Menstrual Cycle Changes as Women Approach the Final Menses: What Matters?

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KEYWORDS

• Menstruation • Menopause • Abnormal uterine bleeding • Menopausal transition

KEY POINTS

- The STRAW+10 bleeding criterion for onset of the early menopausal transition is increased variability (persistent, 7-days or more difference in length of consecutive cycles) and for onset of the late menopausal transition is occurrence of amenorrhea of 60 days or more.
- Twelve percent to 25% of women experience minimal or no change in their menstrual cycle length before their final menstrual period (FMP).
- Women with earlier onset of the menopausal transition have longer transitions. When the transition is not sudden, it may last from approximately 4 to 10 years, with longer duration associated with earlier age at onset.
- Excessive flow and prolonged menstrual bleeding is a hallmark of the menopausal transition. Most women experience repeated bleeding episodes lasting 10 or more days, whereas one-third have heavy menstrual bleeding lasting 3 or more days, with blood loss frequently exceeding 80 mL.
- Anovulation is common in the menopausal transition, but hormonally normal, ovulatory cycles occur up until the FMP.

Since the pioneering publications of Vollman[1] and Treloar and colleagues[2] in the 1950s and 1960s, it has been well-established that marked changes occur in the length and variability of menstrual cycles as women enter the menopausal transition (MT). Classically, increased variability in cycle length marks the onset of the MT, with the likelihood of long cycles increasing as women approach their final menstrual period (FMP), or menopause. Menopause is defined, retrospectively, after 12 months of amenorrhea in women aged 40 and older, although another menstrual bleed may occur in up to 10% of women, especially in women who are younger when they reach this milestone.[3] The challenge for women and their health care providers has been to

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understand what change in menstrual patterns specifically signals that a woman has entered the MT and what signals that she is nearing the FMP.

Over the past 2 decades, longitudinal cohort studies have followed midlife women as they transitioned from reproductive life through to and beyond the menopause, providing a more precise understanding of the specific bleeding changes that mark the onset of the MT and a nuanced understanding of the changes in menstrual bleeding that women may expect at this life stage. These studies, in which midlife women maintained menstrual calendars for various lengths of time, include the multisite, multiethnic Study of Women's Health Across the Nation (SWAN),[4] the Massachusetts Women's Health Study (MWHS),[5] The Melbourne Women's Midlife Health Project (MWMHP),[6] The Seattle Midlife Women's Health Study (SMWHS),[7] and the Penn reproductive aging Study (POAS),[8] among others. Similar to the observations by Treloar and colleagues[2] and Vollman,[1] the MWHS reported that short menstrual cycles were more frequent in early perimenopause whereas cycles longer than 90 days became frequent late in the transition.[5] The MWMHP documented that increasingly longer menstrual cycles were a signal of the approach of the FMP, most notably in the last 20 menstrual cycles before the FMP.[9]

STAGING REPRODUCTIVE AGING: WHAT ARE THE SPECIFIC CHANGES IN MENSTRUAL BLEEDING THAT MARK ONSET OF EARLY AND LATE MENOPAUSAL TRANSITION?

Treloar's landmark paper that defined the concept of an MT[10] was based on visual examination of women's menstrual histories over the 12 years leading to the FMP. He described the phenomenon of increased variability followed by the onset of very long cycles and estimated the average age at entry into the transition to be 45.5 years. In the 1990s, several of the previously mentioned cohort studies proposed different approaches to staging reproductive aging and proposed markers for recognizing the onset of increased variability and of increasingly long cycles. In recognition of the need for consensus regarding stages of reproductive aging and for valid, reliable, and clinically useful criteria to characterize the onset of each stage, the Stages of Reproductive Aging Workshop (STRAW)[11] made initial recommendations for a 7-stage model of reproductive life based on a consensus discussion of the available evidence in 2001. Subsequently, the ReSTAGE Collaboration empirically assessed the validity and reliability of STRAW's menstrual criteria using Treloar's data[10] and data from 3 of the contemporary cohort studies of midlife women: SWAN, the MWMHP, and the SMWHS.[12] The ReSTAGE findings clarified STRAW's recommendations and lead to the 2011 empirically based STRAW+10 recommendations.[13–16]

The STRAW+10 model divides reproductive life into 7 stages: the reproductive years (3 stages), the transition years (2 stages: early and late), and the postmenopausal years (2 stages). Given limitations in the availability of valid, reliable, and widely available assays, STRAW focused on menstrual markers and qualitative changes in follicle-stimulating hormone (FSH) (with quantitative values now defined for the late transition), and to a lesser extent inhibin-B and anti-Mullerian hormone (AMH):

- Entry into the early transition is characterized by increased levels of FSH and increased variability in menstrual cycle length, defined as a persistent, 7-days or more difference in the length of consecutive cycles.
- Entry into the late transition is characterized by the continued elevation of FSH and the occurrence of amenorrhea of 60 days or more.

The bleeding changes that mark onset of the early MT are subtle, yet often apparent to women before they are assessable clinically. No validated standardized questionnaire yet exists that accurately captures these bleeding changes. Longitudinal cohort studies relied on self-reported change or irregularity in menstrual function, with no clear definition of what constituted "change" or "irregularity."The STRAW+10 criterion for ascertaining the change in variability marking entry into the early MT follows from the SMWHS[17] and ReSTAGE,[18] with persistence operationalized as a recurrence within 10 cycles of the first variable-length cycle. After age 40, the median time from occurrence of a persistent 7-day or more difference in consecutive cycle lengths to FMP is 5 to 8 years. SWAN[19] and the Michigan Bone Health and Metabolism Study (MBHMS)[20] found that the initial rise in FSH occurs on average approximately 7 years before the FMP, consistent with the timing of onset of the early transition by this criterion. Other studies[17,21–23] provide further evidence that STRAW's proposed bleeding criteria are valid based on concurrent changes in hormone profiles. Ongoing research suggests that declines in inhibin-B and AMH are also useful qualitative correlates of the onset of the early transition, with more definitive hormonal criteria potentially possible once standardized assays and longitudinal population data on patterns of change in these hormones are available.[24–26]

Menstrual changes associated with the late MT are easier to identify. Although a criterion of amenorrhea of 90 days[27] was in common usage at the time of STRAW, a reanalysis of Treloar's data[28] and data from both SMWHS[17] and MWMHP[9] suggested that a shorter interval of amenorrhea was equally predictive of the approach of the FMP and less likely to misclassify menopausal women as being in late transition. ReSTAGE empirically demonstrated that the optimal bleeding marker of the late transition is an episode of amenorrhea of 60 days or longer.[29] In approximately one-third of women, the first cycle of $\geq$60 days is in fact $\geq$90 days. After age 40, the median time from occurrence of $\geq$60 days of amenorrhea to the FMP is approximately 2.5 to 3.0 years. This criterion also correlates with further elevations in FSH.[30] Clinically, requiring a repeated episode of amenorrhea $\geq$60 days in women younger than 45 may help ensure women are in fact in late menopause as opposed to experiencing amenorrhea secondary to transient stress.[31] Given the availability of international standards for FSH assays, STRAW+10 provided quantitative criteria for FSH, levels greater than 25 IU/L in a random blood draw, being characteristic of late transition. Notably, in SWAN and MWMHP, an episode of amenorrhea $\geq$60 days was a better predictor of proximity to the FMP than was a single early follicular phase serum FSH level. Hot flashes, although common in the late transition, are not predictive of proximity of menopause in the absence of information on amenorrhea and FSH levels.

Limitations of the Stages of Reproductive Aging Workshop Model

The STRAW model, now recognized as the gold standard for staging reproductive aging, are widely applicable to women regardless of age, race/ethnicity, body size, or lifestyle characteristics, including smoking status. However, 3 important gaps remain in the clinical application of the STRAW+10 model:

- Evaluation of reproductive aging in women who have had a hysterectomy or ablation must rely on the STRAW+10 hormonal criteria alone. The Women's Ischemia Syndrome Evaluation study proposed an algorithm based on age, time since last menses, surgery history, and serum hormone values.[32]
- As polycystic ovarian syndrome (PCOS) is characterized by oligomenorrhea, STRAW+10 bleeding criteria cannot be applied to women with this condition. Given higher antral follicle counts and higher AMH levels, and less frequent

cycles,[33] women with PCOS may have enhanced ovarian reserve and a later age at menopause than women without PCOS.[34]

- Distinguishing amenorrhea secondary to chronic illness, including human immunodeficiency virus (HIV),[35,36] cancer and chemotherapy,[37–39] medication use,[35,40] or nutritional compromise or weight loss, from amenorrhea attributable to the MT is challenging. For example, studies have reported lower FSH levels in HIV-infected women, secondary to use of opiates, and elevated E2 among women treated with highly active antiretroviral therapy (HAART).[35]

Menstrual Cycle Patterns Leading to the Menopause Differ Across Women

As clinicians are well aware, bleeding patterns during the transition to menopause can differ markedly in some women from the classic pattern described previously. Characteristics of the MT depend to some extent on the age at menopause, with later age at menopause associated with the experience of longer cycles and greater cycle variability in the 2 years preceding the FMP.[3] Women with later menopause also tend to have had longer cycles throughout their reproductive life[41] and in the 9 years before menopause.[42]

Data on the experience of women who report little change in their menstrual cycles until the FMP are limited. In one clinical study, 12% of women reported sudden amenorrhea,[43] confirming self-reports described in other articles.[44] In the reanalysis of Treloar's[10] data described previously, approximately 15% of women were found to have minimal change in their cycle length before the FMP. In another reanalysis of these same data, approximately 25% of women were classified as having no or minimal change in menstrual cycle variability or mean length before their FMP.[45]

ANOVULATION IS CHARACTERISTIC OF THE MENOPAUSAL TRANSITION

In her early pioneering studies of ovulation across the transition, Metcalf[46] documented that 95% of women aged 40 to 55 with no recent change in menstrual cycle length ovulated consistently, versus only 34% of women who reported a recent history of cycles longer than 35 days. The SWAN Daily Hormone Study (DHS) is one of the few studies that has prospectively evaluated changes in endocrine profiles within a menstrual cycle as women approach their FMP. This study reported not only that very short menstrual cycles, less than 21 days, were common in early perimenopause, but that short and long menstrual cycles are both more likely to be anovulatory.[47] The percentage of menstrual cycles that were ovulatory declined beginning approximately 5 years before the FMP with only 22.8% of cycles within a year of the FMP being ovulatory.[48] Ovulatory cycles in the MT had a mean length of 26 to 27 days, only slightly shorter than that of premenopausal women, and whole cycle hormone levels remained relatively stable until approximately 3 years before menopause (evaluation of cycle length in the SWAN menstrual calendars confirm that although long cycles become longer with the approach of the FMP, median length of cycles changes minimally).[49] Thus, confirming the studies of Metcalf,[46] hormonally normal, ovulatory menstrual cycles become less frequent but continue to occur through the end of reproductive life.

EXCESSIVE FLOW AND PROLONGED BLEEDING ARE COMMON IN THE MENOPAUSAL TRANSITION

Considerably less information is available regarding how menstrual bleeding itself changes with reproductive aging. Although short bleeding and spotting episodes occur more frequently after the onset of the MT,[50] excessive flow and prolonged

menstrual bleeding is often a hallmark of women's experience during this phase of reproductive life. Clinical studies as well as cross-sectional and longitudinal population-based studies of midlife women document an increased duration and amount of menstrual flow.[51–53] The classic study by Hallberg and colleagues[54] documented that 50-year-old women bled approximately 6 mL more than women aged 20 to 45, with heavy bleeding being most common in this age group: the 90th percentile of blood loss was 133 mL in women aged 50, versus 86 to 88 mL for women aged 30 to 45. In a recent study that quantified blood loss across 2 bleeding episodes, the range of menstrual blood loss was significantly greater among women in the late MT, compared with younger women.[52] Blood loss greater than 200 mL was associated with being in late MT and with cycles being ovulatory with high E2 levels.[22,52] Another population-based prospective diary study found that the MT was associated with increases in the reported variability in length of bleeding episodes and increased reporting of spotting and bleeding episodes that lasted $\geq$10 days.[55] Consistent with this study and studies in reproductive-age women,[56] the SWAN DHS[47] reported heavy bleeding less frequently after anovulatory cycles than after ovulatory cycles in the early transition.

Chronic abnormal uterine bleeding (AUB) is bleeding "that is abnormal in duration, volume, and/or frequency and has been present for the majority of the last 6 months.".[57,58] However, given the nature of changes in menstrual function during the MT, identifying what constitutes abnormal in this reproductive life-stage remains a challenge for women and their health care providers. FIGO (International Federation of Gynecology and Obstetrics) defines the limits of normal menstruation by 4 parameters: frequency, regularity, duration of flow, and volume of blood loss.[57,58] During the MT, frequent (more often than every 24 days over a 6-month period), infrequent (less than every 38 days over a 6-month period), and irregular (variation from cycle to cycle within a woman over a 1-year period of more than 20 days) is expected and normative. Prolonged menstrual flow (>8 days of flow occurring on a regular basis) is experienced by most women at some point during their MT.[59] Heavy menstrual bleeding (blood loss >80 mL) can be difficult to measure quantitatively and thus is considered excessive when it interferes with a woman's quality of life. SWAN is one of the few studies to characterize change in menstrual bleeding duration and flow using prospective menstrual calendars.[59] During the MT, three-quarters of SWAN women had 3 of more episodes of menstrual bleeding lasting 10 or more days, one-quarter of whom reported 3 episodes within 6 months of the first such episode. In addition, one-third of SWAN women had 3 or more heavy bleeding episodes lasting 3 or more days, of whom 40% experienced those episodes within 6 months. Although comparable to data from population-based surveys of reproductive-age women where 10% to 35% report symptoms indicative of heavy menstrual bleeding,[60–63] many women with AUB had had a hysterectomy and were not eligible to participate in SWAN. Clinical case series evaluating women with AUB in the MT have found that up to three-quarters may have no anatomic pathology.[64,65]

HOW LONG DOES THE MENOPAUSAL TRANSITION LAST?

Treloar[10] estimated the median duration of the MT to be 4.8 years. Applying the STRAW criteria to the SWAN menstrual calendar data, the median duration of the MT was found to depend largely on the age at which it began, with later onset associated with a shorter duration.[66] Thus, median duration of the MT ranged from 4.4 to 8.6 years depending on age at onset. A reanalysis of the Treloar data grouped women into 6 categories based on the timing and duration of their early and late transitions.[67]

Four subgroups were found to begin the MT on average near age 40 years, whereas 2 other subgroups began the transition much later, on average at age 46.5 years (based on age inclusion criteria most of the cohort studies of midlife women include only women represented by these latter 2 subgroups who represent only one-third of women). The average duration of the transition for the 2 older age onset subgroups and one of the early age onset subgroups was 6 years, whereas for the other 3 early age onset subgroups, the average duration was 9 to 11 years. In women with no obvious change in menstrual patterns, the MT may be quite short.

ETHNICITY

Evidence suggests that age at onset of the MT differs by ethnicity. The Harvard Study of Moods and Cycles reported that women of color had an earlier entry into perimenopause than did white women.[68] Both POAS[69] and SWAN[66] also found that African American women started the MT earlier than white women. In SWAN, duration of the MT was also longer in African American women. Studies of postmenarchal girls and adult women in the United States suggest racial/ethnic differences in menstrual cycle length and bleeding patterns across reproductive life. In the postmenarchal period, white girls have longer menstrual cycle lengths and longer bleeding episodes on average, but are less likely to report heavy bleeding than African American girls,[70,71] and 2 California studies of adult women reported that menstrual cycles of Asian women were on average approximately 2 days longer than those of white women.[72,73] Similarly, in SWAN, Chinese and Japanese women had longer menstrual cycles during the MT than white women.[49] In the SWAN DHS, probability of ovulation was lower in African American and Hispanic women than in white, Japanese, and Chinese women; however, ethnic differences were not observed in the characteristics of menstrual bleeding episodes after adjustment for body mass index (BMI).[47]

BODY SIZE

BMI and nutritional status influence reproductive function, including menstrual cycle length, amount of flow, and timing of reproductive aging. Data on whether BMI influences age at onset of the MT is contradictory.[66,68,69] Both low and high BMI are associated with longer menstrual cycles.[73–77] In SWAN, menstrual calendar data document that, during the MT, obese women have longer menstrual cycles than nonobese women.[49] BMI also influences bleeding duration and heaviness of flow, with low BMI associated with longer bleeds[70,78,79] and high BMI with shorter bleeds[70,74,80] in most, but not all, studies.[81,82] A population-based survey reported that obesity was associated with a higher frequency of flooding in both premenopausal and perimenopausal women.[55] In the SWAN DHS,[47] obesity was associated with an increased number of heavy bleeding days.

CIGARETTE SMOKING AND ENVIRONMENTAL CHEMICALS

Smoking has been associated with earlier age at menopause[83,84] and an early age at onset and shorter MT.[66,69] It is less clear whether smoking influences menstrual bleeding parameters. The evidence for an impact on menstrual cycle length is contradictory, with some studies suggesting that smokers have shorter cycles[77,85,86] and others not.[72,74,81,87] Smoking has been associated with shorter[86,87] and longer periods[81] and heavier menstrual flows,[87] but not in all studies.[47]

MEDICAL CONDITIONS

Although data are limited, medical conditions, their treatment, or their impact on nutritional status can alter or suppress menstrual function. These conditions may be particularly relevant to reproductive aging, as the burden of chronic illness increases in the midlife, but data on the impact of chronic conditions or medication are very limited. In SWAN and other studies, diabetes has been associated with an earlier age at menopause[84,88] and with premature menopause.[89] A few reports suggest that diabetes may be associated with longer menstrual cycles[17,77,90] and longer and heavier bleeding episodes in some[90] but not all studies.[47] In a recent systematic review,[91] type 1 diabetes mellitus was associated with an increased frequency of oligomenorrhea, amenorrhea, and heavy menstrual bleeding throughout reproductive life and may be associated with a shorter reproductive lifespan; however, data on its association with ovarian reserve and age at menopause are limited and inconsistent, and may depend on level of glycemic control. Type 2 diabetes mellitus before or early in the MT has been associated with an earlier age at menopause in prospective studies, but data are inconsistent.

Data are more limited for thyroid disorders. One study reported that women with a history of Graves disease were more likely to report long cycles,[77] whereas another reported that hyperthyroidism was associated with reduced menstrual flow and hypothyroidism with increased frequency of menorrhagia.[92] In SWAN, higher baseline thyroid-stimulating hormone was associated with longer bleed duration in the whole cohort,[93] but self-reported thyroid conditions were not associated with menstrual parameters in the DHS.[47] Data on the impact of uterine leiomyomas on bleeding parameters during the MT are limited, despite their association with AUB and hysterectomy.[94–96] In the SWAN DHS, fibroids were associated with shorter menstrual cycles but longer and heavier bleeding episodes.[47] AUB also may be secondary to use of oral anticoagulants.[40]

CLINICAL IMPLICATIONS

- The classic description of the MT, as a period of increased variability followed by increasingly long cycles until permanent amenorrhea is achieved, describes the experience of many women; however, 15% to 25% of women will have no or minimal change in the regularity of their menstrual cycles before the FMP and little is understood about the transition experience of women with PCOS.
- Short cycles are most frequent early in the transition, whereas long cycles are most frequent late in the transition. Longer menstrual cycles, both during the transition and throughout reproductive life, are associated with having an older age at menopause.
- The length of bleeding episodes is more variable and the amount of blood loss is frequently heavier during the MT, with an increased probability of experiencing 3 or more episodes of prolonged (10 or more days) or excessive blood loss during this reproductive life stage, particularly for obese women and women with leiomyomas. Excessive bleeding is most often associated with ovulatory cycles in this reproductive phase, although spotting and bleeding for longer than 8 days are associated with anovulatory cycles.
- Based on the STRAW+10 model, onset of the early transition is best characterized by a noticeable change in menstrual cycle lengths after age 40, defined as a persistent difference in consecutive menstrual cycles of 7 or more days. The early transition heralds the FMP, on average, 6 to 8 years later. Onset of the late transition is best characterized by a menstrual cycle of 60 or more days, with onset

occurring on average 2 years before the FMP. Identifying onset of the MT and the FMP may be difficult in women with chronic diseases associated with nutritional compromise, or in women using medications that alter hormone profiles (such as HIV-infected women taking HAART).

- Clinicians should pay careful attention to medical factors, including both medical conditions and medical treatments, that may increase menstrual blood loss or alter menstrual cycle characteristics sufficiently to obscure the onset of the MT or the FMP when treating women in the midlife, although scientific data to guide clinical practice are limited.
- Finally, although ovulation and hormonally normal menstrual cycles become rarer as women approach the FMP, such cycles continue to occur up until the FMP, with their concomitant risk of unintended pregnancy.

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