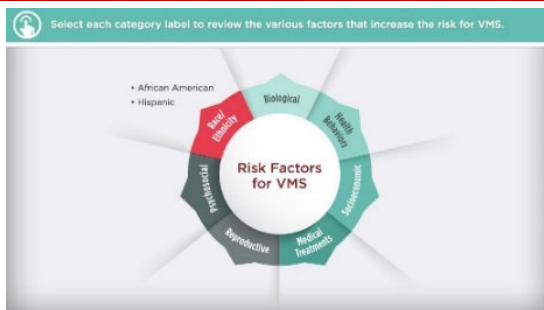
Obesity/greater body mass index (BMI) was once thought to be protective against VMS as adipose (fat) tissue produces estrone (a type of estrogen).⁶ However, the relationship between obesity and VMS appears to be complex.^{13,16} In a SWAN substudy, greater BMI correlated with higher prevalence of VMS and longer VMS duration.^{6,13} In the Penn Ovarian Aging Study, obese women had a shorter duration of moderate-to-severe hot flashes than nonobese women.¹⁶ Moreover, the relationship between greater BMI and VMS appears to vary with age. Higher adiposity in women who are younger or early in the menopause transition is associated with increased VMS, while higher adiposity in women who are older or further along into their post menopause years is associated with decreased VMS.⁶ The different effect of obesity on VMS with age may be due to the fact that in the earlier phases of menopausal transition, higher BMI provides greater heat insulation and predisposes women to increased VMS occurrence, while in postmenopause, the fat tissue acts as a source of estrone (estrogen), thus decreasing the incidence of VMS.¹⁸

Among modifiable health behaviors, cigarette smoking has consistently been shown to be associated with VMS.⁶ The association between VMS and alcohol consumption is mixed.^{6,13} High-fat and high-sugar diets were associated with increased risk of VMS, while Mediterranean-style diets or diets high in fruit intake were associated with a lower risk of VMS.⁶ Physical activity has not been shown to be linked to VMS.^{6,13}

Psychosocial factors that have been shown to be associated with an increased risk of VMS include depressive symptoms, anxiety, perceived stress, and symptom sensitivity.¹⁹ Medical treatments, such as hysterectomy (surgical removal of the uterus) or bilateral oophorectomy (surgical removal of both ovaries) leads to an increased risk of more frequent and severe VMS due to the sudden drop in estrogen.^{2,6} Premenstrual symptoms are also a risk factor for VMS in certain ethnic groups.¹⁹

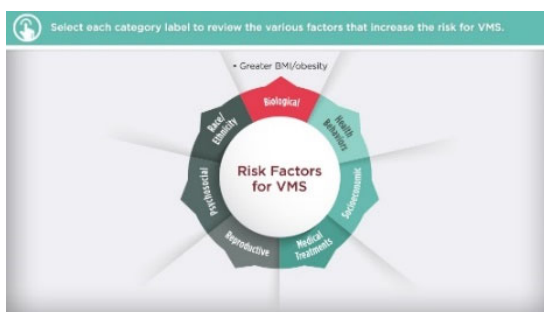
Risk Factors for VMS^{6,13,17,19}

Race/Ethnicity



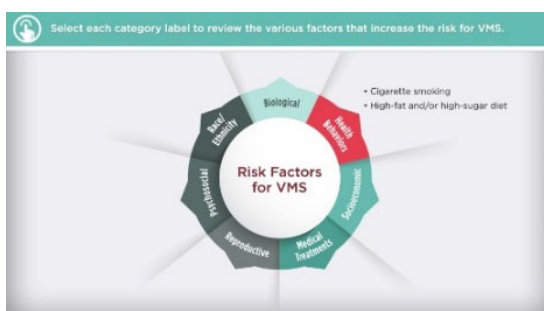
- African American¹⁷
- Hispanic¹⁷
- (Data from the United States)

Biological



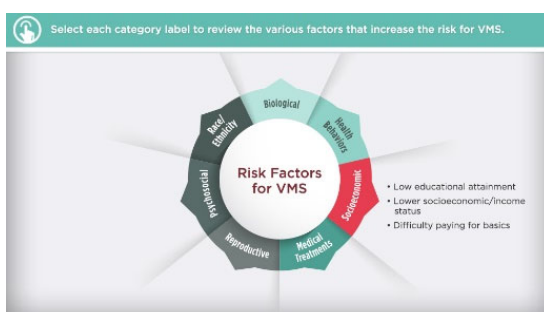
- Greater BMI/obesity^{6,13}

Health Behaviors



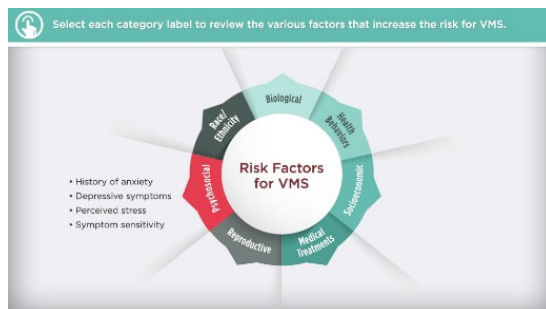
- Cigarette smoking⁶
- High-fat and/or high-sugar diet⁶

Socioeconomic



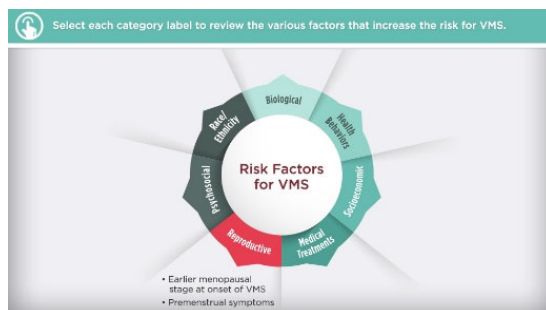
- Low educational attainment⁶
- Lower socioeconomic/income status⁶
- Difficulty paying for basics⁶

Psychosocial



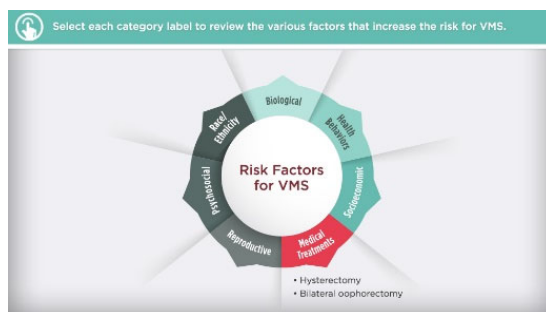
- History of anxiety¹⁹
- Depressive symptoms¹⁹
- Perceived stress¹⁹
- Symptom sensitivity¹⁹

Reproductive



- Earlier menopausal stage at onset of VMS¹³
- Premenstrual symptoms¹⁹

Medical Treatments



- Hysterectomy⁶
- Bilateral oophorectomy⁶

VMS have a significant impact on women's quality-of-life outcomes, including sleep, mood, and cognitive function.⁶ VMS are associated with sleep disturbances that contribute to poor sleep quality and continuity, including falling asleep, staying asleep, and early morning awakening.⁶ Frequent and severe VMS are associated with depressed mood, which can be a consequence of sleep deprivation.⁶ Sleep deprivation and the unpredictable nature of hot flashes may also contribute to the development of anxiety and stress.⁹

In addition to affecting mental and physical health, VMS can exert a significant impact on the overall quality of life for many women.⁹ For example, experiencing hot flashes and sweating in a social or professional setting may lead to extreme anxiety and social isolation.⁹ The lack of sleep (related to night sweats), fatigue, and irritability may also impact familial and social relationships.⁹ VMS may also lead to feelings of embarrassment.⁹

There is a growing body of evidence demonstrating that VMS can be a biomarker for poor future outcomes, including cardiovascular disease and osteoporosis.²⁰

Severe hot flashes and late-occurring VMS have been shown to be linked with accelerated epigenetic aging, indicating biological aging beyond chronological age.²¹

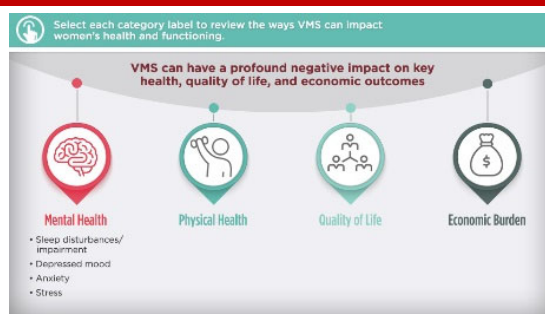
Economic Burden

VMS can have economic impacts as well: the disruption of sleep due to VMS can lead to impaired alertness and decreased work productivity.⁹ Women also utilize the healthcare system for menopause symptoms, leading to high economic burden for the women and for the healthcare system.⁹ The increased economic burden due to healthcare system utilization includes:

- physician visits⁹
- prescription and over-the-counter medication⁹
- laboratory fees⁹
- follow-up visits/phone calls for medication side effects⁹
- visits to medical specialists and alternative medicine practitioners⁹

VMS Impact on Women's Health and Functioning^{6,9,21,22}

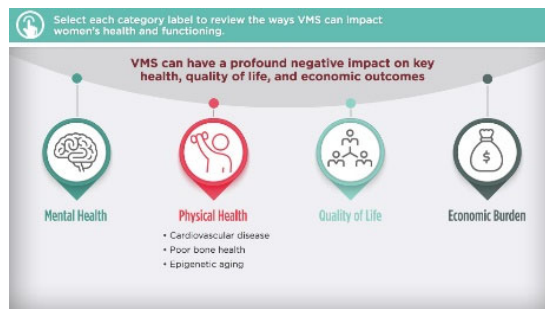
Mental Health



VMS can have a profound negative impact on key health, quality of life, and economic outcomes

- Sleep disturbances/impairment⁶
- Depressed mood⁶
- Anxiety⁹
- Stress⁹

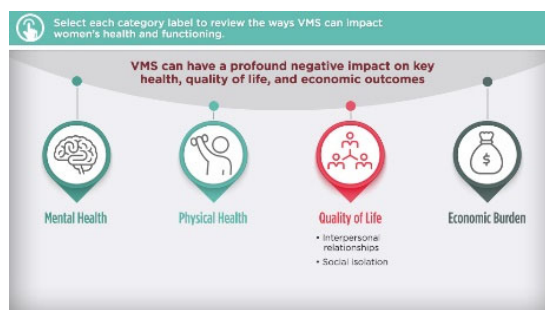
Physical Health



VMS can have a profound negative impact on key health, quality of life, and economic outcomes

- Cardiovascular disease⁶
- Poor bone health⁶
- Epigenetic aging²¹

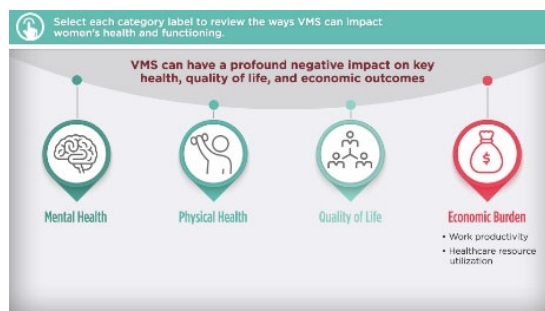
Quality of Life



VMS can have a profound negative impact on key health, quality of life, and economic outcomes

- Interpersonal relationships⁹
- Social isolation⁹

Economic Burden



VMS can have a profound negative impact on key health, quality of life, and economic outcomes

- Work productivity⁹
- Healthcare resource utilization²²

2.3: Potential Mechanisms of VMS

The physiological mechanisms behind VMS likely involve multiple processes that interact with each other.⁶ These potential mechanisms are described below.

Ovarian Estrogen

Decline in ovarian estrogen (estradiol) seems to play a role in VMS.⁶ The degree of change in estradiol levels may play a role, as a more pronounced change over time is associated with more severe VMS.⁶ However, estrogen levels alone do not appear to explain VMS, and other mechanisms likely.⁶

Thermoneutral Zone

The **thermoneutral zone** is defined as a range of temperatures within which normal core body temperature is maintained. In the thermoregulatory model of VMS, the thermoneutral zone is narrowed, and small changes in body temperature can trigger heat-dissipation, like sweating and **vasodilation**, resulting in hot flashes.^{6,23} These thermoregulatory responses are controlled by the part of the brain called the **hypothalamus**.⁶

Within the Hypothalamus

The hypothalamus can use **neurotransmitters** (such as serotonin and norepinephrine) to send a signal that triggers vasodilation or **vasoconstriction** within blood vessels in the skin.⁶ Serotonin and norepinephrine play a role in mood, anxiety, sleep, and sexual behavior, and are thought to be involved in thermoregulation.⁶

Kisspeptin-Neurokinin B-Dynorphin

It is known that in menopause, the secretion of the gonadotropin-releasing hormone (GnRH) in the hypothalamus is increased, and GnRH in turn increases the concentrations of FSH and LH.^{1,6} GnRH secretion is regulated by neurokinin B (NKB), a **neuropeptide** (small protein produced by

neurons) found in the hypothalamus.⁶ The neuropeptides NKB and kisspeptin, along with dynorphin (an opioid peptide), are coexpressed in cells of the hypothalamus as kisspeptin-neurokinin B-dynorphin (KNDy) neurons.⁶ The KNDy neurons are involved in the negative feedback of GnRH release in the hypothalamic-pituitary-gonadal (HPG) axis.²⁴ Since KNDy neurons project to the site within the hypothalamus that is involved in thermoregulation (known as the median preoptic nucleus [MnPO]), evidence suggests that KNDy neurons are involved in the hormonal control of heat-defense mechanisms and contribute to the mechanism of VMS.⁶

KNDy neurons in the hypothalamus are stimulated by NKB (acting at the NK₃ receptor [NK₃R]) and inhibited by estrogen.^{6,24} With declining estrogen levels in menopause, NK₃R-mediated activation is unopposed and leads to hypertrophy of KNDy neurons and altered activity on the thermoregulatory center.⁶ The thermoregulatory center triggers heat-dissipating effectors (vasodilation and sweating).^{6,24}

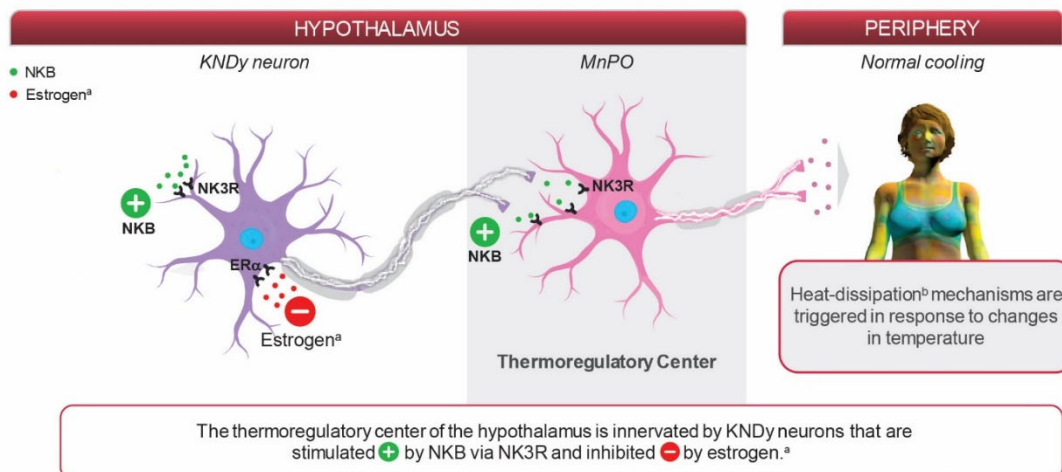
Making the Connection

The role of KNDy neurons in VMS will be described in detail in the *Neurokinin B and VMS eTutorial*.

The interplay of hormones and neuropeptides described above is illustrated in the following figure.

Figure 2.3: KNDy Neuron Signaling^{6,24}

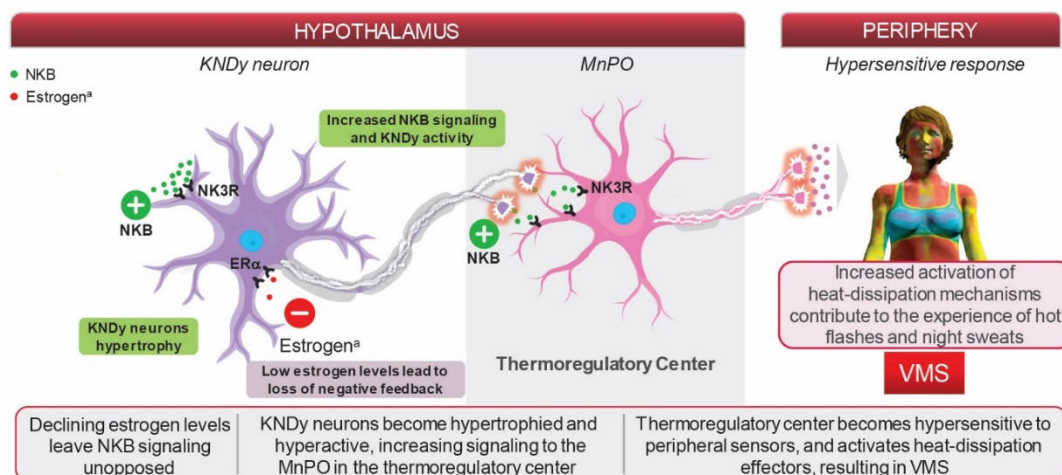
Thermoregulatory Homeostasis



^aAvailable data support an inhibitory effect of estradiol, specifically, on KNDy neurons.

^bCharacterized by vasodilatation and sweating.

Loss of Thermoregulatory Control in Menopause



^aAvailable data support an inhibitory effect of estradiol, specifically, on KNDy neurons.

ERα = estrogen receptor alpha; KNDy = kisspeptin-neurokinin B-dynorphin; MnPO = median preoptic nucleus; MOA = mechanism of action; NK3R = neurokinin 3 receptors; NKB = neurokinin B; VMS = vasomotor symptoms.

Knowledge Checks

2.1 **True or False?** Hot flashes are sudden and intense feelings of heat in the chest, neck, and face, with reddening of the skin.^{1,6}

- A True
- B False

CONFIDENTIAL INFORMATION - FOR INTERNAL USE ONLY - NOT FOR EXTERNAL DISTRIBUTION OR PROMOTIONAL USE.

MAT-ABC-FEZ-2023-00004 06/23

2.2 Which of the following are risk factors for VMS?^{6,16} (Select all that apply.)

- A Higher economic status
- B Cigarette smoking
- C Earlier menopausal stage at onset
- D Low-fat diet

2.3 The median duration of VMS is _____ years.¹³

- A 3.2
- B 7.4
- C 8.9
- D 10.1

2.4 Which part of the brain is involved in thermoregulation?⁶

- A Hypothalamus
- B Amygdala
- C Cerebellum
- D Prefrontal cortex

Answers

- 2.1 A (Section 2.1)
- 2.2 B, C (Section 2.2)
- 2.3 B (Section 2.2)
- 2.4 A (Section 2.3)

Glossary

amenorrhea

the absence of menstruation²⁵

anovulatory

failure of the ovaries to produce, mature, or release eggs/ova; lack of ovulation²⁵

antral follicle count

the count of mature ovarian vesicles that can rupture during ovulation to release the ovum/egg²⁵

dyspareunia

an abnormal pain during sexual intercourse due to a spasm²⁵

endocrinologic

pertaining to a process in which a group of cells secretes a substance (such as a hormone) into the blood or lymph circulation that has a specific effect on tissues in another part of the body²⁵

follicle-stimulating hormone (FSH)

a hormone that stimulates the growth and maturation of antral follicles in the ovary in females and promotes the creation of sperm in males²⁵

glycoprotein

a protein conjugated with a carbohydrate²⁵

hypothalamus

a part of the brain that activates, controls, and integrates the peripheral autonomic nervous system, endocrine processes, and functions such as body temperature, sleep, and appetite²⁵

luteinizing hormone (LH)

a glycoprotein hormone that stimulates the secretion of estrogen by the growing follicle in the ovary in females and testosterone by the cells in the testes in males; it is involved in the maturation of ova/egg and sperm²⁵

neuron

the basic nerve cell of the nervous system that transmits nerve impulses²⁵

neuropeptide

a protein found in the brain that could be a neurotransmitter or a hormone²⁵

neurotransmitter

a chemical that modifies or results in the transmission of nerve impulses between synapses²⁵

pituitary gland

an endocrine gland underneath the brain that supplies numerous hormones that affect and govern many vital functions²⁵

somatic

related to the body, as distinguished from the mind²⁵

thermoneutral zone

a range of temperatures within which the body can maintain its core temperature without major thermoregulatory responses, such as sweating or shivering²³

vasoconstriction

a decrease in the diameter of a blood vessel²⁵

vasodilation

an increase in the diameter of a blood vessel²⁵

Acronyms

AMH = antimüllerian hormone

BMI = body mass index

FMP = final menstrual period

FSH = follicle-stimulating hormone

GnRH = gonadotropin-releasing hormone

HDL = high-density lipoprotein

KNDy = kisspeptin-neurokinin B-dynorphin

LDL = low-density lipoprotein

LH = luteinizing hormone

MnPO = median preoptic nucleus

NKB = neurokinin B

POI = premature ovarian insufficiency

STRAW = Stages of Reproductive Ages Workshop

SWAN = Study of Women's Health Across the Nation

VMS = vasomotor symptoms

References

1. Taylor HS, Pal L, Seli E. Menopause transition and menopause hormone therapy. In: Taylor HS, Pal L, Seli E, eds. *Speroff's Clinical Gynecologic Endocrinology and Infertility*. 9th ed. Philadelphia, PA: Wolters Kluwer, 2020.
2. Santoro NF. Menopause. In: Crandall CJ, Bachman GA, Faubion SS, et al, eds. *Menopause Practice: A Clinician's Guide*. 6th ed. Pepper Pike, OH: The North American Menopause Society, 2019:1-21.
3. Jones RE, Lopez KH. Reproductive aging. In: Jones RE, Lopez KH, eds. *Human Reproductive Biology*. 4th ed. Waltham, MA: Elsevier Academic Press, 2014.
4. Zhu D, Chung HF, Pandeya N, et al. Relationships between intensity, duration, cumulative dose, and timing of smoking with age at menopause: A pooled analysis of individual data from 17 observational studies. *PLoS Med* 2018;15(11):e1002704.
5. Harlow SD, Gass M, Hall JE, et al. Executive summary of the Stages of Reproductive Aging Workshop +10: addressing the unfinished agenda of staging reproductive aging. *Climacteric* 2012;15(2):105-14.
6. Thurston RC. Vasomotor symptoms. In: Crandall CJ, Bachman GA, Faubion SS, et al, eds. *Menopause Practice: A Clinician's Guide*. 6th ed. Pepper Pike, OH: The North American Menopause Society, 2019:43-55.
7. Santoro N, Epperson CN, Mathews SB. Menopausal symptoms and their management. *Endocrinol Metab Clin North Am* 2015;44(3):497-515.
8. Stute P, Spyropoulou A, Karageorgiou V, et al. Management of depressive symptoms in peri- and postmenopausal women: EMAS position statement. *Maturitas* 2020;131:91-101.
9. Utian WH. Psychosocial and socioeconomic burden of vasomotor symptoms in menopause: a comprehensive review. *Health Qual Life Outcomes* 2005;3:47.
10. Nappi RE, Siddiqui E, Todorova L, Rea C, Gemmen E, Schultz NM. Prevalence and quality-of-life burden of vasomotor symptoms associated with menopause: A European cross-sectional survey. *Maturitas* 2023;167:66-74. Epub 2022 Sep 24.
11. Genazzani AR, Schneider HP, Panay N, Nijland EA. The European Menopause Survey 2005: women's perceptions on the menopause and postmenopausal hormone therapy. *Gynecol Endocrinol* 2006;22(7):369-75.
12. Yu Q, Chae HD, Hsiao SM, Xie J, Blogg M, Sumarsono B, Kim S. Prevalence, severity, and associated factors in women in East Asia with moderate-to-severe vasomotor symptoms associated with menopause. *Menopause* 2022 1;29(5):553-63.
13. Avis NE, Crawford SL, Greendale G, et al. Duration of menopausal vasomotor symptoms over the menopause transition. *JAMA Intern Med* 2015;175(4):531-9.
14. SWAN Study of Women's Health Across the Nation. About SWAN. <https://www.swanstudy.org/about/about-swan/>. Accessed 03-24-2023.

15. SWAN Study of Women's Health Across the Nation. SWAN publication list (02-23-2021). https://www.swanstudy.org/wps/wp-content/uploads/2021/03/Publication_List.doc. Accessed 03-24-2023.
16. Freeman EW, Sammel MD, Lin H, Liu Z, Gracia CR. Duration of menopausal hot flashes and associated risk factors. *Obstet Gynecol* 2011;117(5):1095-104.
17. Gold EB, Sternfeld B, Kelsey JL, et al. Relation of demographic and lifestyle factors to symptoms in a multi-racial/ethnic population of women 40-55 years of age. *Am J Epidemiol* 2000;152(5):463-73.
18. Gold EB, Crawford SL, Shelton JF, et al. Longitudinal analysis of changes in weight and waist circumference in relation to incident vasomotor symptoms: the Study of Women's Health Across the Nation (SWAN). *Menopause* 2017;24(1):9-26.
19. Gold EB, Colvin A, Avis N, et al. Longitudinal analysis of the association between vasomotor symptoms and race/ethnicity across the menopausal transition: study of women's health across the nation. *Am J Public Health* 2006;96(7):1226-35.
20. Biglia N, Cagnacci A, Gambacciani M, Lello S, Maffei S, Nappi RE. Vasomotor symptoms in menopause: a biomarker of cardiovascular disease risk and other chronic diseases? *Climacteric* 2017;20(4):306-12.
21. Thurston RC, Carroll JE, Levine M, et al. Vasomotor symptoms and accelerated epigenetic aging in the Women's Health Initiative (WHI). *J Clin Endocrinol Metab* 2020;105(4):1221-7.
22. Sarrel P, Portman D, Lefebvre P, et al. Incremental direct and indirect costs of untreated vasomotor symptoms. *Menopause* 2015;22(3):260-6.
23. Freedman RR. Hot flashes: behavioral treatments, mechanisms, and relation to sleep. *Am J Med* 2005;118(Suppl 12B):124S-30S.
24. Dacks PA, Krajewski SJ, Rance NE. Activation of neurokinin 3 receptors in the median preoptic nucleus decreases core temperature in the rat. *Endocrinology* 2011;152(12):4894-905.
25. Mosby's Dictionary of Medicine, Nursing & Health Professions. 11th ed. St Louis, MO: Elsevier, 2022.