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Urinary LH level and hot flash frequency: a preliminary report.

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Abstract

For many women in the United States, the perimenopause is characterized by irregular menstrual cycles and menopausal discomforts (e.g. hot flashes). Clinically, there is great intra- and inter-individual variation in hormone levels. The purpose of this study was to assess variation in urinary LH levels in relation to menopausal hot flashes. Data were drawn from a study of the menopause transition in Western Massachusetts (n=155). Urine samples from women aged 45 and older who reported at least one menstrual period within the 12 months prior to interview were tested for elevated LH levels using OvuKIT Self-Test (n=54). In this preliminary report, hot flash frequency varied in relation to phases of the menstrual cycle ($p < .05$). High/low levels of urinary LH by menstrual cycle phase (i.e., "on-time" vs. "off-time" elevated LH levels) were not associated with hot flash experience, although the expected trend was demonstrated.

Keywords:

Menopause, perimenopause, luteinizing hormone, hot flashes, symptoms

Resumo

A peri-menopausa da mulher nos Estados Unidos da América é caracterizada por ciclos menstruais irregulares e vários factores de desconforto como, por exemplo, os "calores" ou "afrontamentos". Fisiologicamente, neste período da vida da mulher existe uma grande intra- e inter - variabilidade individual nos níveis hormonais. O objectivo deste trabalho foi determinar a variação urinária dos níveis de LH em relação aos "calores" associados à menopausa. Os dados foram obtidos dum estudo da transição da menopausa em Massachusetts (N=155). As amostras de urina de mulheres com 45 ou mais anos que confirmaram terem tido pelo menos um período menstrual nos 12 meses antes da entrevista foram testadas para avaliar os níveis de LH utilizando o Teste OvuKIT (N=54). Neste estudo preliminar, a frequência de "calores" variaram em relação à fase do ciclo menstrual ($p < 0.05$). Níveis altos/baixos de LH urinário por fase do ciclo menstrual não estiveram associados com a experiência de "calores", embora a tendência esperada tivesse sido demonstrada.

Palavras chave:

Menopausa, peri-menopausa, hormona luteinizante, "calores", sintomas.

Introduction

MENOPAUSE IS BIOMEDICALLY DEFINED as the final menstrual period, identified in retrospect after 12 months of amenorrhea. In contrast, the perimenopausal period is difficult to typify. Perimenopause is the phase of maximum hormonal fluctuation preceding final menses (Kaufert *et al.*, 1986). It includes "the period immediately prior to menopause (when the endocrinological, biological and clinical features of approaching menopause commence) and the first year after menopause" (Utian, 1997).

For many women the perimenopausal period is characterized by irregular menstrual cycles accompanied by a variety of menopausal discomforts (e.g., hot flashes). Hormonally, the perimenopause is characterized by transitory elevations of follicle-stimulating hormone (FSH) and increases in luteinizing hormone (LH) that precede diminished levels of cycling estradiol (E2) and progesterone (Reame *et al.* 1996). There is, however, no definitive hormonal marker for the inception of the perimenopause (Rannevik *et al.*, 1995; Santoro, 1996).

The purpose of this study was to test a hypothesized relationship between one gonadotrophin (LH) and the presence of menopausal hot flashes. It was hypothesized that high urinary LH levels "off-time", that is, during the first and last weeks of the menstrual cycle (when LH levels are generally low), would be associated with the experience of hot flashes. A secondary aim of this study was to test the applicability of an easy test for high/low levels of urinary LH for study of the menopausal transition. Although marketed as a fertility aid for women wishing to detect the pre-ovulatory LH surge, OvuKIT Self-Test can also detect the elevated LH levels of menopause.

LH is produced by the anterior pituitary under the direction of gonadotrophin releasing hormone (GnRH) from the hypothalamus. Both GnRH and LH are secreted as episodic pulses that are influenced by a number of neurotransmitters and neuropeptides (Meites, 1982; Wise, 1989; Wise *et al.*, 1996). In the ovaries, LH (together with FSH) stimulates follicular growth, and the production of estrogen and progesterone. The ovarian hormones (estrogen, progesterone, and inhibin) send feedback to the brain which generally decreases the secretion of FSH and LH (Greenspan and Baxter, 1994; Leidy, 1994; Santoro *et al.*, 1998).

During an ovulatory cycle, LH pulses increase in frequency through the follicular phase (days 1-14). There is an LH surge (equal to or exceeding 40 mIU/mL) 24 to 36 hours prior to ovulation that can be detected in the urine by self-test kits (Elkind-Hirsch *et al.*, 1986). During the luteal phase (days 15-28), LH pulse amplitude and frequency decline. As women finish their 30's and enter their 40's, mean FSH levels, and then LH levels, rise (Rannevik *et al.*, 1995). However, the first episodes of FSH and LH elevation are transient, making it difficult to diagnose perimenopause via a one-time measurement of these hormones (Metcalf *et al.*, 1981). Variation in these hormones may be of interest, however, in explaining intra-population variation in frequency of hot flashes.

Vasomotor flushes, or hot flashes, are experienced more commonly in the United States than in other countries such as Canada and Japan (Avis *et al.*, 1993), India (Flint, 1975), or Mexico (Beyene, 1989). In Western Massachusetts, some women experience hot flashes just once. For others, "head sweats" occur on a weekly or daily basis. Some post-menopausal women describe monthly hot flashes, a sort of phantom PMS of upper body flushing. Other peri- and post-menopausal women notice a daily rhythm to their hot flashes. Still others notice the discomfort of hot flashes only in the humidity of summer. Finally, some women never experience a hot flash (Leidy, 1997).

Hot flashes involve an increase in peripheral blood flow followed by an elevation in peripheral temperature which coincides with a fall in core body temperature (Freedman, 1989; Freedman *et al.*, 1995). The hot flash appears to result from a sudden lowering of the hypothalamic thermoregulatory set point (Walsh and Schiff, 1990) and lasts from 30 seconds to 5 minutes. During a hot flash, plasma LH levels rise 23% above baseline, peaking 12 minutes after the onset of increased peripheral blood flow. However, LH does not induce hot flashes (Kronenberg, 1994), see Figure 1. Most likely, age-related changes account for both the changes in thermoregulation and the release of LH.

No difference has been demonstrated in absolute levels of LH or in number of LH pulses between women with and without hot flashes (reviewed by Kronenberg, 1994). The study presented here considers a different characteristic of LH, that is, the timing of elevated LH in relation to phases of the menstrual cycle to identify whether or not women who demonstrate elevated levels of LH during the early follicular (days

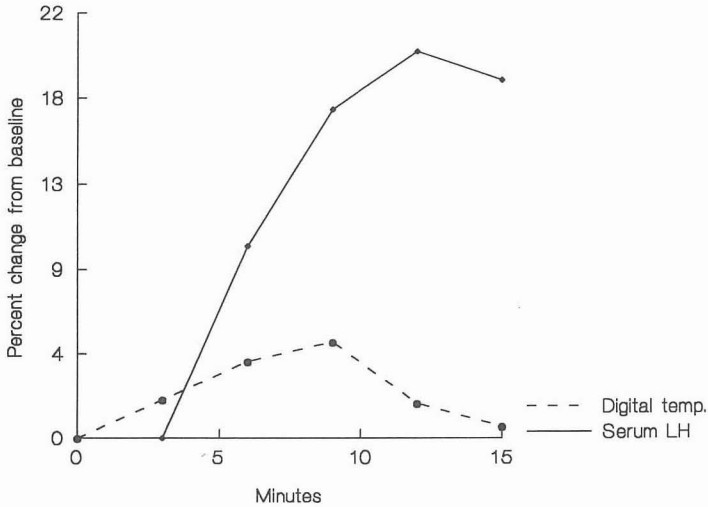


Figure 1: Percent change in finger temperature and serum LH levels from the beginning of augmented digital perfusion. This shows how elevation in LH levels follow changes in finger temperature (after Walsh and Schiff, 1990).

1-9) and late luteal phases (days >18) of the menstrual cycle are more likely to have experienced hot flashes. An elevated LH level during these phases is "off-time" and may indicate perimenopausal changes. In contrast, an elevated LH level during the periovulatory phase (days 10-18) could be indicative of the LH surge needed for ovulation. Are menstruating women with elevated "off-time" LH levels more likely to report the experience of hot flashes compared to menstruating women with no elevation of urinary LH during these same early and late phases? Alternatively, are women with a high "off-time" LH level more likely to report ever having experienced hot flashes compared to women with elevated "on-time" LH levels during the middle of the menstrual cycle?

Sample and methods

Women in Western Massachusetts (n=155) were invited to participate in interviews, body measurements, urine collection, and a structured survey. The women were self-selected to the extent that they were employed in a school district or the University library, attended a Breast

Health Project for low income women or a community-based exercise group, or consulted a chiropractor for care. See Table 1 for sample characteristics.

Table 1 Sample Characteristics

		N
Participation in open-ended interview	84.5% ¹	155
Survey Return Rate	81.3%	155
Mean Age	49.1 (sd 5.4)	155
Socio-economic variables		
% Married	51.6%	124
% with formal education beyond high school	87.3%	126
% employed full-time	64.3%	126
% with yearly family income >\$40,000	45.5%	123
Bio-behavioral variables		
% smoking at time of interview	15.1%	152
Mean parity	1.9 (sd 1.5)	119
Mean BMI (kg/m ²)	25.9 (sd 5.9)	127
Menopause		
% using HRT	19.5%	154
Rate of hysterectomy	10.0%	155
Mean age at natural menopause	49.6 (sd 4.4)	35

¹ Chiropractic clients (n=24) answered open-ended questions in writing, not in interview. Their survey return was 100%.

During open-ended interviews, women were asked to describe their experience with hot flashes, sweating, mood changes, irritability, and head aches in association with the menopause transition. It is important to note that not all women with mood changes, irritability, or head aches attributed those symptoms to the menopause transition. Work-related stress, aging parents, and teenage children were frequently blamed as the cause of these three symptoms. Table 2 reflects the frequency of symptoms that women attributed to menopause. Of importance here is whether or not women had ever experienced what they considered to be a hot flash.

Table 2 Symptoms associated with the menopause (open-ended interviews)

Symptom	N	Frequency
Hot flashes	149	57.7%
Sweating	149	49.7%
Irritability	149	41.6%
Mood changes	149	38.9%
Headaches	148	28.4%

In the structured written survey, women were asked to indicate if, during the past two weeks, they had been bothered by any of a series of complaints such as upset stomach, sore throat, or hot flashes. The complaint list was generously provided by Dr. Sonya McKinlay of the New England Research Institutes (Avis *et al.*, 1993). See Leidy (1997) for a more complete description of complaint list results. Of importance here is whether or not women reported the experience of a hot flash within the past two weeks.

Urine samples were obtained from 54 women age 45 and older who reported at least one menstrual period during the 12 months prior to interview. These samples were tested for elevated LH levels using OvuKIT Self-Test (Quidel Corporation, 10165 McKellar Court, San Diego, CA 92121). The OvuKIT Self-Test is a simple urine test used at home by women who wish to predict the time of ovulation by detecting the pre-ovulatory LH surge. Urine samples can be collected anytime between 10:00 AM and 8:00 PM. Test results are in the form of Test Stick color, numbered 1-5+. Each OvuKIT package provides a Surge Test Guide that resulted in a test color of 3 each time. Study participants with urine testing 3 or above were considered to have elevated LH levels.

Before beginning this preliminary study, the OvuKIT Self-Test was used to examine urinary LH levels from a post-menopausal volunteer (age 50) and two pre-menopausal volunteers (ages 42 and 45) who were in the peri-ovulatory phase of their cycles (days 10-14 of 26 to 30 day cycles). Test results were 4,4,4,4,4 (post-menopausal volunteer) and 1,2,3,3,2 (42-year-old) and 1,2,4,3,2 (45-year-old). According to the manufacturer, OvuKIT Self-Test is 96% accurate in detecting the LH Surge (see also Elkind-Hirsch *et al.*, 1986) and is unaffected by foods, alcohol, aspirin, or other common drugs.

Forty-five participants with LH levels and corresponding dates of LMP are the focus of this report. Urine samples were divided into 3 categories, days 1-9 of the menstrual cycle, days 10-18, and days >18 (See Table 3). Low or elevated levels of LH were examined in relation to age, phase of menstrual cycle, presence/absence of hot flashes during the two weeks prior to interview, and presence/absence of hot flashes ever. Chi square analyses were applied when cell sizes permitted.

Table 3 OvuKIT Self-Test results (1-4) by number of days since start of last menstrual period

LMP	Counts				Totals
	1	2	3	4	
3-9	6	4	1	2	13
10-18	8	4	1	3	16
20-32	3	6	1	3	13
66,120,180	.	1	.	2	<u>3</u>
					45

Results

As Figure 2 demonstrates, OvuKIT test results were spread evenly across age groups (n=54).

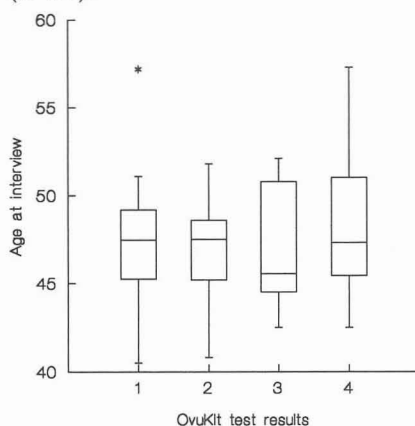


Figure 2: Distribution of OvuKIT Self-Test results by age in women who report a menstrual cycle within the twelve months prior to interview (n=54).

During the early follicular phase (days 1-9), three of thirteen, or 23% of participants, demonstrated "off-time" elevated LH levels. Four of sixteen, or 25% of participants, demonstrated "on-time" elevated LH levels. During the late luteal phase (days 19+), six of fifteen women, or 40% of the sample, demonstrated "off-time" elevated LH levels. In this last category, 12 reported a LMP of less than 35 days, the remaining three reported LMP's of 66-180 days, with two high and one low LH level.

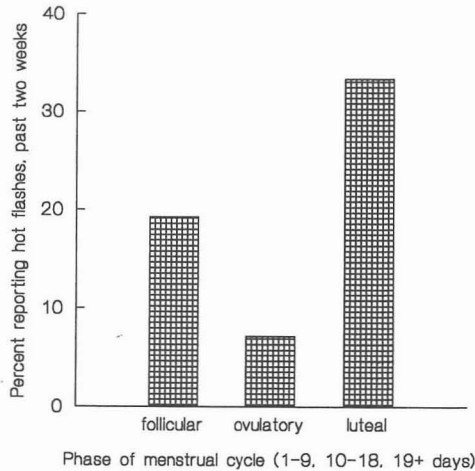


Figure 3: Women in the late luteal phase of the menstrual cycle at interview were significantly more likely to report having had hot flashes during the two weeks prior to interview ($n=96$, $p<.05$). This result supports anecdotal descriptions of hot flashes occurring in monthly cycles.

Figure 3 shows that women in the late luteal phase of the menstrual cycle at interview were significantly more likely to report having had hot flashes during the two weeks prior to interview ($n=96$, $p<.05$).

Women with high levels of urinary LH off-time, that is, during the early follicular and late luteal phases of the menstrual cycle at interview, were not significantly more likely to report having ever experienced hot flashes (44%) compared with women with expected low levels of urinary LH during the early follicular and late luteal phases (39%). From a different perspective, women with high LH levels during the off-time non-ovulatory phases were more likely to report the experience of hot flashes (44%) compared to women with high LH levels on-time, that is, during

the ovulatory phase (25%). However, the difference was not statistically significant (see Table 4 for a further breakdown of results).

Table 4 Experience of hot flashes, ever, in relation to high/low levels of urinary LH by last day of menstrual period

LMP (at interview)	Hot flashes ever	
	N	yes
1-9 days		
LH levels low	9	3 (33%)
high	3	1 (33%) off-time
10-18 days		
LH levels low	12	4 (33%)
high	4	1 (25%)
>18 days		
LH levels low	9	4 (44%)
high	6	3 (50%) off-time

Women with high levels of urinary LH off-time, during the early follicular and late luteal phases of the menstrual cycle at interview, were not more likely to report that they had experienced hot flashes within the last two weeks compared with women with low levels of urinary LH during the early follicular and late luteal phases (see Table 5).

Table 5: Hot flashes presence/absence during two weeks prior to interview in relation to high/low levels of urinary LH by last day of menstrual period

LMP (at interview)	Hot flashes	
	N	present
1-9 days		
LH levels low	7	2 (29%)
high	3	0 off-time
10-18 days		
LH levels low	10	1 (10%)
high	4	0
>18 days		
LH levels low	9	4 (44%)
high	5	2 (40%) off-time

Discussion

This study showed that women in the late luteal phase of the menstrual cycle were significantly more likely to report having had hot flashes during the two weeks prior to interview ($n=96$, $p<.05$). These results support anecdotal descriptions that hot flashes seem to occur in monthly cycles among perimenopausal women (Leidy, 1997) as well as among women of reproductive age (Hahn *et al.*, 1998).

With regard to high/low levels of urinary LH by menstrual cycle phase and experience of hot flashes, this preliminary study is limited by small numbers ($n=45$). In part, the low numbers reflect difficulty encountered in eliciting urine samples from women at job sites.

Also of note is the relatively low number of women who have ever experienced hot flashes (for a population in the United States where 70% is an expected frequency). In interview, 57.7% of women report ever having experienced hot flashes (the question used in Tables 2 and 4); however, on a structured symptom list only 22% report hot flashes *within the past two weeks* (the question used in Table 5). By way of comparison, in Sonya McKinlay's random sample of women across the entire state of Massachusetts ($n=7802$), 34.8% of women reported hot flashes during the 2 weeks prior to interview (Avis *et al.*, 1993).

The effect of hormone replacement therapy (HRT) on OvuKIT Self-Test results is uncertain. In the entire sample of participants, 19.5% use HRT. In the results reported here, only two menstruating women, both over 55 years of age, were taking HRT at interview. One scored low (1), the other high (4) for urinary LH. It is unknown whether or not these women would be menstruating without HRT. In addition, HRT may relieve their hot flashes, although the symptom profile is not so simple. Both women using HRT reported having had hot flashes; however, the woman with an LH level of 1 (LMP 10 days prior to interview) did not report a hot flash in the two weeks prior to interview, whereas the woman with an LH level of 4 ("off-time" high, LMP 27 days prior to interview) did report a hot flash in the two weeks prior to interview.

Another concern is that the time lag between LH levels at interview and hot flash experience ever is too long. Elevations of LH levels to postmenopausal levels are transient at first. For some women this occurs for one or two months, then levels drop back to normal (Metcalf *et al.*, 1981).

The time lag between LH levels at interview and hot flash experience within the past two weeks is more appropriate; however, repeated LH levels at follicular, midluteal, and late luteal phases (e.g., Reame *et al.*, 1996) would be a more appropriate study design in combination with measures of symptom frequency.

In conclusion, OvuKIT Self-Test does provide an easy way to test for "on-time" and "off-time" elevated levels of urinary LH. However, the results of this preliminary study suggest that a one-time test is not as useful as repeated tests would be. There is no definitive hormonal marker for the inception of the perimenopause (Rannevik *et al.*, 1995; Santoro, 1996); however, the OvuKIT Self-Test provides an easy way for women to monitor transient changes. The test would also lend itself well to anthropological fieldwork.

In this small sample, women with high LH levels during the "off-time" non-ovulatory phases were more likely to report the experience of hot flashes (44%) compared to women with high LH levels on-time, that is, during the ovulatory phase (25%). This is the expected trend; however, the difference was not statistically significant. Women with elevated levels of LH during the early follicular and late luteal phases of the menstrual cycle are probably in perimenopause; however, women without elevated levels of LH during these phases may also be in perimenopause. Future study designs should incorporate repeated testing of urinary LH levels across the menstrual cycle.

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