Use of serial FSH measurements to detect menopause transition

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Background

The menopause transition (or perimenopause) is characterized by menstrual cycle irregularities, often accompanied by a variety of symptoms linked to hormonal fluctuations, as well as increasing FSH concentrations. The timing and symptoms vary for each individual complicating the clinical recognition and diagnosis. By taking serial home follicle stimulating hormone (FSH) tests, normal cyclical fluctuations could be accounted for. Utilizing a combination of key factors such as FSH measurements, age, and menstrual cycle variations could provide women with a more accurate indication of their menopause stage. Understanding a woman's menopause stage could provide reassurance and empower her.

Objective

The aim of this study was to determine if serial urinary FSH testing in combination with menstrual cycle history could be used to indicate a woman's menopause stage.

Methods

The study was conducted on data from the Menopause Sample Collection Study (NCT04853472). Women (n=108) were recruited based on their self-reported experience of menstrual cycle variability. Females aged 45–60 years of age, who suspected they were going through, or had been through, menopause, were included in the study.

The women were asked to collect daily early morning urine samples for up to 90 days. Quantitative urinary FSH levels were measured using a validated method on the AutoDELFIA analyzer (PerkinElmer). For cycles where length could be determined based on last menstrual period, effort was made to ensure daily samples were collected for ≥80% of the cycles. To further maximize the number of cycles available for analysis, this cycle selection criteria was relaxed for late perimenopausal women, for whom cycles are typically longer with a 90-day collection unlikely to cover ≥80% of the cycle. All data for postmenopausal women were included. An FSH concentration >25 IU/L was classified as 'positive' as per STRAW+10 (1).

Testing on a single day in a cycle (days 2 – 5, in line with STRAW+10) was compared to testing on 5 consecutive days in the cycle. The percentage of cycles with positive tests were summarised by testing strategy. Every cycle was included repeatedly in the analysis with every possible single test selected and every possible set of five consecutive results. Five tests were chosen as comparator to allow for a range of days where there may be sustained high levels of FSH. This mitigates the risk of capturing a normal peak FSH day(s) around ovulation, as in this case the FSH level would decrease within the testing period (i.e., would not remain consistently high).

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Results

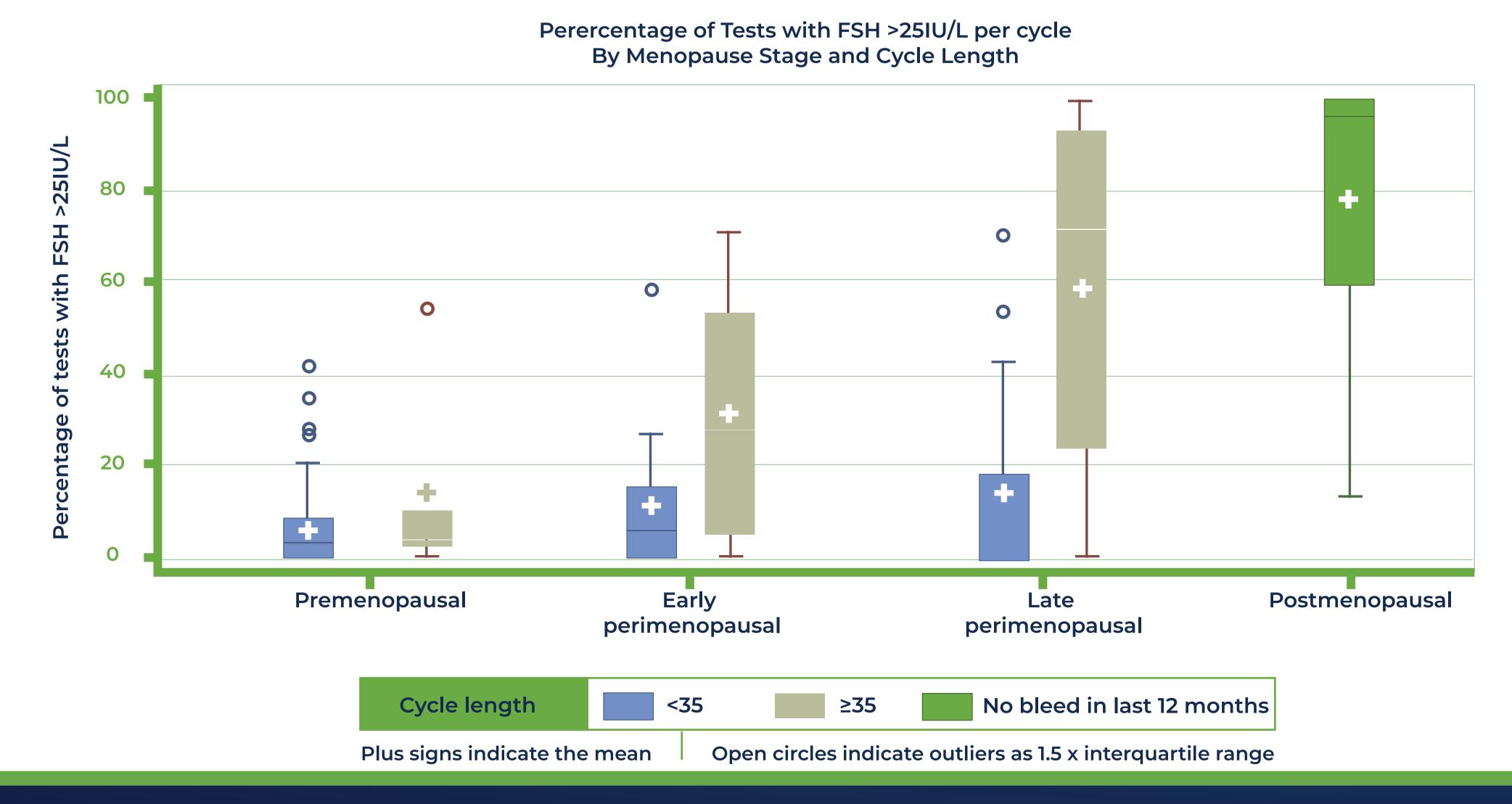
The individual hormone profiles of participants demonstrated that FSH levels varied throughout the menopause transition. The median urinary FSH levels increased as the menopause transition progressed. The median FSH level for premenopausal cycles was 6.4 IU/L. Early perimenopausal cycles presented with a median FSH of 10.6 IU/L, and those categorized as late perimenopause presented a significant rise of median FSH levels (32.8 IU/L). Cycles which were ≥35 days in length, independent of the menopause stage, tended to show higher levels of FSH outside of the expected peak when compared to cycles of <35 days. Postmenopause cycles had consistently high levels of FSH above 40 IU/L (**Table 1**).

Table 1. Average FSH concentration for each STRAW+10 status group

Menopause stage	Number of FSH observations	Median (LQ, UQ)	Min - Ma	
Premenopausal	1232	6.4 (3.6, 12.1)	0.4, 120.5	
Early perimenopausal	1044	10.6 (5.2, 22.4)	0.4, 203.3	
Late perimenopausal	2725	32.8(13.0, 59.1)	0.0, 247.4	
Postmenopausal	872	45.0 (27.2, 75.2)	0.0, 373.2	

The percentage of positive FSH tests can help distinguish between premenopause and postmenopause groups. The median percentage of positive tests for premenopausal cycles was the lowest at 3.7% (LQ,UQ: 0.0%, 9.1%), whilst for the postmenopausal data, the median was highest at 96.4% (LQ,UQ: 60.0%, 100%). These are distinct and do not overlap. Further subdividing cycles by length (<35 and ≥35 days), demonstrates that both early and late perimenopausal cycles with a higher percentage of positive tests are also likely to be longer (≥35 days). Additionally, late perimenopausal cycles are more likely to be longer per se.

Figure 1: Percentage of positive FSH test (FSH>25IU/L) per cycle, by STRAW+10



1. Harlow, S. D., Gass, M., Hall, J. E., Lobo, R., Maki, P., Rebar, R. W., Sherman, S., Sluss, P. M., & de Villiers, T. J. (2012). Executive summary of the stages of reproductive aging. Journal of Clinical Endocrinology and Metabolism, 97(4), 1159–1168. https://doi.org/10.1210/jc.2011-3362

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Fewer positive tests were recorded for early perimenopausal cycles of less than 35 days (5.7%), when compared to cycles of ≥35 days in the same category (27.8%). Moving to the late perimenopausal stage further increased this difference, with a median of 71.6% positive tests for cycles ≥35 days in length (Table 2).

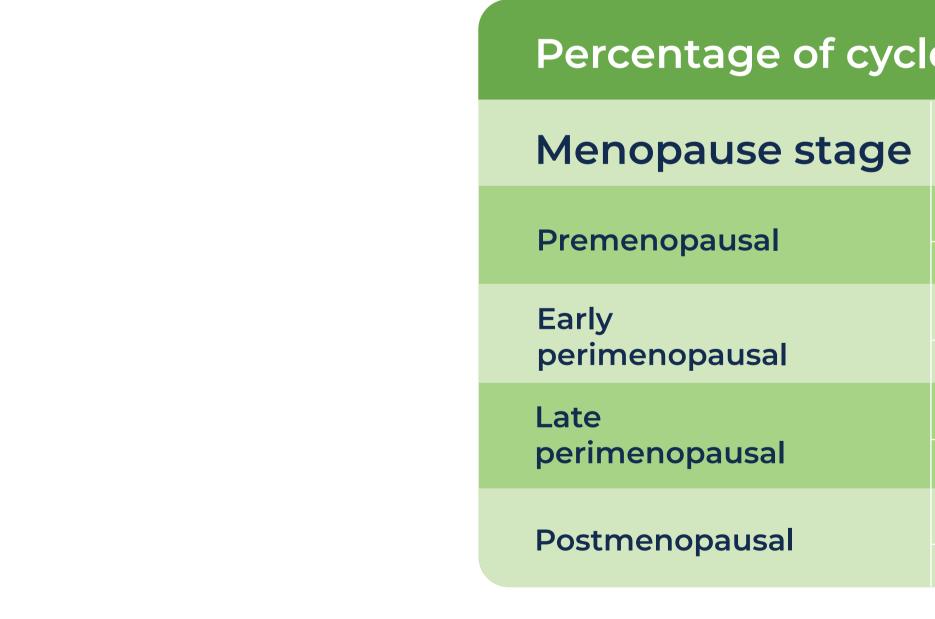
Table 2. Average percentage of tests with FSH >25IU/L per cycle for each STRAW+10 status group

Menopause stage	Cycle Length	Number of cycles	Mean (SD)	Median (LQ, UQ)	Min - Max
Premenopausal	<35	40	6.5 (10.1)	3.6 (0.0, 8.4)	0.0, 41.7
	≥ 35	5	14.1(22.7)	3.8(2.8, 10.0)	0.0, 54.2
	Overall	45	7.3 (12.0)	3.7(0.0, 9.1)	0.0, 54.2
Early perimenopausal	<35	28	10.0 (13.0)	5.7(0.0, 15.7)	0.0, 58.1
	≥ 35	8	30.6 (28.4)	27.8 (5.6, 53.3)	0.0, 71.2
	Overall	36	14.6 (19.1)	7.8(0.0, 19.2)	0.0, 71.2
Late perimenopausal	<35	17	14.4(22.1)	0.0 (0.0, 17.9)	0.0, 70.0
	≥ 35	35	60.4 (36.4)	71.6 (23.7, 93.3)	0.0, 100
	Overall	52	45.4 (38.9)	37.6 (3.7, 87.5)	0.0, 100.0
Postmenopausal	Overall	27	77.9 (29.9)	96.4(60.0, 100.0)	13.3, 100.0

When testing on a single day, a similar percentage of cycles in the early perimenopause and late perimenopause group had one positive test (21.5% vs 25.0% cycles respectively). However, when testing on 5 consecutive days of the cycle, there was greater distinction between early (39.2%) and late perimenopausal cycles (71.5%) showing 1 or more positive test(s) (**Table 3**).

Consecutive testing showed that the majority of premenopausal cycles (90.5%) included either none or 1 positive test, likely coinciding with the expected FSH peak. Most postmenopausal cycles included one or more positive tests (95.1%) (Table 3). Serial testing allows greater distinction between menopause stages, when compared to a single day test.

Table 3. Percentage of cycle with positive FSH test, when testing on a single day (2-5 of cycle) or on 5 consecutive days



Conclusion

A single urinary FSH measurement allows distinction between premenopause and postmenopause, whilst serial FSH testing provides improved distinction between early and late perimenopause. Cycle length information (< 35 days) helps differentiate the menopause stages (premenopause, early perimenopause, late perimenopause and postmenopause). A combination of these criteria could be used to provide women with an indication of where they are in their menopause journey. It may also aid healthcare professionals by affording data about menopause stage that could guide next steps and possible treatment options.

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es with positive test	N	%	Ν	%	Ν	%
Testing						
5 Consecutive days	850	79.1	122	11.4	224	20.9
Single	163	90.6	17	9.4	17	9.4
5 Consecutive days	557	60.8	86	9.4	359	39.2
Single	113	78.5	31	21.5	31	21.5
5 Consecutive days	734	28.5	176	6.8	1842	71.5
Single	90	75	30	25	30	25.0
5 Consecutive days	38	4.9	70	9.0	740	95.1
Single	-	-	-	-	-	-