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Menstruation and the Menopause Transition

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SYNOPSIS

This paper characterizes changes in menstrual bleeding during perimenopause, including bleeding changes that represent markers of the menopausal transition. Recent results from the Study of Women's Health Across the Nation (SWAN), a multiethnic cohort study of midlife women, as well as data from other cohort studies of women in the midlife are reviewed. Emerging data describing subpopulation differences in the transition experience is highlighted . Early transition, defined as a persistent difference in consecutive menstrual cycle length of seven or more days, begins on average 6-8 years before the FMP. Late transition, defined by an episode of 60 or more days of amenorrhea, begins on average two years before the FMP. When treating women in the midlife, clinicians should pay careful attention to medical factors, including both conditions and treatments, that may increase menstrual blood loss or alter menstrual cycle characteristics sufficiently to obscure the onset of the menopausal transition or the FMP.

Keywords

menstruation; menstrual cycle; menopause; perimenopause

Introduction

In broad strokes, the nature of change in menstrual bleeding patterns as women approach and transition through the menopause were well defined over forty years ago by the classic menstrual calendar studies of Treloar[1], Vollman[2] and others[3, 4]. Our current attribution of menopause, defined retrospectively after 12 months of amenorrhea have been observed and derived from the groundbreaking paper on the probability of natural menopause after age 40, is based on the Treloar data (now referred to as TREMIN)[5]. However, these early studies told us little about subpopulation differences in the menopausal experience, nor did they provide clear insights into the specific bleeding changes that mark the onset of the transition. Over the past 15 years, a more nuanced understanding of the range and variability of women's experience has begun to emerge from the several longitudinal cohort studies of the midlife that have had women maintain menstrual calendars as they transition from pre-

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menopause to post-menopause, including the multi-site, multi-ethnic Study of Women's Health Across the Nation[6-12]

The classic studies demonstrated that menstrual characteristics change across the reproductive lifespan, with the population mean menstrual cycle length and variability declining as women age from 20 to 40 years. Prior to menopause, population variability in menstrual cycle length increases[1, 2] with the transition to menopause being characterized by an increased frequency of both very long and very short cycles. This pattern of change in menstrual cycle characteristics has been confirmed in smaller clinical studies of predominantly Caucasian women[13, 14] as well as in the more recent cohort studies where midlife women have maintained menstrual calendars[6-12]. The Massachusetts Women's Health Study (MWHS) found that, among women over age 50 years, short menstrual cycles and short bleeding/spotting episodes occurred more frequently during early perimenopause while menstrual cycles of 90 days or longer occurred later in the transition[15]. Increasingly longer menstrual cycles generally signal proximity to the final menstrual period (FMP). The Melbourne Women's Midlife Health Project (MWMHP) reported that menstrual cycle length increased in the last 20 menstrual cycles before the FMP as compared to earlier menstrual cycles.[16] The SWAN Daily Hormone Study also observed that short menstrual cycles less than 21 days were common in early perimenopause, with both short and long menstrual cycles more likely to be anovulatory.[17]

Treloar was the first to define the concept of a menopausal transition and to estimate age at onset of the transition based on visual inspection of the menstrual history of 291 women during the 12 years preceding the FMP.[18] He estimated the median age of entry into the transition to be 45.5 years, with a median duration of the transition of 4.8 years. The concept of late perimenopause was introduced by Brambilla and colleague, in order to predict the likelihood, based on interview questions, that a woman would be postmenopausal at subsequent interviews.[19] Based on data from the MWHS, they estimated the median age at entry into the late perimenopause, defined as a self-report of 3 to 11 months of amenorrhea, to be 47.5 years.[8]

Clinicians have long been aware that women's menopausal experiences differ markedly, and that the classic patterns described above capture the experience of many but not all women. In one clinical study, 12 % of women experienced sudden amenorrhea[20], while another study documented women's self report of experiencing regular cycles until the onset of menopause[21]. Recently, several studies have begun to examine subpopulation variability in the experience of the menopausal transition. The limited data to date corroborates this clinical understanding, identifying subgroups of women whose menstrual patterns differ from the normative pattern described by Treloar and colleagues, and assessing factors associated with differences in timing of the transition and in women's experience of changes in cycle characteristics. Using the TREMIN data, the first author of this paper and colleagues modeled within-woman change in menstrual cycle variability after age 35 and calculated that the menopausal transition lasts from 6-10 years following the onset of increased variability, depending on a woman's characteristic menstrual patterns prior to and during the transition as well as on the age at onset of the transition[21]. Approximately 15 percent of women experienced minimal change in their menstrual characteristics before the FMP. In another analysis of TREMIN data, Gorrindo and colleagues proposed that women's menstrual patterns could be categorized into five subtypes based on several key features related to mean and variability across the lifespan.[22] Although they did not explicitly assess changes at the time of transition, they noted that in addition to the most common pattern (where menstrual cycle lengths increase as menopause approached), about 25 per cent of women appeared to have no or minimal change in menstrual cycle variability or mean length

before their FMP.[22] In SWAN, longer menstrual cycle lengths as well as more variable menstrual cycles are associated with a shorter time to FMP.[23]

Menstrual cycle characteristics during the menopausal transition differ, to some extent, by age at menopause. Women with later menopause have longer mean cycle length and greater variability two years before menopause than women with earlier menopause,[5] with differences most notable at the extremes of menopausal age. Women with later menopause have also been found to have longer mean cycle lengths throughout reproductive life[24] and in the nine years prior to menopause[25].

Bleeding markers of the early and late menopausal transition

At the turn of the millennium, the stages of ovarian aging were not yet understood. Recognizing the importance of clearly defining the stages of reproductive aging as well as of identifying valid, reliable and clinically useful criteria for the onset of each stage of the menopausal transition, the Stages of Reproductive Aging Workshop (STRAW) was convened in 2001. Based on a consensus discussion of scientific evidence, STRAW recommended that reproductive life be characterized by 7 stages.[26] Prior to menopause, reproductive life was divided into the reproductive years (3 stages) and the transition years (2 stages). Postmenopausal years (2 stages) follow the final menstrual period (FMP). Given limitations at that time in the scientific understanding of ovarian aging and in the availability of valid, reliable, and widely available assays, STRAW staging criteria were limited to menstrual markers and qualitative changes in follicle-stimulating hormone (FSH). STRAW characterizes entry into the early transition by increased levels of follicle stimulating hormone (FSH) and increased variability in menstrual cycle length, defined as menstrual cycle length >7 days different from normal. Entry into the late transition was characterized by the continued elevation of FSH and the occurrence of >= 2 skipped cycles or amenorrhea of >= 60 days.

STRAW's recommended staging approach is conceptually consistent with prior definitions of the menopausal transition, however the proposed bleeding criteria for the early and late transition included important departures from then current clinical and research practice. Following STRAW, the ReSTAGE Collaboration conducted empirical analyses to assess the validity and reliability of STRAW's menstrual criteria in four cohort studies including SWAN, TREMIN, the Melbourne Women's Midlife Health Project (MWMHP) and the Seattle Midlife Women's Health Study (SMWHS).[27] Their findings supported and clarified many of the STRAW recommendations.

Specifically, based on results from the MWHS[19], SWAN[10] and other longitudinal cohort studies of midlife women[6] have used amenorrhea of 90 days or more as their criterion for entry into the late stage of the menopausal transition, the definition also commonly used in clinical practice. STRAW's recommendation to use a shorter duration of amenorrhea, specifically 60 or more days, was based on emerging results from menstrual calendar data in TREMIN[28], the SMWHS[9] and the MWMHP[16] studies. Each of these studies observed that a somewhat shorter interval of amenorrhea was equally predictive of the approach of the FMP and less likely to misclassify the subpopulation of women who do not experience extended episodes of amenorrhea prior to their FMP as late perimenopausal when they were in fact already postmenopausal. The SWMHS had recommended occurrence of a skipped cycle as a criterion for onset of the late menopausal transition[9], the MWMHP had recommended the 42-day running range (difference between the longest and shortest cycle across 10 cycles) as a criterion[16], and a reanalysis of TREMIN had recommended a 60-day cycle[28].

Re-STAGE analyses demonstrated that, across the four cohort studies, an episode of amenorrhea of 60 days or longer cycle occurred on average 0.5 to 1.5 years earlier than an

episode of amenorrhea of 90 days or longer, although in roughly one-third of the women the first occurrence of a 60 day or longer cycle was in fact 90 days or longer.[29] In contrast, a remarkable concordance was noted between the age at occurrence of each of the other proposed criterion. For example, in 65-74% of women, a 60-day or longer cycle occurred on the exact same bleeding episode as a running range > 42-days occurred on the exact same bleeding episode, and occurred within one year of each other in 86-94% of women. After age 40, the median time from occurrence of these bleeding markers of late transition to FMP was on average 1.5-2.3 years for at least 90-days of amenorrhea and 2.6-3.3 years for the other three bleeding markers. All the proposed bleeding markers of late transition identified women who were closer to achieving their FMP compared to women who had not yet experienced these menstrual changes.

Based on these findings and the fact that 90 or more days of amenorrhea was not observed in 10-20% of women across the four studies, while 60 or more days of amenorrhea was observed in 90-100% of women, ReSTAGE recommended using 60 or more days of amenorrhea after age 40 as the bleeding criterion for onset of the late menopausal transition[27]. Occurrence of 60 or more days of amenorrhea is also the most easily identified description -- by women, clinicians, and researchers -- of the menstrual phenomenon of interest. Evaluation of the association between these bleeding criteria and changes in serum FSH levels suggests that the 60-day criterion correlates well with underlying hormonal changes that characterize the transition.[30] In the clinical setting, among women age 40-44 years old, requiring the repeated occurrence of an episode of amenorrhea of at least 60 days may help distinguish women who are in fact in late menopause from women who are experiencing an aberrant long cycle secondary to life stress or other environmental insults[31]. In SWAN and MWMHP, a single annual early follicular phase serum FSH level was less predictive of proximity to the FMP than occurrence of an episode of amenorrhea of at least 60 days, but given an episode of amenorrhea, women with higher serum FSH concentrations were more likely to achieve their FMP than women with lower levels of FSH[30]. Notably, although experience of hot flashes is a marker of the late menopausal transition in the absence of information about occurrence of 60-day cycles or FSH level, it adds no information about the proximity of the FMP when information on these other, latter markers of the transition are available.[30]

Bleeding criteria for entry into the early transition have been more controversial,[9, 16, 28] as the bleeding changes that mark initial onset of the transition tend to be more subtle, often being apparent to women before they can be easily assessed by a clinician or researcher. Most longitudinal cohort studies to date, including SWAN and the MWMHP, have relied on women's self report of changes in menstrual function, with no clear definition of what constituted "change" or "irregularity". Following results from the SMWHS[9], STRAW proposed that the criterion for defining the increased variability that marks entry into the early menopausal transition be a "change in cycle length of 7 or more days from normal"[2]. After evaluating several proposed menstrual criteria for the early transition, including those proposed by the MWMHP (the occurrence of more than two menstrual cycles outside the 21 to 35 day range over 10 cycles)[16], the SMWHS (the occurrence of a 7 or more day difference in length between consecutive menstrual cycles that repeated within the next 12 months)[9], and TREMIN (standard deviation in menstrual cycle length greater than 6 or 8 days or a 45 day menstrual cycle)[28], ReSTAGE suggested that a change in cycle length of 7 or more days may be the most appropriate criterion for onset of the early menopausal transition[32].

ReSTAGE found that across the four cohort studies, a persistent 7 or more day difference in consecutive menstrual cycles occurred earliest and was the only proposed criterion that occurred consistently earlier than 60 days of amenorrhea.[32] After age 40, the median time

from occurrence of a persistent 7 or more day difference in consecutive cycle lengths to FMP was 5-8 years. Annual measures of serum FSH were strongly associated with occurrence of each of the bleeding criteria, although at any given FSH value, associations were highest for the persistent 7 or more day difference in menstrual cycle length. Thus ReSTAGE's empirical findings supported the STRAW recommendation that this relatively small but marked change in menstrual cycle length be used as the bleeding criterion for early transition. Recently published data from SWAN[33] and the Michigan Bone Health and Metabolism Study (MBHS)[12] on trajectories of change in FSH from late-reproductive life through the FMP, indicate that the initial rise in FSH occurs on average about 7 years prior to the FMP, which is consistent with the timing of onset of the early transition defined by the 7 or more day difference in cycle length criterion.

Other investigators[7, 34-36] have provided additional evidence regarding the validity of STRAW's proposed criteria based on their association with predicted changes in hormone profiles. The Penn Ovarian Aging Study has demonstrated that small changes and single occurrences of change in menstrual cycle length are associated with change in inhibin-B and FSH levels.[7] Efforts are continuing to identify the most useful menstrual marker of the onset of early menopausal transition. Several recent studies suggest that declines in inhibin-B and anti-mullerian hormone (AMH) may prove the most useful markers of onset of the early transition.[11, 37, 38]

The STRAW criteria are now widely considered the gold standard for staging ovarian aging. However. STRAW specifically excluded 7 categories of women, including those with chronically irregular menstrual cycles or hysterectomies, smokers and women with a body mass index >30 kg/m^2.[26] Emerging data from SWAN and other studies suggest that while smoking and body size influence endocrine levels and the timing of transition, these factors do not alter the pattern or stages of ovarian aging.[33,39,44]

Defining menopausal status in women who have had a hysterectomy and in women with endocrine or medical conditions that may have an impact on menstrual bleeding patterns is more challenging. The Women's Ischemia Syndrome Evaluation (WISE) study proposed an algorithm based on age, time since last menses, surgery history and serum hormone values to classify women as peri- or post-menopausal in their population of women.[45] When applied to the SWAN cohort, substantial concordance with SWAN's menstrually-based classifications was observed, but further development of this algorithm is needed to distinguish between early and late peri-menopause. Recent advances in our understanding of trajectories of change in FSH, E2, AMH and Inhibin-B should facilitate development of such an algorithm.

Polycystic ovarian syndrome (PCOS) is characterized by oligomenorrhea. Current evidence suggests that women with PCOS have more antral follicles and higher serum AMH than control women[46], which implies that women with PCOS may have increased ovarian reserve and a later age at menopause[47]. Ongoing analyses focused on identifying subtypes of change in menstrual patterns as women approach the menopausal transition and FMP, like that reported by Gorrindo and colleagues[22], should help clarify how best to stage women with this condition and others who do not menstruate regularly. Distinguishing amenorrhea secondary to weight loss and nutritional compromise from onset of the late transition or menopause can be particularly complex in women with chronic medical conditions, such as HIV/AIDS. Recent studies have also demonstrated lower FSH levels in HIV-infected women, secondary to use of opiates, and elevated E2 among women treated with HAART.[48]

Developing clear, easily observable and easily communicable criteria for menopausal staging is of particular importance to ensure that women, clinicians and researchers are

describing the same phenomenon, as women currently appear to rely only partially on menstrual characteristics to define their menopausal status[49]. In an early SWAN study of the correspondence between women's attributions and SWAN's classification of menopausal status, menstrual patterns explained about half the variance between menstrually-based and self-defined menopause status, with older women classifying themselves later in the transition. Notably, women with vasomotor symptoms tended to self-designate themselves as being in transition regardless of their menstrual patterns.

In the MWMHP, information on self-reported change in frequency improved prediction of proximity to the FMP, as more than half the women reporting change became postmenopausal within 4 years, compared to only a small proportion of those reporting no change. [50]

Characteristics of menstrual bleeding

Another hallmark of the menopausal transition is change in the amount and duration of menstrual flow. Increased duration of menstruation as well as heaviness of bleeding episodes have been reported in both clinical studies, population based-surveys and cohort studies of midlife women.[4, 51-53] The classic study of menstrual blood loss volume documented that 50-year-old women bled about 6 ml more than women aged 20-45, while heavy bleeding is experienced most commonly by women approaching the FMP, as indicated by the 90th percentile of menstrual blood loss being 133 ml in women aged 50, versus 86-88 ml for women aged 30-45.[54] A similar result was found in a recent study that quantified blood loss across two bleeding episodes in Australian women aged 21-55. Although mean blood loss did not differ during late menopausal transition, the range of menstrual blood loss was significantly greater among women in late transition[52]. Consistent with data on the relationship between high estradiol (E2) and increased blood loss, Hale and colleagues found that menstrual blood loss in excess of 200 mL was associated in ovulatory cycles with high E2 levels,[33,55] as well as with the late menopausal transition itself[52]. In a population-based menstrual calendar study of Danish women, onset of irregular cycles as women entered the menopausal transition was associated with increased variability in the duration of bleeding, with increased frequency of spotting and bleeds lasting 10 or more days and with increased variability in women's subjective reports of the amount of menstrual flow.[56]

The SWAN Daily Hormone Study has examined menstrual characteristics in early perimenopausal women.[17] Consistent with Hale (2010), in the SWAN Daily Hormone Study, self-reported heavy bleeding was less frequent following anovulatory cycles than followiung ovulatory cycles, with 20% of cycles being anovulatory cycles.[17] However both short (1-3 days) and long (>8 days) duration of menstrual bleeding were associated with anovulation. Self reports of heavy bleeding were associated with obesity and self-reported leiomyomata, but were unrelated to steroid hormone concentrations. Ethnic differences in heavy bleeding were not apparent after adjustment for self-reported leiomyoma and body mass index.

Factors that influence menstrual characteristics during the menopausal transition

Although few studies have examined factors that influence menstrual cycle characteristics during the menopausal transition, available data indicate that factors known to influence menstrual cycle length as well as the amount and duration of menstrual flow throughout reproductive life[57] also influence population differences in bleeding patterns at the end of reproductive life. Mostly, research from SWAN and other studies has focused on factors that

influence differences in hormone levels and hormone trajectories. That data is summarized elsewhere in this volume.

Ethnicity

Data on racial and ethnic differences in menstrual bleeding patterns remains relatively limited. Studies of postmenarcheal girls have found that Caucasian girls have longer menstrual cycle lengths and longer menstrual bleeding, but are less likely to report heavy bleeding than African-American girls.[58,59] The Semiconductor Health Study and the Women's Reproductive Health Study found, based on menstrual calendar data, that Asian women had adjusted menstrual cycle lengths that were approximately two days longer than cycles for Caucasian women.[60,61] In one European study which utilized retrospective questionnaire data, Caucasian women reported having mean cycle lengths that were a half day longer than non-Caucasian women.[62] Studies of ethnic differences in the perimenopause have primarily examined timing and hormone parameters, and not menstrual characteristics. In the Harvard Study of Moods and Cycles, women of color had an earlier entry into perimenopause than white women,[63] while in the Penn Ovarian Aging Study, African-American women started the menopausal transition earlier than Caucasian women, but no ethnic difference was observed in timing of transition to later stages[64]. In contrast, SWAN reported that older age was associated with a higher hazard ratio for menopause in African-American, Japanese and Chinese women than in Caucasian women.[23] As discussed in detail elsewhere in this volume, ethnic differences in hormone profiles across the menopausal transition have been observed in SWAN; however, in the SWAN Daily Hormone Study ethnic differences were not observed in the characteristics of menstrual bleeding episodes[17].

Body Size

Both low and high body mass index are well known to influence menstrual cycle characteristics.[57] Low BMI has been associated with longer menstrual cycle length in postmenarcheal girls[59] and young adult women[65,66]. Higher BMI has also been associated with longer menstrual cycle length.[61,62,66-68] In the *MBHS* , the lowest body fat mass deciles and the highest body fat mass deciles were associated with longer menstrual cycle length.[66] BMI has been associated with bleeding duration and heaviness of flow. Low BMI has been associated with longer bleeding duration.[58,69,70] High BMI has been associated with shorter bleeding duration.[58,65,71,72] The MBHS did not find an association with bleeding duration and BMI.[73] In a Danish study of premenopausal and perimenopausal women, obesity was associated with higher frequency of flooding.[56] In the SWAN DHS, heavier women had shorter cycles than women with BMI <25kg/m^2;[43] but obesity was also associated with an increased number of heavy bleeding days.[17] The Harvard Study of Moods and Cycles found the age-adjusted incidence rate of perimenopause to be 1.58 times higher among obese women as compared to normal weight women.[63] However, the Penn Ovarian Aging Study did not find an association between BMI and entry into any stage of menopause.[64] Similarly, SWAN has not found an association between BMI and age at or proximity to the FMP.[23,74]

Medical Conditions

Although less frequently examined, evidence suggests that medical conditions also impact menstrual characteristics, and consideration of such conditions may be particularly relevant during the menopausal transition as the burden of chronic illness increases. Endocrine disorders including diabetes have been associated with an earlier age at menopause.[75] In SWAN, diabetes has been associated with premature ovarian failure[76] and with earlier age at menopause[74]. Diabetes may also be associated with longer menstrual cycles,[68,77] as well as with longer bleeding duration and heavier bleeding episodes[77]. In the SWAN Daily Hormone Study, women with diabetes had longer menstrual cycles than non-diabetic women[17]; however, no difference was found in the duration or amount of menstrual

bleeding. Abnormal thyroid function has also been linked with menstrual dysfunction and women with a history of Grave's disease were more likely to report long cycle lengths[68]. An early descriptive study of women with hyperthyroidism found the more severe the disease, the less menstrual blood flow. The same study found that women with hypothyroidism had higher frequencies of menorrhagia.[78] In SWAN, higher baseline thyroid stimulating hormone (TSH) levels were associated with increased duration of menstrual bleeding.[79] However, in the SWAN Daily Hormone Study, thyroid conditions were not associated with menstrual cycle characteristics.[17] Although some evidence suggests that uterine leiomyomas are associated with abnormal bleeding and menstrual cycle length, the evidence is contradictory[80-84] In the SWAN DHS/menstrual calendar study, fibroids were associated with shorter menstrual cycle length, but longer bleeding duration and heavier bleeding episodes.[17] Menorraghia may also be secondary to use of oral anticoagulants.[85]

Cigarette Smoking

Studies on the impact of tobacco smoking on menstrual characteristics are inconsistent, with some studies suggesting an association with shorter menstrual cycle lengths[62,68,86] and others finding no difference.[60,,65,73,87] Smoking has been associated with both shorter[86,87] and longer bleeding duration[73], and increased amount of bleeding.[87] In the SWAN Daily Hormone Study, smoking history was not independently associated with cycle length, bleeding duration, or heavy bleeding.[17] However , current smoking was associated with earlier age at and closer proximity to the FMP.[23, 74] In the Penn Ovarian Aging Study, smoking was also associated with an increased probability of transition into each stage of the menopausal transition, such that smokers had a shorter transition than non smokers.[64]

Summary and Clinical Implications

Although the classic description of the menopausal transition--[18] as a stage first marked by increased variability in menstrual cycle lengths followed by increasing frequency of very long cycles until permanent amenorrhea occurs--describes the experience of the majority of women, marked differences occur in the magnitude of change in women's menstrual experience. Approximately 15-25% of women experience minimal or no change in menstrual regularity prior to their FMP. Short cycles are most frequent in the early transition while long cycles are most frequent in the late transition, with older age at menopause associated with longer menstrual cycles, both during the transition and throughout reproductive life. The duration and amount of blood loss during the menopausal transition is more variable, and women are most likely to experience excessive blood loss during this reproductive life stage, particularly during the late transition. Excessive bleeding is most often associated with ovulatory cycles in this reproductive phase, although spotting and bleeding more than eight days are associated with anovulatory cycles. Heavy bleeding during the transition is more common in obese women and in women with leiomyomas.

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 seven or more days, which occurs on average 6-8 years before the FMP. Onset of the late transition is best characterized by an episode of 60 or more days of amenorrhea, which occurs on average two years before the FMP. Evidence suggests that the STRAW stages are applicable to women who smoke and to women of all body sizes, however, identifying onset of the menopausal transition 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). PCOS appears to be associated with a later age at menopause, and more research is needed to assess how women with PCOS experience the menopausal transition. 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 menopausal transition or the FMP when treating women in the midlife.

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