Association of Various Dimensions of Hot Flashes with Systemic Levels of Gonadal Steroids

ANNA RATKA,*[,1] VANESSA MILLER,† KIMBERLY BROWN,† MONICA JENSCHKE,† AND JAMES SIMPKINS†

*Texas A&M Health Science Center College of Pharmacy, Kingsville, Texas 78363; and †Institute for Aging and Alzheimer's Disease Research and Department of Pharmacology & Neuroscience, University of North Texas Health Science Center at Fort Worth, Fort Worth, Texas 76107

Hot flashes, the cardinal sign of menopausal vasomotor symptoms, are experienced by millions of women. The experience of hot flashes is characterized by significant inter- and intra-individual variability among women. The goals of this study were to compare concentrations of gonadal hormones between menopausal women with hot flashes (HF) and those with no HF, and to characterize the association between steroid levels and multiple dimensions of hot flashes. Menopausal women, with HF and with no HF, participated in four study sessions, one every 2 months. The Menopausal Vasomotor Symptom (MVS) survey was used to collect subjective data on various dimensions of hot flashes. Concentrations of gonadal hormones were measure at each bi-monthly session. Steroid levels were correlated to duration, frequency, length of each episode, timing, intensity, and bothersomeness of hot flashes. Data from twenty ($n = 20$) women with HF and fifteen ($n = 15$) with no HF with similar demographic profiles were analyzed. The results from the present study showed that systemic levels of estrone and progesterone were significantly lower in women experiencing HF than in asymptomatic women. There was a significant association between levels of estradiol, estrone, progesterone, and androstenedione, but not testosterone, with duration, frequency, timing, intensity, and bothersomeness of HF. The findings from this preliminary study suggest that management of symptoms associated with vasomotor HF should be individualized and guided by two factors: (i) thorough assessment of subjectively reported multiple dimensions of hot flashes, and (ii) levels of circulating gonadal steroids representing an average from 2–4 measures. This approach may lead to more targeted, effective, and safe management of vasomotor symptoms in the rapidly growing population of menopausal women. Exp Biol Med 234:395–402, 2009

Key words: hot flashes; gonadal hormones; menopause; vasomotor symptoms

Introduction

Menopause may be associated with highly variable and unpleasant symptoms that diminish health and quality of life of millions of women. The experience of vasomotor symptoms shows significant inter-individual variability among menopausal women and may change in the same woman throughout the menopausal transition. Hot flashes, the cardinal sign of menopausal vasomotor symptoms, are experienced by up to 75% of women (1). Management of menopausal symptoms remains a challenge. Women with vasomotor symptoms seek help from clinicians but about 75% of them are not satisfied with the quality of care received during menopause (2).

The causes of hot flashes in peri- and post-menopausal women are not clearly identified; however, menopausal vasomotor instability is believed to be associated with a decline in circulating levels of gonadal hormones (3). Almost all symptomatic women over the age of 50 demonstrate high levels of follicle stimulating hormone (FSH) and low estrogen levels (4). Consequently, for over 40 years, treatments with gonadal steroid preparations have been regarded as the most effective therapeutic measure to alleviate menopausal vasomotor symptoms (5, 6).

Circulating levels of gonadal hormones show high intra- and inter-individual fluctuations (7). In recent years, the interest in the relationship of endogenous hormones and vasomotor symptoms has increased. Overlie and colleagues

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[1] To whom correspondence should be addressed at Irma Lerma Rangel College of Pharmacy, Texas A&M Health Science Center, 1010 West Avenue B, MSC 131, Kingsville, TX 78363. E-mail: aratka@pharmacy.tamhsc.edu

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(5) reported association of hormones to occurrence, frequency, and distress of vasomotor symptoms during menopausal transition. During annual assessments recorded for 5 years, they found out that low estradiol and high FSH were correlated to vasomotor complaints, and that a high testosterone level was a significant predictor of recovery from hot flashes. Another study on the longitudinal changes in reproductive hormones concluded that only FSH was significantly associated with vasomotor symptoms prevalence and frequency (8).

Due to the very high intra- and inter-individual fluctuations in gonadal hormone levels, use of steroid plasma concentrations as a guide for the treatment of menopausal vasomotor symptoms is debatable. MacLennan and Sturdee (4) argue that hormonal testing at menopause may be "unnecessary and inaccurate." Changes in hormone levels were shown to be associated with non-hormonal factors that influence the experience of hot flashes and other symptoms of menopausal transition (9–11). The goals of this pilot clinical study were to (i) compare the profile of systemic gonadal hormone levels between menopausal women with and without hot flashes (HF), and (ii) to find out if ovarian steroids can be associated with specific measures of HF, as assessed with the Menopausal Vasomotor Symptom (MVS) survey in menopausal women (12).

Methods

Recruitment of Study Participants. The study protocol and informed consent were approved by the Institutional Review Board of the University of North Texas Health Science Center in Fort Worth, Texas. Advertisements for study participants were distributed in local newspapers, by e-mail, and flyers posted in areas frequented by the target population. Interested women who responded to and inquired about the study underwent initial telephone screening by a clinical research nurse. To qualify for this study women had to be 45 to 55 years old and have no serious health problems. Women who had used any estrogen, progestin, androgen, or phytoestrogen within 6 months prior to the study were excluded. Written informed consents were obtained from all study participants. A total of 51 women responded to the advertisement. Forty-three qualified women started the first session and 35 women completed all four study sessions (81% retention rate).

Study Procedures. The study consisted of four sessions, performed one every 2 months to capture any time-related changes in symptoms of hot flashes. Individual sessions, lasting about 30 minutes, were scheduled between 8 AM and 3 PM. During each study session, participants had a blood sample drawn by venipuncture, body weight and height measured, and responded to the Menopausal Vasomotor Symptom (MVS) survey.

The MVS survey is a valid and reliable tool to assess various dimensions of hot flashes (12). The MVS survey collects subjective information regarding various measures of hot flashes such as duration, frequency, timing, intensity, length of each hot flash episode, and effect of hot flashes on activities of daily living (bothersomeness). The MVS survey also allowed us to collect data about the age of the women when they began to have hot flashes and any procedure or therapy that might have affected hot flashes, such as a hysterectomy or oophrectomy, use of hormones, oral contraceptives, or herbal preparations.

A trained surveyor read the MVS survey questions to each participant and recorded her responses. Surveyed women from both study groups answered "Yes" or "No" to most questions and provided either the age or year when specific events occurred. The survey was completed in 10 minutes or less. Inter-surveyor variability was eliminated by having the same surveyor administer the MVS survey to all women for all sessions. Simple answers such as "Yes" or "No" also helped to reduce the variability in responses. Individual participant responses were recorded on a separate survey form coded only with the participant's identification number.

Assay of Hormone Levels. Plasma concentrations of testosterone (free and total), estradiol, estrone, androstenedione, and progesterone were determined using commercially available immunoassay kits from DSL (Webster, TX), and from ALPCO (Salem, NH) for the FSH assay. The lower limits of assay detection were: 7 pg/ml estrone, 0.13 ng/ml progesterone, 0.04 ng/ml total testosterone, 0.03 ng/ml androstenedione, 2.5 mIU/ml FSH, 0.19 pg/ml free testosterone, and 10 pg/ml estradiol. FSH concentrations were only measured in Session 1. Samples were run in duplicates. Mean intra- and inter-assay coefficient of variability was below 10% for all assays.

Data Analysis. Statistical analysis was conducted using Statistical Package for the Social Sciences (SPSS Inc., Chicago, IL, USA) version 15.0 for Windows. Descriptive statistics were used to assess measures of central tendency and statistical variability. Descriptive statistics revealed large standard deviations in several of the measures. Therefore, nonparametric analysis was deemed appropriate to test the relationships between steroid levels and various dimensions of hot flashes. The Mann-Whitney (Rank Sum) U test was used to test the null hypothesis that there is no difference in the hormone levels in women with HF and women with no HF. Spearman's Rho was also computed to measure the association between hormone levels and various subjective reports of vasomotor symptoms. In an effort to decrease standard deviations, and increase generalizability of the findings, when appropriate, hormone levels which were statistically determined to be outliers were eliminated from the statistical analyses. Data from 35 women were used in the final analysis.

Results

Characteristics of Study Participants. In this study, results from 20 women with HF and 15 women with

Table 1. Demographic Characteristics of Menopausal Women Participating in the Study ($n = 35$)[a]

Characteristic	Women with HF $n = 20$	Women with no HF $n = 15$
Age (years)	50.0 ± 3.4	48.0 ± 3.0
BMI [kg.m^{-2}]	30.0 ± 7.5	29.6 ± 6.0
Married	55.0%	67.0%
Single	20.0%	20.0%
Divorced	25.0%	13.0%
Caucasian	90.0%	60.0%
African American	5.0%	20.0%
Hispanic	5.0%	13.0%
Asian	0.0%	7.0%
Non-smokers	80.0%	87.0%
Current smoker	20.0%	13.0%
Income (per year)		
<$20.000	10.0%	13.0%
$20,000–$39,999	25.0%	33.0%
$40,000–$59.999	25.0%	20.0%
$60,000–$80,000	20.0%	7.0%
>$80,000	20.0%	7.0%
Education, average (years)	15.3 ± 2.2	15.2 ± 2.5
Education (years)		
12	5.0%	20.0%
13–16	75.0%	47.0%
17–20	20.0%	33.0%
Hysterectomy	45.0%	20.0%
Age at hysterectomy	39.2 ± 6.2 years	

[a] Values represent mean ± SD.

no HF were used and analyzed. These two groups of women were comparable in respect to most of the demographic measures (Table 1). In the HF group, 90% were Caucasian, 5% African American, and 5% Hispanic. The no HF group consisted of 60% Caucasian, 20% African American, 13% Hispanic, and 7% Asian. The mean age for the HF group was 50 ± 3.4 years versus 48 ± 3.0 years for the no HF group. This age difference was not significant ($P = 0.845$). The average BMI for the HF women was 30.0 ±7.5 [kg × m^{-2}] and 29.6 ± 6.0 [kg × m^{-2}] for the no HF women. This difference in BMI was not statistically significant ($P = 0.181$). Fifty-five percent of the HF women were married compared to 67% of the no HF group. Twenty-five percent of the HF women were divorced compared to 13% of the no-HF women. Although there was no difference in the average education years, the HF women reported a higher income than the no HF women. Of those women who had had a hysterectomy (45% in HF group and 20% in no HF group), the mean age of hysterectomy was 39.2 ± 6.2 years. The HF women reported past use of hormone therapy (50%), herbal preparations (30%), and hormonal contraceptives (95%) (data not shown).

Hot Flashes Profile. Subjective responses to the MVS survey provided information on various dimensions of HF and associated conditions in menopausal women. The MVS survey questions address overall duration of HF experience, frequency, timing (day or night), duration of one episode, intensity, and bothersomeness (interruption of activities) of HF. Table 2 presents different dimensions of hot flashes self-reported by menopausal women. In the group of 20 symptomatic women, the representative profile of the experience with HF was characterized by duration of more than 2 years, frequency of less than five HF in 24 hours, timing during both day and night, duration of one HF episode of up to 5 minutes, and experience of mild sweating. Majority of the surveyed women reported no interruption of daily activities by HF. This overall HF profile remained similar across all four study sessions.

Hormone Levels. Plasma levels of gonadal steroids in women with HF and women with no HF are shown in Table 3. In women with HF, during the first session, levels

Table 2. Dimensions of Hot Flashes (HF) Self-Reported in Response to the Menopausal Vasomotor Symptom (MVS) Survey by Menopausal Women ($n = 20$)[a]

Dimension of HF	Survey question	Session 1	2	3	4
Duration	Have you had menopausal HF for less than 2 years?	45	40	30	35
	Have you had menopausal HF for 2 or more than 2 years?	60	55	70	65
Frequency	Do you have less than 5 HF per day (in 24 hrs)?	70	65	75	55
	Do you have 5 to 10 HF per day (in 24 hrs)?	25	30	25	35
	Do you have more than 10 HF per day (in 24 hrs)?	20	0	0	20
Timing[b]	Do you have most of your HF during day?	95	80	75	90
	Do you have most of your HF during night?	75	70	80	35
Duration of one episode	Do your HF last 5 minutes or less?	100	85	95	95
	Do your HF last longer than 5 minutes?	5	10	5	5
Intensity[c]	Do you feel mildly sweaty during your HF?	75	90	85	75
	Do you feel drenched with sweat during your HF?	45	50	40	50
Bothersomeness	Do your HF interrupt your daily activities?	25	15	20	30

[a] Numbers represent percent (%) of women who answered "Yes."
[b] One woman stopped having HF between sessions 1 and 2. One woman started having HF between sessions 3 and 4.
[c] Women could answer 'Yes' for both questions.

Table 3. Steroid Hormone Levels in Menopausal Women with Hot Flashes (HF) and with No Hot Flashes (No HF)

	HF			No HF			
Hormone and session number	*n*	Mean	SD	*n*	Mean	SD	*P*
Estradiol 1 (pg/ml)	18	129.40	121.69	12	157.09	125.87	0.33
Estradiol 1, 2	18	82.16	37.64	8	117.51	69.79	0.17
Estradiol 1, 2, 3	18	78.02	32.30	8	111.96	71.89	0.22
Estradiol 1, 2, 4	18	77.33	33.22	8	108.72	66.14	0.20
Estrone 1 (pg/ml)	18	660.55	293.69	14	620.65	213.99	1.00
Estrone 1, 2	18	520.24	159.44	10	612.20	117.94	0.04
Estrone 1, 2, 3	18	476.02	125.92	10	555.10	101.63	0.05
Estrone 1, 2, 3, 4	18	444.17	113.21	10	510.94	90.06	0.08
Progesterone 1 (ng/ml)	16	8.44	5.56	14	12.08	15.00	0.93
Progesterone 1, 2	16	5.78	3.26	10	8.98	7.33	0.37
Progesterone 1, 2, 3	16	4.56	2.44	10	8.65	5.39	0.04
Progesterone 1, 2, 3, 4	16	4.67	2.39	10	7.58	4.45	0.22
Testosterone 1 (ng/ml)	17	1.23	0.60	14	0.93	0.32	0.32
Testosterone 1, 2	17	1.07	0.55	10	0.84	0.23	0.39
Testosterone 1, 2, 3	17	1.11	0.56	10	0.83	0.24	0.29
Testosterone 1, 2, 3, 4	17	1.18	0.62	10	0.86	0.23	0.15
Free testosterone 1 (ng/ml)	16	3.52	1.77	15	3.77	2.07	0.75
Free testosterone 1, 2	16	3.23	1.52	11	3.05	1.93	0.62
Free testosterone 1, 2, 3	16	3.37	1.63	11	2.94	1.78	0.40
Free testosterone 1, 2, 3, 4	16	3.40	1.69	11	2.82	1.65	0.44
Androstenedione 1 (ng/ml)	17	0.80	0.20	14	0.90	0.35	0.50
Androstenedione 1, 2	17	1.08	0.50	10	1.23	0.38	0.21
Androstenedione 1, 2, 3	17	1.20	0.55	10	1.22	0.43	0.80
Androstenedione 1, 2, 3, 4	17	1.36	0.56	10	1.26	0.43	0.82

of estradiol were lower than in women with no HF, and levels of testosterone were higher than in no HF women, but none of these differences were statistically significant. Steroid hormone levels measured during Session 1 did not differ significantly between HF and no HF groups. Hormone levels showed high inter-individual variability; the standard deviation for estradiol, estrone, and progesterone decreased when concentration values from multiple sessions were averaged. When average hormone levels from all four sessions were used in the analysis, statistically significant group differences were found for estrone (Sessions $1 + 2$, $P = 0.04$; Sessions $1 + 2 + 3$, $P = 0.05$) and for progesterone (Sessions $1 + 2 + 3$, $P = 0.04$), but not for estradiol, testosterone, free testosterone, and androstenedione.

Association Between Various Dimensions of Hot Flashes and Hormone Levels. Analysis of potential associations between individual hormones and HF was performed on the HF group of women. Results of the relationship between steroid hormone levels and subjective reports on specific measures of menopausal hot flashes obtained during Session 1 showed that women who reported experiencing HF for more than 2 years had significantly lower ($P = 0.01$) estradiol levels than those who denied having menopausal HF for more than 2 years; no other significant associations were noted in the hormone levels and woman's reports on menopausal vasomotor symptoms (data not shown).

The analysis of the relationship between averaged steroid levels and subjectively reported characteristics of hot flashes (Table 4) revealed that women who experienced hot flashes for more than 2 years had significantly lower levels of progesterone ($P = 0.03$), a tendency for significantly lower estradiol ($P = 0.09$), and higher level of free testosterone ($P = 0.10$) as compared to women who experienced hot flashes for less than 2 years. Estradiol levels had a significant association with the frequency of HF in 24 hours; women with less than five HF had significantly higher estradiol levels than women who reported having more than five HF in 24 hours ($P = 0.04$). Significantly lower levels of estradiol were associated with reports of interruption of daily activities caused by HF ($P = 0.03$). Estrone was significantly lower in women who experienced HF mostly at night ($P = 0.03$). There was also an indication that estrone could be significantly lower in women who reported being drenched with sweat during HF ($P = 0.06$). Women who reported being mildly sweaty had a tendency for much higher levels of progesterone compared to women who reported being drenched with sweat during HF ($P = 0.06$). Significantly higher levels of androstenedione were associated with higher frequency of HF ($P = 0.05$), predominantly occurring during the day, and being bothersome (interruption of daily activities). Testosterone levels were not significantly related to any of the characteristics of HF.

Table 5 shows the correlation between individual hormone levels and subjective reports on different charac-

Table 4. Association Between Averaged Steroid Hormone Levels and Subjective Reports of Menopausal Hot Flashes[a]

Hot flash (HF) characteristics	Survey answer	Steroid hormone levels[b]											
		n	Estradiol	*n*	Estrone	*n*	Prog	*n*	Test	*n*	F test	*n*	Andro
HF > 2 years	Yes	10	63.94	10	420.40	9	3.57	10	1.1	8	3.59	8	1.25
	No	2	99.97	2	535.96	2	9.57	2	1.69	3	2.09	4	1.53
			$P = 0.09$		$P = 0.18$		$P = 0.03$		$P = 0.67$		$P = 0.10$		$P = 0.61$
<5 HF per day	Yes	8	80.13	8	467.83	6	4.29	8	1.29	6	3.27	7	1.17
	No	4	49.57	4	383.32	5	5.10	4	1.00	5	3.07	5	1.58
			$P = 0.04$		$P = 0.23$		$P = 0.71$		$P = 1.00$		$P = 0.47$		$P = 0.22$
5–10 HF per day	Yes	2	41.51	2	382.09	3	6.30	2	0.89	4	2.34	3	1.90
	No	10	75.63	10	451.17	8	4.05	10	1.26	7	3.66	9	1.16
			$P = 0.03$		$P = 0.39$		$P = 0.61$		$P = 0.67$		$P = 0.13$		$P = 0.05$
>10 HF per day	Yes	2	57.63	2	384.56	2	3.30	2	1.12	1	5.98	2	1.11
	No	10	72.41	10	450.68	9	4.96	10	1.21	10	2.90	10	1.39
			$P = 0.67$		$P = 0.52$		$P = 0.29$		$P = 0.67$		$P = 0.21$		$P = 0.52$
HF during day[c]	Yes	10	70.68	10	453.60	10	4.80	10	1.30	9	3.31	10	1.42
	No	2	66.23	2	369.96	1	3.27	2	0.70	2	2.60	2	0.94
			$P = 0.52$		$P = 0.28$		$P = 0.34$		$P = 0.20$		$P = 0.81$		$P = 0.09$
HF at night[c]	Yes	9	57.52	9	399.79	9	4.56	9	1.10	9	2.90	9	1.41
	No	3	107.22	3	559.28	2	5.11	3	1.47	2	4.42	3	1.14
			$P = 0.12$		$P = 0.03$		$P = 0.81$		$P = 0.78$		$P = 0.24$		$P = 0.71$
HF longer than 5 minutes	Yes	0	0	0	0	0	0	0	0	0	0	0	0
	No	12	69.94	12	439.66	11	4.66	12	1.20	11	3.18	12	1.34
			NA		*NA*		*NA*		*NA*		*NA*		*NA*
Mildly sweaty	Yes	8	77.24	8	470.93	7	5.47	8	1.27	8	3.13	7	1.40
	No	4	55.36	4	377.13	4	3.25	4	1.06	3	3.32	5	1.26
			$P = 0.17$		$P = 0.17$		$P = 0.06$		$P = 0.73$		$P = 0.68$		$P = 0.94$
Drenched with sweat	Yes	5	71.48	5	393.02	3	3.39	5	0.95	4	2.59	6	1.34
	No	7	68.85	7	472.97	8	5.14	7	1.37	7	3.51	6	1.35
			$P = 0.81$		$P = 0.06$		$P = 0.41$		$P = 0.57$		$P = 0.71$		$P = 0.58$
HF interrupt daily activities	Yes	2	41.51	2	382.09	3	6.30	2	0.89	4	2.34	3	1.90
	No	10	75.63	10	451.17	8	4.05	10	1.26	7	3.66	9	1.16
			$P = 0.03$		$P = 0.39$		$P = 0.61$		$P = 0.67$		$P = 0.13$		$P = 0.05$

[a] NA, not applicable; Prog, progesterone; Test, testosterone; F test, free testosterone; Andro, androstenedione.
[b] Units provided in Table 2.
[c] Women could answer 'Yes' for both questions.

Table 5. Correlation (Spearman's Rho Coefficient) Between Hormone Levels and Subjective Reports of Vasomotor Symptoms

Hormone		Frequency of HF episode	Duration of HF	Duration of each HF episode	Intensity of HF	FSH
FSH	Rho coefficient	0.481[a]	0.425	−0.211	−0.187	1.000
	Sig (2-tailed)	0.032	0.061	0.371	0.458	
	n	20	20	20	18	20
Estradiol	Rho coefficient	−0.234	−0.701[b]	−0.063	0.158	−0.540[a]
	Sig (2-tailed)	0.322	0.001	0.791	0.531	0.014
	n	20	20	20	18	20
Estrone	Rho coefficient	0.046	−0.441	−0.159	0.043	−0.289
	Sig (2-tailed)	0.847	0.052	0.503	0.865	0.217
	n	20	20	20	18	20
Progesterone	Rho coefficient	−0.103	−0.337	0.358	0.158	−0.442
	Sig (2-tailed)	0.665	0.147	0.121	0.531	0.051
	n	20	20	20	18	20
Testosterone	Rho coefficient	0.014	−0.239	−0.175	0.014	0.167
	Sig (2-tailed)	0.953	0.31	0.461	0.955	0.482
	n	20	20	20	18	20
Free testosterone	Rho coefficient	0.08	0.306	0.027	−0.331	0.112
	Sig (2-tailed)	0.737	0.19	0.912	180	0.638
	n	20	20	20	18	20
Androstenedione	Rho coefficient	0.115	0.019	−0.102	−0.187	0.223
	Sig (2-tailed)	0.628	0.937	0.669	0.458	0.346
	n	20	20	20	18	20

[a] Correlation significant at the 0.05 level (2-tailed).
[b] Correlation significant at the 0.01 level (2-tailed).

teristics of menopausal vasomotor symptoms. There was a significant correlation between FSH and frequency of hot flash episode (Rho = 0.48; $P = 0.03$) and a significant negative correlation between duration of hot flashes and estradiol levels (Rho = –0.701; $P = 0.001$).

Since FSH levels are an essential diagnostic criterion for the evaluation of menopause, the association between FSH levels and women's subjective reports of vasomotor symptoms was analyzed (Table 6). The level of FSH in women who reported having had menopausal HF for longer than 2 years was significantly higher than that of women who denied having menopausal HF for longer than 2 years ($P = 0.06$). The FSH level of women who reported having less than five HF in 24 hours was significantly less than that of women who denied having less than five HF in 24 hours ($P = 0.05$). One woman who reported having more than 10 HF in 24 hours had very high level of FSH compared to women denying having more than 10 HF in 24 hours ($P = 0.03$). Women who reported that their HF interrupted their daily activities had significantly higher levels of FSH ($P = 0.05$) than women who denied that their HF were bothersome.

Discussion

The present study has found significant associations between plasma levels of individual gonadal hormones and various dimensions of hot flashes self-reported by menopausal women. These findings contribute new knowledge to our understanding of the relationship between individual gonadal steroids and hot flashes (HF).

Concomitant analysis of two different measures, symptomatic (multiple dimensions of HF) and biochemical (plasma steroid levels), collected during this clinical study, identified significant associations between specific measures of HF and circulating levels of hormones. We found out that more significant associations between HF and hormone levels can be identified using average than single levels of hormones. In the pilot group of 20 women with vasomotor symptoms, the analysis of the relationship between steroid levels and subjectively reported characteristics of HF revealed that the experience of HF lasting more than 2 years was associated with significantly lower levels of progesterone, lower estradiol, and higher levels of free testosterone. The number of HF in 24 hours (frequency) increased significantly as estradiol levels decreased. Significantly lower level of estradiol was also associated with interruption of daily activities. Estrone was significantly lower in women who experienced HF mostly at night and who reported to be drenched with sweat. Women who reported to be drenched with sweat had significantly lower levels of progesterone. Significantly higher levels of androstenedione were associated with higher frequency of HF, predominant occurrence of HF during the day, and bothersomeness (interruption of daily activities). In our study, testosterone levels were not found to be significantly related to any of the subjective measures of HF.

Previous clinical studies reported associations of vasomotor symptoms with steroid hormones (5, 8). The results from our very preliminary study concur with these reports

by showing relationship of estradiol and FSH but not testosterone to menopausal vasomotor symptoms. In contrast to the other studies in which only 2 or 3 measures of HF were taken into account (i.e., the occurrence, frequency, and distress), our study investigated and analyzed more dimensions of HF. With the MVS survey instrument used in this pilot study, we analyzed associations between duration, frequency, timing, duration of one episode, intensity, and bothersomeness (interruption of daily activities) and individual hormone levels.

The overall experience of HF self-reported by women in present pilot study was similar to other literature reports (1, 5, 8, 13–16). The majority of symptomatic women who participated in our study self-reported having HF for more than 2 years, with a frequency of less than five HF in 24 hours, occurring during the day as well as at night, with one HF episode lasting no longer than 5 minutes, and having their daily activities interrupted by HF.

In previously reported clinical studies on steroid levels during menopause, a single measure of an individual steroid was used. Hutton and colleagues (7) used one measurement of plasma level and showed that levels of steroid hormones in symptomatic and non-symptomatic menopausal women were similar. In the present study, we did not find difference in steroid levels between HF and no HF women when only one measurement was used, but when more bi-monthly measures of hormone levels were averaged, levels of estrone and progesterone were found significantly lower in women with HF than in women with no HF. This finding implies that a single measurement of a steroid level may not be reliable in assessing the role of individual steroid hormones in the occurrence of specific features of HF.

The findings from this pilot clinical study suggest that a woman's experience of HF may be determined by a change in circulating levels of a specific steroid hormone. In the group of symptomatic menopausal women participating in our study, estradiol, estrone, progesterone, and androstenedione showed strong correlation to five different dimensions of HF, i.e., duration, frequency, timing, intensity, and bothersomeness.

The relatively small group size in this pilot clinical project was a major limitation. The inherent variability in the two main measures used in this study, i.e., physiological fluctuations of circulating steroids and highly individualized physiological variability of HF experience, limited the extent of statistical analysis of the findings (e.g., inability to perform modeling). The small sample of participants, limited decisions on the study outliers. It is likely that a larger sample size may reveal that outliers are really not outliers and should be considered valid and included in the pool of collected data. Lack of adequate representation from major ethnic groups, such as Hispanics, African Americans, and Asians in this small pilot study, is also a limitation. Moreover, the assessment of menopause status and estrous cycle phases in study participants were not included in the design of this preliminary project. The women recruited for this study have on average 15 years of education, thus the study group was skewed toward a more educated population. The fact that educated women participated in this study may be a result of our recruitment strategy; more educated women are more likely to read newspaper ads, e-mail messages, and more willing to volunteer for research study.

Table 6. Associations Between FSH Levels and Subjective Symptoms of Hot Flashes

Hot flash (HF) characteristics	Survey answer	*n*	FSH[a]
HF for > 2 years	Yes	12	53.74
	No	8	33.44
			$P = 0.06$
<5 HF per day	Yes	14	38.96
	No	6	61.15
			$P = 0.05$
5–10 HF per day	Yes	5	53.98
	No	15	42.83
			$P = 0.39$
>10 HF per day	Yes	1	97.00
	No	19	42.91
			$P = 0.03$
HF during day[b]	Yes	18	47.98
	No	2	24.40
			$P = 0.31$
HF at night[b]	Yes	14	45.75
	No	6	45.32
			$P = 0.97$
HF longer than 5 minutes	Yes	1	4.07
	No	19	47.80
			$P = 0.08$
Mildly sweaty	Yes	15	42.79
	No	5	54.1
			$P = 0.47$
Drenched with sweat	Yes	8	38.16
	No	12	50.59
			$P = 0.28$
HF interrupt daily activities	Yes	5	64.88
	No	15	39.20
			$P = 0.05$

[a] Units provided in Table 2.
[b] Women could answer 'Yes' for both questions.

Despite the above limitations, mostly related to the small group size, data analysis of these preliminary results revealed statistically significant associations between individual hormones and specific features of HF. In comparison to previous literature reports, this study is more advanced in the experimental approach. First, it employed the MVS survey that allowed a standardized subjective assessment of multiple dimensions of HF. Second, it demonstrated that average values from multiple measurements of steroid levels taken bi-monthly proved more useful in characterizing the association between of HF and hormones. Third, it showed that each of the steroids influences a specific feature of HF and woman's experience with vasomotor symptoms. Moreover, in contrary to many reports from similar studies on problems with participant retention, in our study, the

retention rate was relatively high (81%), implying women's commitment to this research.

The findings from this preliminary study suggest that management of symptoms associated with vasomotor HF should be individualized and guided by two factors: first, thorough assessment of subjectively reported multiple dimensions of hot flashes, and second, levels of circulating gonadal steroids representing an average from 2–4 measures taken bi-monthly. This approach may lead to more targeted, effective, and safe management of vasomotor symptoms in the rapidly growing population of menopausal women. Current preliminary findings on the associations between steroids and various dimensions of HF need to be confirmed in a much larger cohort of menopausal symptomatic women including various ethnic groups. In addition to steroid levels, there are many other factors that influence the experience of hot flashes. Many recent reports indicate that during reproductive aging, hormones interplay with non-hormonal factors and have a significant impact on the well-being of midlife women (17). Therefore, future study should gather more broad scope of data on multiple factors associated with menopausal transition.

In conclusion, the results from the present study showed that systemic levels of estrone and progesterone were significantly lower in women experiencing HF than in asymptomatic women, and levels of estradiol, estrone, progesterone, and androstenedione, but not testosterone, have significant associations with duration, frequency, timing, intensity, and bothersomeness of HF. Moreover, the findings from this pilot clinical research study show that a well-designed data collection, use of a comprehensive vasomotor symptom assessment tool such as the Menopausal Vasomotor Symptom (MVS) survey for monitoring of woman's subjective reports about her experience with menopausal vasomotor symptoms, may help to identify patient-specific hormone therapy. This pilot research project should be expanded to a larger population of menopausal women with a better representation of the U.S. ethnic groups.

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