'Persistence' improves the 60 days amenorrhea marker of entry to late stage menopausal transition for women aged 40–44

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Abstract

Background—The ReSTAGE collaboration evaluated four menstrual markers of entry to late stage menopausal transition

Objective—To assess the additional usefulness of 'persistence' in relation to a clinically accessible menstrual marker of late menopausal transition, taking age into account

Methods—Secondary analysis of menstrual calendar data in two ReSTAGE-collaborating studies with comparatively low age at entry

Results—Sixty days of amenorrhea is as useful for predicting time to the final menstrual period as the currently accepted 90-day marker for women aged over 45. For those aged between 40 and 44 years, recurrence of the 60-day marker within the next 10 cycles is a better indicator than a single occurrence of the 60-day marker or the 90-day marker.

Conclusions—60-day amenorrhea is as reliable a marker of late menopausal transition as the traditional 90-day marker for women aged over 45. For those aged 40–44, keeping menstrual records to check for a recurrence of the 60-day marker will be useful.

Keywords

ReSTAGE [1,2] is a multi-study[3,4,5,6] collaboration that draws together information provided by longitudinal studies of mid-life women that have incorporated the collection of menstrual calendars.

ReSTAGE has used the menstrual calendar evidence provided by these studies to evaluate several menstrual 'markers' of the menopausal transition proposed in 2001 by the Stages of Reproductive Aging Workshop (STRAW)[2,7]. Markers are defined in terms of the intervals between consecutive dates of onset of menstrual bleeding (*segments*). An interval of at least 90 days is currently recognised as a marker of the late menopausal transition[8]. ReSTAGE recommended that the 60-day interval proposed by STRAW should be used instead of the 90-day interval as a marker of the beginning of late-stage transition[1].

Two other menstrual markers of entry to late stage transition considered by ReSTAGE required knowledge of a history of at least 10 of a woman's immediately preceding segments, making them much less accessible in a clinical situation than the single-segment-dependent 60-day and 90-day markers. These other markers (running range over 42 days and 'skipped segment') often occurred on the same segment as the 60-day marker, and their distributions of age at first occurrence after a woman had reached age 40 were very similar to that of the 60-day marker. Among women whose final menstrual period (FMP) was observed in the four studies, 92% to 100% had experienced the 60-day marker after age 40. The corresponding percentages were very similar for the running range and skipped segment markers, but they were somewhat lower (79% to 91%) for the 90-day marker.

In the context of considering markers of entry to *early* menopausal transition, ReSTAGE made use of the concept of the 'persistence' of a menstrual marker[9,4]. A marker is said to occur persistently, or 'with persistence', if it recurs within the next 10 bleeding segments following its initial occurrence. In this article we consider whether the concept of persistence can be useful in a clinical context in relation to the late-stage 60-day marker, taking into account whether or not the woman is aged under 45 years.

Methods

This analysis is based on menstrual calendar data recorded by women from a minimum age of 35 years in the TREMIN (735 women) and SWMHS (279 women) studies.

The institutional review boards at the Universities of Michigan and Washington have approved the secondary analyses by ReSTAGE of the data from the TREMIN and SMWHS studies.

Detailed information comparing the scope and design of these population-based prospective studies is available elsewhere[1, 9, 10]. Women in both studies completed yearly menstrual calendar cards.

A bleeding segment is defined, according to World Health Organisation recommendations,[11] as a bleeding episode followed by a bleeding-free interval. ReSTAGE defined a bleeding-free interval as consisting of at least 3 days, so that gaps of 1 or 2 days between bleeding days are regarded as part of the same bleeding episode, which must consist of at least 1 day. Segments associated with pregnancies, and the first 3 segments after a birth or abortion are excluded from the analyses, as are segments associated with the use of hormone therapy or hormonal contraception. The age at which a marker occurs is the woman's age on the day beginning the segment at which the marker event is first observed for the woman, after the age of 40 years. If the marker event recurs within the 10 segments following this day, the age at *persistence* of the marker concurs with the age at the marker.

Results are stated in terms of time from marker to FMP (verified retrospectively by 12 months subsequent amenorrhea), which was observed in the menstrual calendars of 211 women (29%) in the TREMIN study and for 52 women (19%) in the SWMHS. Kaplan-Meier estimates of age at FMP were generated for those women whose FMP was not observed in their calendar data. The time between the first occurrence of a marker and FMP is calculated as the difference between her age, or estimated age, at FMP and her age at the occurrence of the marker.

Results

Table 1 shows for the 60-day and 90-day markers the classification of women in the two studies aged over 40 into those for whom the marker was not observed, those for whom it was observed or estimated to first occur within 5 years of FMP and those for whom it was observed or estimated to first occur earlier than 5 years before FMP. The percentages for the marker without and with recurrence in the next 10 segments ('persistence') are contrasted.

One in eight women does not experience the 90-day marker, whereas only one in 25 does not experience the 60-day marker. Approximately equal proportions (more than 4 in 5) women experience both the 60-day and the 90-day markers within 5 years of their final menstrual period. For one in seven the first occurrence of the 60-day marker is earlier than 5 years before FMP. This happens for only one in thirty three women for the 90-day marker.

The more stringent requirement of persistence results in greater percentages of women not experiencing the markers, with the effect being more marked for the 90-day marker. The proportion of women experiencing the 60-day marker within 5 years of FMP is hardly affected (still 4 in 5), whereas this proportion drops to only about 1 in 2 for the 90-day marker.

Table 2 shows estimates of the probability of reaching FMP within 5 years for women over 40 who experience the 60- and 90-day markers with and without recurrence in the next ten segments (persistence), grouped by the age at which they first experience the marker. Each of the markers is more likely to first occur in the age range 45–49 than earlier or later.

If the 90-day marker occurs with persistence at any age over 40, or if either marker first occurs with or without persistence at age 50 or over, it is almost a foregone conclusion that FMP will occur within 5 years. However, for women first experiencing the markers between the ages of 40 and 49 the percentages reaching FMP within 5 years are higher for the 90-day marker than for the 60-day marker, but fewer women experience the 90-day marker.

A similar number and percentage of women first experiencing the 90-day marker and the 60-day marker with persistence between the ages of 45 and 49 reach their FMP within 5 years (n= 193 and 189, 94% and 93% respectively). For women first experiencing these markers between the ages of 40 and 44 the 60-day marker with persistence shows a higher percentage (84%) reaching FMP within 5 years than the 90-day marker (77%), which also occurs to fewer women. Both of these markers have higher percentages reaching FMP within 5 years than the 60-day marker without persistence (61%).

Discussion

Two of the studies brought together by the ReSTAGE collaboration, the TREMIN, begun in the 1930s and the Seattle Midlife Women's Health Study, begun in 1990, have menstrual calendar data which allow comparison between women first experiencing menstrual markers of the menopausal transition in the age ranges from 40 to 44 years and from 45 to 49 years.

Two of the markers of the late stage of the menopausal transition assessed by ReSTAGE[1], the accepted 90-day marker and the recommended 60-day marker, depend on information about

a single bleeding segment, and so are more readily accessible in a clinical setting than markers depending on information about a history of segments.

We have shown that the idea of persistence, or early recurrence, of a menstrual marker of a stage of the menopausal transition, first considered by ReSTAGE in relation to an early transition marker, can add to the value of the 60-day marker of late transition in a clinical setting, and that the value added varies with the woman's age. Specifically, recurrence within the next ten segments of the 60-day marker when it is first experienced between the ages of 40 and 44 is as informative about the arrival of the final menstrual period within 5 years as is the first experience of a single segment of 60 or more days in length between the ages of 45 and 49 years. Both these events have a probability of about .85, or odds of between 5 and 6 to 1.

Conclusions

The traditional 90-day marker itself performs better among women aged 45–49 (94% success predicting FMP within 5 years) than among those aged 40–44 (77%) but its relative rarity means that applying the idea of persistence to it gives a poor trade-off for better prediction efficiency – the persistent 90-day marker happens to too few women. The 60-day marker performs almost as well without as with the persistence requirement among women first experiencing it in the 45–49 years age range. The persistent 60-day marker has better characteristics than the 90-day marker for women first experiencing it between the ages of 40–44 years.

Acknowledgments

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Table 1

Percentages of women in 3 categories related to the final menstrual period (FMP) for 3 markers, with and without persistence

Marker	Not observed	Observed within 5 years of FMP[*]	Observed earlier than 5 years before FMP[*]
60-day	4	82	14
90-day	13	84	3
60-day(p)	16	81	4
90-day(p)	43	56	1

Notes (p) means 'with persistence'

[*] includes Kaplan-Meier estimates of ages at FMP for those in whom FMP is not observed

Table 2

Percentage experiencing markers within 5 years of final menstrual period (FMP)[*], by age at first occurrence of marker (among those for whom the marker is observed)

Age	60-day		60-day(p)		90-day		90-day(p)	
	%	n	%	n	%	n	%	n
40–44	61	85	84	52	77	45	100	25
45–49	86	234	93	189	94	193	97	107
50+	96	122	100	118	100	146	100	90

Notes (p) means 'with persistence'

[*] includes Kaplan-Meier estimates of ages at FMP for those in whom FMP is not observed