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The ReSTAGE Collaboration: Defining Optimal Bleeding Criteria for Onset of Early Menopausal Transition

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Abstract

Study objective—Criteria for staging the menopausal transition are not established. This paper evaluates five bleeding criteria for defining early transition and provides empirically-based guidance regarding optimal criteria.

Design/Setting—Prospective menstrual calendar data from four population-based cohorts: TREMIN, Melbourne Women's Midlife Health Project(MWMHP), Seattle Midlife Women's Health Study(SMWHS), and Study of Women's Health Across the Nation(SWAN) with annual serum follicle stimulating hormone (FSH) from MWMHP and SWAN.

Participants—735 TREMIN, 279 SMWHS, 216 MWMHP, and 2270 SWAN women aged 35-57 at baseline who maintained menstrual calendars.

Main outcome measure(s)—Age at and time to menopause for: standard deviation >6 and >8 days, persistent difference in consecutive segments >6 days, irregularity, and >=45 day segment. Serum follicle stimulating hormone concentration.

Results—Most women experienced each of the bleeding criteria. Except for persistent >6 day difference which occurs earlier, the criteria occur at a similar age and at approximately the same age as late transition in a large proportion of women. FSH was associated with all proposed markers.

Conclusions—The early transition may be best described by ovarian activity consistent with the persistent >6 day difference, but further study is needed, as other proposed criterion are consistent with later menstrual changes.

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Keywords

Menopausal Transition; Menopause; Menstrual cycle; Aging; Ovarian Function; Follicle Stimulating Hormone

INTRODUCTION

A staging system for reproductive aging is of increasing interest to clinicians and investigators in order to better predict the timing and duration of the menopausal transition and to standardize definitions for cross-study comparisons. Although the final menstrual period (FMP) marks a period of critical change in a woman's physiology and reproductive status (1), definitive criteria for determining when the transition to the FMP begins have yet to be established. Treloar first described the menopausal transition as a phase of menstrual life when a persistent increase in variation between menstrual intervals occurred (2). He defined the onset of the transition by visual inspection of women's menstrual calendars. However, sequential menstrual histories are not available for most women and the lack of a specific replicable method to identify the onset of the transition prospectively has hindered research in this area and been a source of frustration to midlife women and their clinicians.

At the Stages of Reproductive Aging Workshop (STRAW) in 2001, an initial consensus was reached on an approach to staging reproductive aging including specific menstrual and hormonal changes that could be used as markers of the onset of each stage(3). STRAW proposed that reproductive life could be characterized by seven stages. Prior to menopause, reproductive life is divided into the reproductive years (3 stages) and the transition years (2 stages, early and late transition). Postmenopause (2 stages) follows the final menstrual period (FMP).

STRAW's recommended bleeding criterion for onset of the early menopausal transition was a variable cycle length, more than seven days different from normal. This definition was based on an adaptation of recent results from three studies(4-7). Together these three studies identified five different criteria, or marker events, for the onset of early transition.

Taffe and Dennerstein, using data from the Melbourne Women's Midlife Health Project (MWMHP), suggested that onset of the transition could be defined by the onset of "irregularity", defined as the occurrence of more than two menstrual cycles outside the 21 to 35 day range over 10 cycles (5). Mitchell and colleagues, using data from the Seattle Midlife Women's Health Study (SMWHS), proposed as a criterion the occurrence of greater than a 6 days difference in length between consecutive menstrual cycles that repeated within the next 12 months (4). Analyses of TREMIN data suggested a standard deviation in menstrual cycle length greater than 6 or 8 days or a 45 day menstrual cycle as possible criteria for onset of early transition (7). The STRAW recommendations also included increase in FSH values as a criterion for the early transition, but no specific numerical criterion was provided (3).

Although based on expert consensus, STRAW's recommendations were not empirically driven and have not been validated. Subsequently, investigators from several major cohort studies of the menopausal transition formed the ReSTAGE Collaboration to identify the most reliable and most easily definable markers for onset of the early and late menopausal transition and to validate STRAW's recommendations empirically. Key questions are whether the various proposed bleeding criteria for the onset of the menopausal transition define a similar time in women's reproductive lives and whether criteria developed within one cohort are replicable in other cohorts. This paper addresses these questions, focusing on the early menopausal transition stage, using menstrual calendar data from four large cohort studies of the menopausal

transition: TREMIN (8), MWMHP (9), SMWHS (4), and the multi-site, multi-ethnic, Study of Women's Health Across the Nation (SWAN) (10). Specifically we compare the five proposed bleeding criteria for onset of the early stage of the menopausal transition within and across the four data sets. For each criteria, we assess their frequency of presentation, and their timing relative to each other, relative to onset of the late menopausal transition and relative to the FMP. We also assess the longitudinal association between occurrence of these criteria and underlying hormonal changes using annual measures of serum FSH levels available from MWMHP and SWAN. The assays used in these two cohort studies have been cross-validated to provide comparability.

MATERIALS AND METHODS

We conducted secondary analyses using prospectively collected menstrual calendar information from four cohort studies of midlife women, as well as data on annual serum FSH in two of these cohorts. These analyses were approved by Institutional Review Boards at the Universities of Michigan, Washington, Massachusetts and Melbourne. Although slightly different in format, the menstrual calendars identified the dates of bleeding in a comparable manner.

Briefly, *TREMIN* (8) obtained prospectively recorded menstrual calendars across the entire reproductive life span. From 1935-1939, 1997 women students at the University of Minnesota were enrolled and maintained menstrual calendar cards that covered one year. At the end of each year, women completed a short questionnaire on marital status, medical treatments for menstrual difficulties, contraception and pregnancies. This analysis includes records from 735 premenopausal women who were still participating and not using hormones at age 35, the baseline age for these analyses, and who contributed at least 10 untreated bleeding segments (the term bleeding segment is used in lieu of menstrual cycle as menstrual calendar data do not distinguish menstrual from nonmenstrual bleeds) (11). (Data tape TRUST998. FINAL supplied by TREMIN in March 1993).

The Melbourne Women's Midlife Health Project (MWMHP) initiated a cross-sectional survey in 1991 of 2001 Australian-born women of Anglo-European heritage identified by random telephone digital dialing (9). Subsequently, 438 women, aged 45 -55 years, who had menstruated in the prior 3 months (premenopausal or early perimenopausal), and were not using hormones, were enrolled in a longitudinal study (12). They maintained prospectively recorded menstrual calendar cards that covered one year (13). Annual assessments included symptom experience, measured height and weight, smoking history, hormone use, experience of hot flashes, and blood sampling to measure follicle stimulating hormone (FSH). This analysis included 216 participants who contributed at least 10 untreated bleeding segments, 193 of whom provided at least one serum sample for FSH measurement prior to initiation of exogenous hormones.

Fasting morning blood samples for hormone assays were taken between days 4 and 8 of the menstrual cycle for those still cycling, or after 3 months of amenorrhea as previously described (14). FSH was measured initially by radioimmunoassay (RIA) in year one (12). Two subsequent changes in method were used, the automated Microparticulate Enzyme Immunoassay (Abbott Diagnostics IMX Analyser Chicago, IL, USA) (years 2 and 3) and for all samples from year 4 onwards, the TOSOH AIA1200 automated Enzyme Immunoassay. Correlation coefficients were: FSH (IMX) and RIA, 0.98, and FSH (TOSOH) with IMX 0.99. Inter- and intra-assay coefficients of variation were 5.4% and 4.0% respectively.

The Seattle Midlife Women's Health Study (SMWHS), an ongoing longitudinal study, began in 1990 (4) with a population-based sample of 508 English-speaking pre or perimenopausal

women aged 35-55, with at least one menstrual period in the previous 12 months, at least one intact ovary, and not pregnant/lactating. They maintained a prospectively recorded menstrual calendar that covered one year. Height and weight were measured in 1997 and 2000. An annual health questionnaire acquired information on self-reported weight, height, smoking history and hormone use. This analysis includes records of 279 women who contributed at least 10 untreated bleeding segments.

Study of Women's Health Across the Nation (SWAN) is an ongoing multi-ethnic, multi-site longitudinal community-based study of middle-aged women begun in 1995(10). A cross-sectional survey randomly selected women who were aged 40-55 years and self-designated in one of two targeted racial/ethnic groups per site. About 450 women per site were recruited into a longitudinal study including Caucasian women and women from one minority group (African Americans at four sites; and Japanese, Chinese, and Hispanic women at one site each). Eligible women were aged 42-52 years with intact uterus, not using hormones, and had a menstrual period in the previous 3 months (premenopausal or early perimenopausal). Women maintained prospectively recorded monthly menstrual calendar cards. Annual assessments included symptom experiences, measured height and weight, smoking history, hormone use, and blood sampling to measure FSH. This analyses includes up to six years of menstrual records of 2270 women who contributed at least 10 untreated bleeding segments 2223 of whom provided at least one serum sample for FSH measurement prior to initiation of exogenous hormones.

Blood was drawn between days 2-5 of the follicular phase of the menstrual cycle in regularly cycling women. Serum was frozen at -80 degrees Centigrade and sent on dry-ice to the SWAN Endocrine Laboratory at the University of Michigan. Hormone assays were conducted using an ACS-180 automated analyzer (Bayer Diagnostics Corp, 115 Norwood Park South, Norwood, MA. 02062-4658). Serum FSH concentrations were measured with a two-site chemiluminometric immunoassay that uses constant amounts of two monoclonal antibodies (provided by Bayer Diagnostics). Each antibody is directed to different regions on the beta subunit (one coupled to paramagnetic particles and the other labeled with DMAE) with specificity for intact FSH. Inter- and intra-assay coefficients of variation were 12.0% and 6.0 %, respectively.

Cross-validation of FSH serum assays used in the Melbourne and SWAN studies was conducted. As neither measure can be treated as the gold standard, we created standardized values using an equating procedure (15) such that the standard scores (z scores) of the log FSH distribution from each assay are equated to each other. MWMHP assays are equated to SWAN values and all analyses used these standardized FSH values. For MWMHP, SMWHS and SWAN, body mass index (BMI) is a linear interpolation of annual height and weight measures.

Defining bleeding parameters

Ascertainment of the onset of early and late transition and the date of the final menstrual period (FMP) were based on the menstrual calendar data. Using definitions recommended by WHO (11), a bleeding episode is a period of consecutive bleeding days; a bleeding-free interval is a period of consecutive bleeding free days; and a bleeding segment is a bleeding episode and the subsequent bleeding-free interval. In ReSTAGE, a single day of bleeding as well as consecutive days of spotting/bleeding were coded as bleeding episodes. Bleeding-free intervals had to consist of at least three days. One or two bleed-free days between two bleed days were considered part of the bleeding episode. Pregnancies and the first three segments post birth/abortion were considered nonmenstrual intervals and were excluded from analyses (16). For each bleeding segment, we indicated whether a woman was using any type of hormonal medication. Gaps in the menstrual record were coded as missing.

All untreated bleeding segments of each eligible woman are included in these analyses, with women contributing up to 321 eligible bleeding segments. From 41-51% of the women had intermittent missing data with a median of two gaps per woman. We developed an approach to impute missing menstrual segments; however, since results from imputed data differed little from results from unimputed data (data not shown), we present only the latter here. Gaps less than two years are ignored. Women with gaps longer than two years were censored at the gap.

Defining Bleeding Criteria for the Early Menopausal Transition

Currently, there is no accepted standard bleeding criterion for onset of the early menopausal transition. Bleeding changes proposed to mark the onset of the early transition include a defined change in menstrual segment length, segment length variability or the occurrence of segments of defined lengths. This paper compares the following five recently proposed bleeding criteria (4-7) adapted for these cross-cohort analyses:

- a. The first segment whose length is more than six days different than the previous segment and this magnitude of difference is observed again within 10 segments (persistent >6 day difference) (4);
- b. The first observation of a standard deviation (SD) over a 10-segment window greater than 6 days (SD >6 days) (7,17), with age at this marker defined as the first day of the final segment in the sequence;
- c. The first observed segment of at least 45 days (≥ 45 day segment) (7);
- d. The first observation of a standard deviation over a 10-segment window greater than 8 days (SD >8 days) (7,17), with age at this marker defined as above; and,
- e. The first observed occurrence of more than 2 segments in 10 that are <21 or >35 days, with the age at marker defined as the first day of the third extreme segment (irregularity) (5)

We specify the bleeding episode that marks when each bleeding criterion is met (hereafter referred to as the “marker event”). For comparison purposes, we also consider our recommended bleeding criterion for onset of the late menopausal transition -- the first observed bleeding segment of at least 60 days (2,7,18).

Analysis

Women were censored when they had a hysterectomy or bilateral oophorectomy, or when they began using hormonal birth control, hormone therapy or chemotherapy (Table 1). Segments during which a short-course of hormonal medication, including fertility medications, was used to treat a menstrual disorder were treated as gaps in the menstrual record.

Ideally, we would have a gold standard against which to evaluate these bleeding criteria for onset of the early menopausal transition. In the absence of such a standard, we focus on how frequently bleeding criteria occur, the timing of their occurrence and their relationship to onset of the late transition and FMP. We also consider whether bleeding criteria are associated with increasing FSH levels. In all analyses, we examine the comparability of results for the five bleeding criteria within each study and assess the consistency of results across studies.

After determining each woman's age at each of the five bleeding markers, that is the age at which each marker event occurred in her menstrual calendar record, we calculated, among women with an observed FMP, the proportion in whom a given bleeding criterion was observed before the FMP occurred. We then examined similarities in age at occurrence among the five different proposed markers of early transition and the relationship between age at these markers and age at late transition. We first determined the median age at occurrence of at each marker

event using Kaplan-Meier survival analysis which incorporates information on observed age at marker and, for censored women, age at censoring to estimate the distribution of age at transition. Percentiles from the survival curves were used to generate side-by-side box plots. We next assessed whether the criteria identify a similar time in an individual woman's reproductive life by calculating within-individual differences in age at markers. Paired t-tests were used to assess whether these differences were significant. As several of the markers are defined by patterns observed over a 10-segment sequence, we consider whether two markers occur within one year of each other. We then considered each criterion's proximity to FMP. We modeled the hazard function of FMP given age at marker using a varying-coefficient Cox model(19) that incorporates censored and uncensored women. Both age at marker and age at menopause events were subject to censoring and their association varies with age at the marker (6). We plotted the estimated time from marker to menopause, by age at marker for TREMIN. We estimated time from marker to menopause for women who had not experienced the markers by the end of a given age interval and for women who experienced the marker within that age interval.

To determine associations of markers with serum FSH in SWAN and MWMHP, we conducted pooled logistic regression analyses (20) as an approximation of Cox regression analysis with time varying predictors for time to first occurrence of each bleeding marker. In this approach, observations are pooled over timepoints and a logistic regression model for occurrence of the bleeding marker is estimated; observations after the first occurrence of the bleeding marker are omitted, analogous to removing them from the risk set in survival analysis. Each marker occurrence was modeled as a function of time-varying log-transformed serum FSH, before and after adjusting for concurrent chronologic age, baseline body mass index and, in SWAN, ethnicity. We tested interactions between log FSH and each covariate with the bleeding markers. Models were estimated separately for SWAN and MWMHP. Based on these models, we plotted the estimated probability that a marker had occurred for various values of FSH, and computed odds ratios for marker occurrence by categorized serum FSH. Estimated probabilities of marker occurrence reflect not only the role of FSH but also the age distribution of each study. In contrast, the odds ratios indicate the association with FSH apart from age.

RESULTS

Mean age of participants at baseline varied across cohorts. All participants were aged 35 years in TREMIN, while the mean age was 41.3 years in SMWHS, 45.9 in SWAN and 48.7 in MWMHP. Mean BMI at cohort enrollment was 25.3 kg/m² in SMWHS, 25.5 in MWMHP and 27.6 in SWAN. Fourteen to 18% of the women were current smokers and 13-22% reported having hot flashes at the time of their baseline visit. TREMIN did not assess BMI, smoking or hot flashes. In SWAN 23% of the women were African American, 51% Caucasian, 9% Chinese, 6% Hispanic and 11% Japanese. In SWMHS, 83% of the women were Caucasian, 7% were African American, and 10% were other ethnicities. All women in TREMIN and MWMHP are Caucasian. Median menopausal age in women with an observed FMP was 50.5 years in TREMIN, 51.2 years in SWAN, 52.3 years in SMWHS and 53.8 years in MWMHP.

For all proposed criteria, 95% to 100% of the women in each of the cohorts experienced the criterion, with the exception that, in SWAN, the two criteria based on standard deviation were observed in just 85% of women (Table 2). This is attributable to the requirement of a 10-segment reference window and the shorter duration of follow-up in SWAN.

Figure 1 presents boxplots of the Kaplan Meier estimates of the distribution of age-at-marker for the bleeding criteria within each cohort. The distributions of age at the five markers of early transition overlap considerably. However, within each study, the persistent >6 day difference occurred earliest, with median age at its occurrence being 3-4 years earlier than the other

markers of early transition in TREMIN and SMWHS and 0.8-1 year earlier in the two older cohorts, MWMHP and SWAN. The difference in median age of the other four proposed markers of the early transition was just six months in the older cohorts, one year in SWMHS and 2 years in TREMIN. Although the proposed bleeding markers of the early transition tend to occur earlier than the bleeding marker of late transition, a segment of at least 60 days, the distributions do overlap. For example, in the TREMIN, the median age at presentation of a persistent >6 day difference in consecutive segment lengths is 41.0 years as compared with median ages of 44.2 to 46.4 years for the other four bleeding markers and 48.8 years for age at onset of the late transition. Similarly in MWMHP the median ages were 49.5 years as compared with 50.3-50.9 years and 52.0 years, respectively. Systematic differences in the median age-at-marker across studies are a function of the different ages at which women were enrolled, with TREMIN being the youngest and MWMHP being the oldest.

When we examined within-woman differences in age at the early markers (Table 3), results varied by age of the cohort. In SWAN and MWMHP, all pairs of markers occurred within one year of each other in 69-91% of the women with a mean difference of less than four months in age at markers other than persistent difference > 6 days. This latter marker occurred on average 8-12 months before the other markers. In the younger cohorts, TREMIN and SWMHS, persistent difference > 6 days occurred about 2-3 years earlier than the other markers. In TREMIN only, the SD >6 day marker occurred 8-21 months earlier than the other three markers.

The difference in age at each of the markers of the early transition and age at onset of the late transition (Table 3) was significant ($p < 0.001$) for all early markers in each of the cohorts with age at persistent >6 day difference most dissimilar from age at late marker across studies. In SMWHS, SWAN and MWMHP, SD >6 days occurred within a year of onset of late transition in about half of the women, while for SD >8 days and 45 day this was true for about two-thirds of the women. A larger proportion of the TREMIN women experienced each early marker more than a year before onset of the late transition.

When we assessed time from observation of the early markers to FMP, occurrence of a marker before age 40 was not indicative of the FMP being proximate. (Median time to menopause was greater than 15 years in TREMIN, the only study with relevant data.) After age 40, the median time from the early markers to menopause was 5-8 years for persistent >6 day difference, 4-6 years for SD >6 days, and 4-5 years for ≥ 45 day segment, SD >8 days and irregularity. Women who have entered the transition should be closer to the FMP, on average, than women who have not yet entered the transition. Table 4 shows the median difference in age at FMP of women who experience the marker within a given age interval and women who have not yet experienced the marker by the end of that age interval in the two datasets with adequate sample size for this analysis. In TREMIN the median difference in age at FMP is about 2-3 years earlier, and in MWMHS about 1-2 years earlier given experience of a bleeding marker of onset of the early transition.

Serum FSH was strongly related to time to first occurrence of each of the bleeding markers in the two studies with serum FSH data (Figure 2). The steepest increase in the marker probability occurred with an increase in FSH from 10 to 20 IU/L. At any given FSH value, estimated probabilities are highest for persistent >6 day difference and lowest for SD >8 days and irregularity. Upon adjustment for age, the increase in the marker probability with an increase in FSH was less steep, but FSH remained significantly positively associated with each marker. Age-adjusted odds ratios for the association between categorized FSH level and probability of first marker occurrence are presented in Table 5. Further adjustment for BMI or ethnicity resulted in little additional change in the FSH associations with markers, and including interactions of FSH with these covariates did not improve model fit in terms of the Akaike

Information Criterion (21) (data not shown). After age-adjustment, elevated odds ratios were observed in SWAN for all markers when FSH reached 20 IU/L as compared with 40 IU/L in MWMHP.

Discussion

This paper is among the first to compare proposed criteria for onset of the early menopausal transition (STRAW stage –2) within and across four large cohort studies of the menopausal transition. Across these studies, almost all women who experienced a natural menopause experienced each of the changes in menstrual function described by the proposed bleeding markers of early transition. Thus, all of the markers appear to be descriptive of change in the characteristics of menstrual bleeding as women age and transition to the FMP. Persistent >6 day difference occurs earlier than the other proposed markers. The other four proposed markers of the early transition appear to capture a relatively similar time in women's reproductive life and occur at approximately the same time as onset of the late menopausal transition in a large proportion of women. This paper also found that higher FSH levels were associated with occurrence of each of the proposed bleeding criterion for onset of the early menopausal transition.

Treloar (8) and others (22) described a pattern of increasing variability in menstrual cycles beginning at approximately 40-years of age across the population. Irregularity, as defined by Taffe and Dennerstein (5), has been associated with increasing frequency of anovulation, which presages the FMP, in other studies (23). Treloar did not divide the transition into multiple stages, and defined the onset of transition by increased variability not by length of amenorrhea. Median age at onset of transition was 45.5 years with a median duration of 4.8 years. The term "late perimenopause" was first coined by Brambilla and colleagues who, in an effort to predict the approach of the FMP, defined late peri-menopause to include both self-reported menstrual irregularity and 3-9 months of amenorrhea because both were predictive of reaching the FMP within 3 years (24). Articulation of the concept of late perimenopause led to efforts to define early and late phases of the transition (3-5,23,25,26).

The early transition has been defined in terms of within-woman variability, e.g., self-reported irregularity, while the late transition focuses on the onset of sustained amenorrhea (3). Both MWMHP (24) and SWAN (10) used self-reported change in menstrual frequency to define the early transition. Taffe and Dennerstein proposed a definition for irregularity, associated with onset of the early menopausal transition (5) as the occurrence of more than two cycles <21 or >35 days in a ten cycle sequence. This criterion predicted time to FMP in the MWMHP (6) and also in a Scandinavian study (23). Mitchell and colleagues from the SMWHS (4) proposed a system that defines three stages within the menopausal transition, with the later two stages corresponding to STRAW's early and late transition. In SMWHS, average time to FMP following onset of their second stage was 4.6 years, which is similar to Treloar's original estimate.

Our empirical comparison of proposed criteria for defining the onset of early transition raises several conceptual questions. If, on the one hand, we require that a marker of early menopause occur in all women and that it be clearly distinct from late menopausal transition, then the persistent >6 day difference may be the best candidate marker of early transition, supporting the recommendation of STRAW. However, persistent >6 day difference occurs relatively early in many women's reproductive lives, with median age at occurrence in TREMIN being 41 years old. Selection of this marker as the bleeding criterion for onset of the early menopausal transition defines the early transition as a phenomenon of the late thirties and early forties. Such timing is consistent with data on ovarian aging (27-29), with studies suggesting an increase in the rate of atresia of ovarian follicles at age 37 (30) and with studies showing an

inflection point for the increase in population-averaged FSH levels at a similar age (31). Using a marker comparable to the persistent >6 day difference marker, Gracia and colleagues found statistically significant differences in serum inhibin-B and FSH levels between women who reported this relatively subtle change in menstrual cycle length and women who did not (25).

If, on the other hand, we were to adopt any of the other proposed markers of the early transition, the proximity in timing of these markers with the onset of late transition in many women, raises a question as to whether the menopausal transition really occurs in two distinct stages in all women. Differences between women with a defined early transition versus those without might then be of scientific and medical interest. Resolution of this question needs to be addressed by establishing a link between the defined changes in menstrual bleeding patterns and additional biologic markers of the decline in ovarian reserve.

Single annual serum follicle-stimulating hormone concentrations, an indirect measure of the change in ovarian function, have been associated previously with the menopausal transition (23,25,32), but they have not been rigorously related to proposed bleeding markers of early menopausal transition. FSH levels were qualitatively included in the STRAW model for reproductive aging (3), but criterion levels were not specified. We demonstrated that increasing FSH concentrations are associated with changes in menstrual bleeding characteristics defined by each of the proposed bleeding criteria for early menopausal transition. Although an FSH level of 40 IU/L was strongly associated with the occurrence of these markers, this FSH level was similarly associated with occurrence of bleeding markers of the late menopausal transition (33). A recent publication from the cross-sectional population based National Health and Nutrition Study reported a geometric mean FSH value of 21.4 mIU/mL for women identified as being in transition (34). Additional studies of the association of bleeding criteria with other biologic markers of ovarian reserve such as inhibin and anti-mullerian hormone (14,28,31, 32,35,36) are needed.

This study has some limitations. Retrospective recall of specific menstrual events is unreliable (37-41). These analyses are based on similarly designed menstrual calendars with prospectively recorded data on menstrual bleeding. However, non-participants in the menstrual calendar component of these studies were older, heavier, and more likely to smoke currently. Thus selection bias cannot be ruled out. Left censoring and left truncation occurs in three of the studies. Among women who entered the study at later ages, the first observed occurrence of the marker may not in fact have been the actual first occurrence – the marker may have first occurred prior to study entry at an unknown age. Left censoring would cause the differences in age distributions of the markers seen in Figure 1. Left censoring – when a participant has begun the transition prior to enrollment -- can be compared to the situation in which a woman presents to a clinician in her 40's and the clinician must base her evaluation on subsequent observations. Left truncation occurs when women who began the transition at an earlier age are excluded from the cohort. Both left censoring and left truncation are likely to bias upwards estimates of age at marker and age at menopause. The impact of these biases requires further assessment. Intermittent missing data, although of potential concern, did not have a large influence on our results. We did not have information about prior menstrual history, and women with chronic irregularity throughout reproductive life may have different characteristics that signal the onset of their transition. Inclusion of these women may bias our results. We did not have information on abnormal uterine or ovarian anatomy as periodic imaging of the uterus and ovaries was not performed in these studies. Thus we were not able to document when uterine bleeding was due to organic pathologies as opposed to hormonal changes (3).

Currently proposed staging criteria(3-7,25) apply only to the case where women are not using exogenous hormones. Omission of hormone users is potentially problematic both because they represent a significant proportion of women, and because hormone users are of specific interest

given that use is more frequent among symptomatic women (42,43). Future studies should extend criteria for staging reproductive aging to apply to hormone users.

Occurrence of any of the proposed early markers before age 40 was not related to the timing of the final menstrual period. Thus before age 40, menstrual characteristics consistent with the proposed markers of early transition may be more likely to reflect a lifetime pattern of highly variable cycles or isolated perturbations in menstrual function. Future studies should incorporate information on women's menstrual history over the reproductive life course and further evaluate whether a lower age boundary for normal reproductive aging should be defined for the menopausal transition.

In conclusion, this paper provides information necessary to refine the STRAW recommendations and to facilitate development of a consensus regarding which of the extant bleeding criteria may be most optimal for defining onset of the early transition. Evaluation of the concordance between approaches and their relative ability to predict the approach of the FMP across multiple cohort studies demonstrates that several of the extant criteria are similar, suggesting that they robustly define a critical stage in reproductive life. Notably, however, currently proposed markers of the early transition appear to define two distinct times in women's reproductive lifespan. A decision as to which of these times is actually the onset of the early menopausal transition requires further consideration of the underlying biology (23) as well as studies of the association between the proposed bleeding criteria and additional markers of ovarian reserve such as inhibin or anti-mullerian hormone ((14,28,31,32,35,36). Selection of the most appropriate criterion should incorporate biological considerations such as which marker correlates best with the timing of the decline in ovarian reserve. This empirical assessment has demonstrated that relatively simple descriptions of bleeding characteristics can be used to pinpoint the occurrence of increased menstrual variability. This finding suggests the potential for developing a short questionnaire to assess reproductive stage as such descriptions may be easily observed and reported by women.

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Figure 1.

Distribution of Kaplan Meier estimates of age at markers of the Early (a is persistent >6 day difference, b is SD> 6 day, c is >=45 day, d is SD>8 day, e is irregular) and Late (f is >= 60 day segment) menopausal transition by cohort study (bold line represents 50th percentile, box represents 25th and 75th percentile, dashed line represents 10th and 90th percentiles).

Figure 2.
Estimated unadjusted associations between bleeding markers and FSH longitudinal data in a) SWAN and MWMHP

Table 1
Characteristics of the final status of women in their menstrual calendar record by cohort.

	TREMIN (n=735)		MWMHP (n=216)		SMWHS (n=279)		SWAN (n=2270) ⁺	
	N	%	N	%	N	%	N	%
FMP observed	211	28.7%	42	19.4%	52	18.6%	132	5.8%
Hysterectomy	68	9.3%	11	5.1%	9	3.2%	17	0.8%
Still menstruating	0	0	53	24.5%	34	12.2%	953	42.0%
Stopped calendar/ still menstruating	119	16.2%	48	22.2%	86	30.8%	187	8.2%
Endometrial Ablation	0	0	3	1.4%	0	0	0	0
Began Hormone Therapy	334	45.4%	59	27.3%	94	33.7%	981	43.2%
Began Radiation/Chemotherapy	3	0.4%	0	0	4	1.4%	0	0

⁺ Analysis to date of the SWAN calendar is based on the first 6 years of menstrual calendar data.

Table 2

Proportion of Women with FMP Observed in Whom Marker Events of the Early Menopausal Transition are Observed in Four Cohort Studies

	Number of Women with FMP Observed	Percent with Marker Observed
<i>Persistent Difference > 6 days</i>		
TREMIN	211	100
SMWHS	52	98.1
MWMHP	42	100
SWAN	132	100
<i>10 segment SD > 6 days</i>		
TREMIN	211	99.5
SMWHS	52	96.2
MWMHP	42	97.6
SWAN	132	85.6
<i>>=45 day segment</i>		
TREMIN	211	100
SMWHS	52	100
MWMHP	42	95.2
SWAN	132	97.7
<i>10 segment SD > 8 days</i>		
TREMIN TRUST	211	98.6
SMWHS	52	96.2
MWMHP	42	95.2
SWAN	132	84.8
<i>Irregular</i>		
TREMIN	211	100
SMWHS	52	100
MWMHP	42	95.2
SWAN	132	96.2

TABLE 3

Percent of women with difference of < one year in age of two markers and mean (se) of the difference for pairs of markers of the menopausal transition by cohort

	Tremin Percent <1 year	Mean(SE)	SMWHS Percent <1 year	Mean(SE)	SWAN Percent <1 year	Mean(SE)	MWMHP Percent <1 year	Mean(SE)
<i>Early-Early</i>								
SD>6 day – persist 6 day difference	48.4	1.69(0.17) ^a	53.6	1.70(0.18) ^a	79.8	0.67(0.02) ^a	88.1	0.71(0.05) ^a
SD>8 day – persist 6 day difference	33.5	3.10(0.21) ^a	36.9	2.30(0.22) ^a	69.2	0.94(0.02) ^a	73.7	1.03(0.07) ^a
>=45 day – persist 6 day difference	35.2	2.40(0.21) ^a	41.3	2.00(0.22) ^a	71.6	0.55(0.03) ^a	72.6	0.71(0.08) ^a
irregular – persist 6 day difference	33.1	3.48(0.20) ^a	49.7	1.91(0.21) ^a	74.1	0.76(0.02) ^a	82.2	0.93(0.07) ^a
SD>6 day - SD>8 day	75.3	-1.32(0.14) ^a	79.0	-0.68(0.12) ^a	90.0	-0.27(0.02) ^a	90.8	-0.30(0.05) ^a
SD>6 day - >=45 day	33.1	-0.67(0.12) ^a	81.1	-0.35(0.12) ^b	82.0	0.04(0.03)	88.2	-0.01(0.07)
SD>6 day – irregular	49.0	-1.74(0.21) ^a	73.4	-0.38(0.15) ^b	81.2	-0.12(0.03) ^a	87.0	-0.19(0.07) ^b
SD>8 day - >=45 day	82.7	0.64(0.13) ^a	85.3	0.30(0.13) ^b	84.1	0.31(0.02) ^a	84.8	0.30(0.07) ^a
SD>8 day – irregular	46.5	-0.40(0.23)	64.9	0.27(0.18)	80.5	0.16(0.03) ^a	86.8	0.14(0.07)
>=45 day – irregular	38.1	-1.09(0.24) ^a	61.5	-0.05(0.22)	73.7	-0.18(0.03) ^a	72.9	-0.21(0.09) ^b
<i>Late-Early</i>								
>=60 day–persist 6 day difference	12.4%	5.63(0.26) ^a	23.4%	3.17(0.27) ^a	49.7%	1.26(0.04) ^a	38.9%	1.72(0.10) ^a
>=60 day – SD>6 day	29.6%	3.90(0.24) ^a	46.3%	1.63(0.21) ^a	54.9%	0.67(0.05) ^a	55.6%	0.97(0.12) ^a
>=60day – SD>8 day	47.0%	2.38(0.20) ^a	63.8%	0.94(0.17) ^a	67.0%	0.45(0.04) ^a	69.5%	0.65(0.11) ^a
>=60 day – >=45 day	47.4%	3.06(0.23) ^a	66.0%	1.10(0.16) ^a	71.2%	0.72(0.03) ^a	70.9%	0.96(0.10) ^a
>=60 day – irregular	34.7%	1.95(0.26) ^a	50.9%	1.35(0.24) ^a	67.1%	0.55(0.04) ^a	72.6%	0.75(0.09) ^a

^a t-test p<0.0001;

^b t-test p<0.05

Median age at Final Menstrual Period (FMP) among Women who have and have not yet experienced an early stage marker within a given age category^a

	Age Interval	TREM			MWMHP		
		Marker occurred within Age Interval	Median Age at FMP Marker has not yet occurred by end of Interval	Difference in Median age at FMP (years)	Marker occurred within Age Interval	Median Age at FMP Marker has not yet occurred by end of Interval	Difference in Median age at FMP (years)
Persistent >6 day difference	40-44	50.5	52.7	-2.2	** ^c	55.3	na
SD > 6 days	45-49	52.5	na ^b	Na	54.2	55.8	-1.6
	40-44	50.4	52.4	-2.0	**	55.3	na
	45-49	52.1	54.6	-2.5	54.1	55.8	-1.7
>= 45 days	40-44	49.7	52.3	-2.6	**	55.3	na
	45-49	51.4	54.4	-3.0	53.7	55.8	-2.1
SD > 8 days	40-44	49.7	52.3	-2.6	**	55.3	Na
	45-49	51.7	54.4	-2.7	53.7	55.5	-1.8
Irregular	40-44	49.0	52.2	-3.2	**	55.3	na
	45-49	51.4	54.1	-2.7	54.5	55.5	-1.0

^aData are not presented for SWAN and SMWHS as small numbers of FMP by age category yield unstable estimates.

^bna= not applicable all women have experienced marker by end of this age interval

^cMWMHP minimum age at entry is 47

Table 5

Estimated associations of serum FSH with occurrence of early-stage bleeding markers from pooled logistic regression, before and after adjustment for age in SWAN and MWMHP.

Marker	Odds Ratio (95% CI) for occurrence of marker			
	SWAN (2223 women)		MWMHP (193 women)	
	Unadjusted	Age-adjusted	Unadjusted	Age-adjusted
<i>Persistent > 6-day</i>				
<i>Difference:</i>				
FSH < 10 IU/L	Reference	Reference	Reference	Reference
10 – 19.9 IU/L	1.05 (0.89, 1.25)	1.04 (0.87, 1.23)	1.90 (1.18, 3.06)	1.64 (1.01, 2.68)
20 – 39.9 IU/L	1.87 (1.56, 2.24)	1.67 (1.39, 2.01)	1.91 (1.08, 3.37)	1.48 (0.82, 2.67)
40+ IU/L	2.73 (2.18, 3.40)	2.09 (1.66, 2.63)	7.21 (3.65, 14.24)	4.51 (2.17, 9.37)
# observations	5271	5271	464	464
<i>SD > 6 days</i>				
FSH < 10 IU/L	Reference	Reference	Reference	Reference
10 – 19.9 IU/L	1.10 (0.91, 1.32)	1.09 (0.91, 1.31)	1.49 (0.91, 2.43)	1.32 (0.80, 2.18)
20 – 39.9 IU/L	1.64 (1.35, 1.99)	1.51 (1.24, 1.84)	1.28 (0.71, 2.31)	1.05 (0.57, 1.93)
40+ IU/L	1.94 (1.57, 2.40)	1.53 (1.22, 1.91)	4.04 (2.38, 6.87)	2.61 (1.42, 4.80)
# observations	6416	6416	556	556
<i>45-day segment</i>				
FSH < 10 IU/L	Reference	Reference	Reference	Reference
10 – 19.9 IU/L	0.92 (0.77, 1.10)	0.90 (0.75, 1.09)	1.29 (0.78, 2.13)	1.18 (0.71, 1.97)
20 – 39.9 IU/L	1.73 (1.43, 2.09)	1.52 (1.26, 1.85)	1.42 (0.79, 2.56)	1.23 (0.67, 2.26)
40+ IU/L	3.87 (3.13, 4.79)	2.91 (2.33, 3.62)	5.10 (2.99, 8.70)	3.87 (2.13, 7.02)
# observations	6213	6213	574	574
<i>SD > 8 days</i>				
FSH < 10 IU/L	Reference	Reference	Reference	Reference
10 – 19.9 IU/L	1.10 (0.90, 1.34)	1.09 (0.90, 1.34)	1.19 (0.70, 2.00)	1.13 (0.66, 1.91)
20 – 39.9 IU/L	1.75 (1.42, 2.15)	1.57 (1.27, 1.93)	1.19 (0.65, 2.16)	1.07 (0.58, 2.00)
40+ IU/L	2.40 (1.92, 2.98)	1.76 (1.40, 2.22)	3.25 (1.94, 5.43)	2.64 (1.44, 4.84)
# observations	6922	6922	632	632
<i>Irregular</i>				
FSH < 10 IU/L	Reference	Reference	Reference	Reference
10 – 19.9 IU/L	0.96 (0.79, 1.16)	0.94 (0.77, 1.14)	1.27 (0.77, 2.10)	1.06 (0.63, 1.77)
20 – 39.9 IU/L	1.85 (1.52, 2.26)	1.60 (1.31, 1.96)	1.78 (1.02, 3.10)	1.37 (0.77, 2.43)
40+ IU/L	3.49 (2.80, 4.34)	2.48 (1.98, 3.12)	2.74 (1.60, 4.68)	1.53 (0.82, 2.85)
# observations	6726	6726	626	626
<i>>= 60 days</i>				
FSH < 10 IU/L	Reference	Reference	Reference	Reference
10 – 19.9 IU/L	0.61 (0.47, 0.80)	0.61 (0.47, 0.80)	1.41 (0.71, 2.80)	1.31 (0.66, 2.62)
20 – 39.9 IU/L	1.73 (1.35, 2.22)	1.45 (1.12, 1.86)	2.75 (1.41, 5.37)	2.38 (1.19, 4.77)
40+ IU/L	5.63 (4.41, 7.18)	3.61 (2.80, 4.65)	6.36 (3.49, 11.57)	4.97 (2.55, 9.70)
# observations	7757	7757	766	766