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Defining the menopausal transition

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Menopause signifies the permanent cessation of ovarian function and the end of a woman's reproductive potential. A universal experience in women's aging, it is the culmination of some 50 years of reproductive aging—a process that unfolds as a continuum from birth through ovarian senescence to the menopausal transition and the postmenopause. The menopausal transition is known to play a major role in the etiology of many symptoms common in middle age and may contribute to chronic conditions and disorders of aging such as osteoporosis and cardiovascular diseases. However, the mechanisms underlying ovarian senescence and the occurrence of various short- and long-term biological and psychological sequelae are poorly understood. Progress in researching reproductive aging and the menopause has been impeded by the lack of a staging system based on meaningful, reliable, and objective criteria for staging reproductive aging and specifying menopause-related status. Current nomenclature is described and its limitations are discussed. Specifically, contemporary terminology lacks the sensitivity and specificity needed to operationally define a woman's reproductive status in the continuum of reproductive aging. A number of proposed staging systems are currently being evaluated for their suitability in identifying appropriate demarcations across the span of reproductive aging. Further research and a better understanding of the menopausal transition are necessary to establish the validity, practicality, and acceptability of these proposed staging systems.

A universal experience in aging women, menopause is a biologic event that has attained high visibility as the postwar baby boomers began reaching this milestone at the close of the last millennium. Menopause signifies the permanent cessation of menstruation and the end of reproductive potential. It is the culmination of some 50 years of reproductive aging—a process that unfolds as a continuum from birth through ovarian senescence to the menopausal transition and the postmenopause. A result of aging changes in the ovary and in hypothalamic-pituitary-ovarian axis function,[1] the menopausal transition encompasses a period of dynamic changes in reproductive and nonreproductive tissues. The menopausal transition is known to play a major role in the etiology of symptoms such as hot flashes, night sweats, uterine bleeding problems, and vulvovaginal atrophy.[2] Mood changes,[3] sleep disturbances,[4] and sexual dysfunction[5] also are commonly reported and may be attributable to the hormonal aberrations experienced during the transition.

The opinions offered at the National Institutes of Health (NIH) State-of-the-Science Conference on Management of Menopause-Related Symptoms and published herein are not necessarily those of the National Institute on Aging (NIA) and the Office of Medical Applications of Research (OMAR) or any of the cosponsoring institutes, offices, or centers of the NIH. Although the NIA and OMAR organized this meeting, this article is not intended as a statement of Federal guidelines or policy.

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The impact of the menopause on quality of life is not limited to middle age. The sequelae may also contribute to the chronic diseases of aging and thus extend to the later years as well. The notion that reproductive aging and the timing of menopause may play significant roles in healthy aging is supported by reports that a late natural menopause is associated with lower rates of cardiovascular disease (CVD) and osteoporosis and with reduced all-cause mortality, although it also is correlated with an increased risk of breast cancer.[6]

Despite the surge of interest in the menopausal transition and in research on this topic over the past 2 decades, the mechanisms underlying ovarian senescence, the timing of menopause, symptom occurrence, and the various biological and psychological sequelae remain poorly understood. There has been a growing awareness that progress in researching reproductive aging and menopause has been impeded by the lack of meaningful, reliable, and objective criteria for designating menopause-related status in women participating in observational studies and clinical trials.[7–9] Importantly, the lack of unambiguous, nonoverlapping criteria for classifying women into menopausal status categories that reflect homogeneous physiologic phenotypes has been a barrier to the comparison, generalization, integration, and dissemination of findings for promoting public health as well as the development of new investigations.[7]

Efforts to formally define and promote the use of appropriate menopause terminology gained momentum in a working group of the First Congress of the International Menopause Society (IMS) in 1976.[10] Subsequently, a World Health Organization (WHO) Scientific Group on Research in the Menopause was organized and published initial recommendations in 1981 on nomenclature for terms such as "perimenopause," "menopause," and "postmenopause."[11]

In the interim, in 1985 a workshop was convened in Korpilampi, Finland, with the objectives of identifying methodologic issues in conducting research on the menopause, particularly in cross-cultural settings, and clarifying menopause-related definitions. Participants emphasized the importance of developing menopause terminology for research investigations that indicated whether menopause was "natural" (i.e., spontaneous) or surgically induced (which they defined as hysterectomy with or without bilateral oophorectomy) because "significant differences have been reported in [patients'] health and health behavior."[12] In addition, because pregnant or nursing women can also experience a "natural" amenorrhea of 12 months (the 1981 WHO definition of menopause), it was deemed necessary to identify the reason why menstruation had stopped "naturally" or artificially (i.e., whether due to pathology, chemotherapy, behaviors such as extreme exercise, anorexia nervosa, hysterectomy, and/or bilateral oophorectomy). Furthermore, because menopause was believed to be a biocultural event, a better understanding of its effects on quality of life mandated consideration of the psychosocial transcultural milieu in which menopause was experienced. It was recommended that future efforts aimed at refining the boundaries of the "perimenopause" focus on integrating "analyses of hormone levels with self-reported changes in menstrual pattern and symptom experience."[12]

More recent effort to refocus and refine menopause terminology have adopted most of the 1996 WHO recommendations,[13] which updated the 1981 treatise with definitions for premenopause, menopausal transition, induced menopause, hysterectomy, and premature menopause. The WHO group discouraged use of the term *climacteric* as ambiguous and confusing.[13] The WHO recommendations were later reviewed and endorsed in 1999 by the IMS, after this group incorporated the terms *climacteric* and *climacteric syndrome* because of the widespread international popularity of these descriptors outside the United States.[14] The terminology below includes that recommended by the WHO in 1996 as well as the IMS-proposed addition of *climacteric*.

1. *Natural menopause* is defined as the permanent cessation of menstruation resulting from the loss of ovarian follicular activity. It is recognized to have occurred after 12 consecutive months of amenorrhea, for which there is no other obvious pathologic or physiologic cause. Menopause occurs with the final menstrual period (FMP), which is known with certainty only in retrospect $\geq$1 year after the event. An adequate independent biologic marker for the event does not exist.
2. *Perimenopause* should include the period immediately before the menopause (when the endocrinologic, biologic, and clinical features of approaching menopause commence) and the first year after menopause. The term *climacteric* should be abandoned to avoid confusion.
3. *Menopausal transition* should be reserved for that period before the FMP when variability in the menstrual cycle is usually increased.
4. *The climacteric* is the phase in the aging of women marking the transition from the reproductive phase to the nonreproductive state. This phase incorporates the perimenopause by extending for a longer variable period before and after the perimenopause.[10]
5. *Premenopause* is often used ambiguously either to refer to the 1 or 2 years immediately before the menopause or to refer to the whole of the reproductive period before the menopause. The group recommended that the term be used consistently in the latter sense to encompass the entire reproductive period before the FMP.
6. *Induced menopause* is defined as the cessation of menstruation that follows either surgical removal of both ovaries (with or without hysterectomy) *or* iatrogenic ablation of ovarian function (e.g., by chemotherapy or radiation).
7. *Simple hysterectomy*, where $\geq$1 ovary is conserved, is used to define a distinct group of women in whom

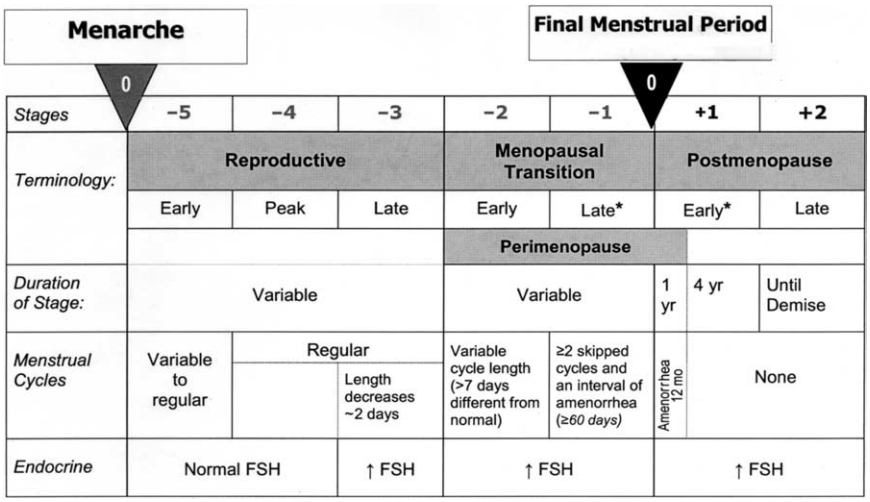

Figure 1 Stages most likely to be associated with reports of vasomotor symptoms. FSH = follicle stimulating hormone; mo = month; yr = year. (Adapted from *Fertil Steril.*[7])

ovarian function may persist for a variable period after surgery.

8. *Postmenopause* is defined as the period dating from the FMP, regardless of whether the menopause was induced or spontaneous.
9. *Premature menopause* ideally should be defined as menopause that occurs at an age <2 standard deviations below the mean estimated for the reference population. In practice, in the absence of reliable estimates of the distribution of age at natural menopause in populations in developing countries, the age of 40 years is frequently used as an arbitrary cut-off point, below which menopause is said to be premature.

Although, the WHO–IMS definitions may have a place in the clinical setting, terms such as *premenopause, menopausal transition, climacteric*, and *perimenopause* clearly lack the sensitivity and specificity needed to operationally define a woman's menopausal status to produce physiologically homogenous phenotypes for scientific investigations of the menopausal transition. Even the definition of *menopause*—because it is based on the criterion of 12 months of amenorrhea for confirming (retrospectively) the occurrence of the FMP—is lacking in specificity. This criterion is an imperfect predictor of the FMP because the likelihood of another period after 360 days of amenorrhea ranges from 4.5% in women who are ≥53 years old to 10.5% in those aged 45 to 49 years.[15] Thus, because there is no fully adequate independent biologic marker for the menopause, a lengthy period of amenorrhea of 1 year or even more (depending on a woman's age) is required to be reasonably certain that the FMP is indeed final.

To address the lack of comparability in categorizing menopausal status in published studies, the Stages of Reproductive Aging Workshop (STRAW) was convened in 2001. The objective of this meeting was to develop a standardized, practical staging system for reproductive aging in women that could be used reliably both in scientific investigations and in the clinical setting. The second goal was to produce more precise definitions for confusing or ambiguously defined terms such as *menopause, menopausal transition, postmenopause,* and *perimenopause*. In attempting to stage reproductive aging, aging changes in domains such as menstrual cycling, endocrine status, pelvic anatomy (ovarian imaging), and the presentation of menopause-related symptoms were evaluated for their potential usefulness in specifying demarcations and hence stages in the continuum of reproductive aging across the life span.[7]

The proposed STRAW consensus staging system is anchored by the menarche and the menopause and consists of 7 stages that are independent of age (**Figure 1**). The STRAW guidelines recommend the term *perimenopause* be used only by patients and in the lay press (if at all) and not in scientific papers. According to STRAW, 5 stages, constituting the reproductive interval (3 stages) and the menopausal transition (2 stages) precede the FMP, which is then followed by the postmenopause (2 stages). The stages are variable in duration and may be distinguished principally by changes in menstrual cycle length and regularity, and, after establishing stage-specific cut points, follicle-stimulating hormone (FSH) levels.[16]

Menarche signals entrance into the reproductive period (at stage −5), during which cycles that are initially irregular become regular, fertility becomes optimal (stage −4) and then wanes with subtle increases in FSH and cycles that remain regular but decrease slightly (by ~2 days) in length (stage −3). The conclusion of the reproductive period and entrance into the (early) menopausal transition (stage −2) is marked by increased variability in menstrual cycle length, i.e., by a change in cycle length of ≥7 days from "normal" (or stage −3) cycle lengths and further increases in circulating FSH that continue to increase throughout the menopausal transition and early postmenopause. The late stage (−1) of the menopausal transition commences with ≥2 skipped cycles and an interval of ≥60 days of amenorrhea.

It should be noted that currently there are no unequivocal markers or clear demarcations between stage −5 and stage −1 or between stage +1 and stage +2.

The term "menopause" is synonymous with the FMP anchor point and is defined retrospectively after 12 months of amenorrhea without an obvious natural or pathologic cause (similar to the WHO[16] and IMS[11]conventions). Division of the postmenopause into an early and late stage is premised on the observation of an unstable environment for the skeleton. This metabolic instability is manifested by ≥3 years of accelerated bone loss, followed by an additional period during which rates of bone loss decline and stabilize at lower rates characteristic of "normal" age-related loss.[17]

Although the monotonic rise in FSH, a hallmark of the menopausal transition, is believed be an indicator of decreased follicular reserves and hence proximity to the menopause, currently there is "no single reliable hormonal marker of menopausal status for an individual woman."[18] Nevertheless, because FSH continues to rise throughout the menopausal transition and on into the postmenopause, FSH has significant potential as a marker of reproductive aging and menopausal status and was thus included in the STRAW schema. Specification of FSH ranges for staging the menopausal transition is currently premature and awaits the identification and validation of suitable reference ranges for levels that could meaningfully subdivide the reproductive and postreproductive timeline into appropriate stages. The utility of other reproductive hormones such as estradiol, testosterone, luteinizing hormone, progesterone, or inhibin A or B as markers was evaluated. However, these hormones were considered unlikely to be practical in designating stages, either because the natural variability is extremely high or because values do not relate to menopausal transition changes in menstrual bleeding or time to the FMP.

The presentation of various symptoms was likewise deemed to be unsuitable for establishing cut points in a staging system. Although the frequency of symptoms such as hot flashes and night sweats increases markedly during the menopausal transition, they do not correlate well with changing endocrine profiles or bleeding patterns and they are not universally experienced. Other symptoms, such as vaginal dryness, urine leakage, and stiffness or soreness, may be associated with the menopausal transition, but, like vasomotor symptoms, may vary significantly by race/ethnicity, body mass index, and lifestyles and behaviors and are otherwise not sufficiently sensitive and specific to demarcate entry into the menopausal transition or progression to subsequent stages.

Ovarian imaging has great conceptual promise as an objective tool for staging reproductive aging because menopause reflects the end result of the attrition of ovarian follicles—a process that commences in utero and continues until the ovary is completely depleted. Findings from studies of primordial follicle counts in ovaries obtained from autopsy or oophorectomy[19] and of ovarian antral follicle counts using transvaginal ultrasound technology in vivo[20] have demonstrated a strong correlation with chronologic age. These parallel findings suggest that antral follicle counts may be a sensitive index of the numbers of primordial follicles remaining in the ovary, and, hence, of reproductive age. However, further research is needed to clarify the relation between endocrine and menstrual cycle parameters and antral follicle counts to determine the sensitivity and practicality of this technology in assessing reproductive age.

Undoubtedly, the basis of a transparent, accurate, and meaningful staging system for reproductive aging across the life span requires the clear conceptualization of the biologic mechanisms underlying the menopausal transition and then the validation of proposed markers and their classification algorithms to demonstrate that a designated stage represents an "essential state" in the reproductive aging process.[21]

Currently, there are several proposed staging systems or classification schemes with work in progress. The STRAW algorithms for entry into stage −2 and stage −1 are undergoing rigorous data-driven iterations[22] using menstrual cycle data from a number of cohort studies well positioned to elucidate the biology of the menopausal transition. A new proposed classification system based on menstrual cycle parameters and reproductive history and reproductive hormone levels was recently evaluated and shown to have promise in accurately categorizing menopausal status in women for epidemiologic studies that are limited to only 1 contact with the study participant.[23] Preliminary findings from another investigation comparing proposed definitions from STRAW, the Penn Ovarian Aging Study, and the Study of Women's Health Across the Nation (SWAN) have demonstrated significant differences in the levels of both inhibin B and FSH in the Penn cohort that corresponded to the inception and early stages (under each study's definition) of the menopausal transition. These data, which suggest that subtle changes in bleeding patterns reflect early changes in hormonal status, are necessary in supporting the conceptual framework of staging systems based on changes in menstrual cycle parameters. However, although progressive changes in hormone levels may coincide with advancing menstrual-based menopausal transition stage in a study population, the magnitude and sources of variability are not characterized adequately to specify cut points with which to classify individual women.

Additional research is needed to develop an operational, useful, and acceptable staging system that is sensitive and specific for classifying individual women. Criteria for defining (1) "normal" (or peak reproductive stage) menstrual cycle lengths and algorithms for determining when menstrual cycles become irregular, and (2) hormonal cut points for entry into and progression through the menopausal transition must be developed and validated.

The elimination of ambiguous, redundant, and/or overlapping definitions and their replacement with reliable standardized nomenclature and a system for staging reproductive aging will be a tremendous boon to scientific

investigations of the menopausal transition and its influences on quality of life, aging, and the development of the chronic diseases of the elderly. The ability of a woman to determine where she is in the menopausal transition also will be of great value in understanding her need for contraception, whether anomalous signs and symptoms are likely to reflect the hormonal fluctuations of the menopausal transition or underlying pathology, and whether menopausal symptoms and problematic bleeding patterns are self-limiting or in need of intervention. Lastly, the timely initiation of screening and preventive strategies for menopause-associated pathology (such as excessive rates of bone loss) will help optimize quality of life and healthy aging.

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