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A large multinational study of vasomotor symptom prevalence, duration, and impact on quality of life in middle-aged women

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Abstract

Objective: The aim of this study was to determine vasomotor symptom (VMS) prevalence, duration, and impact on quality of life in middle-aged women using a validated menopausal tool.

Methods: The Menopause Rating Scale (MRS) and an itemized questionnaire containing personal sociodemographic data were used to examine 8,373 women aged 40 to 59 years from 22 healthcare centers in 12 Latin American countries.

Results: Less than half (48.8%) of all women studied were postmenopausal, 14.7% used hormone therapy (HT), 54.5% presented VMS of any degree, and 9.6% presented severe/bothersome symptoms. The rate of VMS (any degree) significantly increased from one menopausal stage to the next. HT users presented more VMS (any degree) than did nonusers (58.6% vs 53.8%, $P = 0.001$). When surgical postmenopausal women were compared, non–HT users displayed a higher prevalence of severe VMS (16.1% vs 9.0%, $P = 0.0001$). The presence of VMS of any degree was related to a more impaired quality of life (higher total MRS score; odds ratio, 4.7; 95% CI, 4.1-5.3). This effect was even higher among women presenting severe VMS. Logistic regression analysis determined that the presence of severe psychological/urogenital symptoms (MRS), lower educational level, natural perimenopause-postmenopause status, nulliparity, surgical menopause, and living at high altitude were significant risk factors for severe VMS. HT use was related to a lower risk. A second regression model determined that surgical menopause, intense psychological/urogenital symptoms, and a history of psychiatric consultation were factors related to severe VMS persisting into the late postmenopausal stage (5 or more years).

Conclusions: In this Latin American middle-aged series, VMS prevalence was high, persisting into the late postmenopausal phase in a high rate and severely impairing quality of life. HT use was related to a lower risk of severe VMS.

Key Words: Vasomotor symptoms – Prevalence – Menopause Rating Scale – Menopause – Latin America.

During the menopausal transition, women display an array of symptoms related to estrogen deficiency and/or to the aging process per se. According to the National Institutes of Health (NIH), hot flushes, night sweats, and vaginal dryness are considered symptoms clearly related to menopause.[1] Greene[2] has also reported that vasomotor symptoms (VMS), hot flushes, and night sweats constitute an independent group of symptoms typical of this female reproductive stage. More evidence linking VMS with menopause and hypoestrogenism can be derived from the important number of clinical trials demonstrating symptom improvement after estrogen treatment.[3] VMS may significantly impair quality of life and are currently considered risk markers of chronic illnesses such as osteoporosis[4] and cardiovascular disease[5]; hence, assessing their prevalence and duration is of utmost importance.[6] A recent meta-analysis found that 2 years before menopause, VMS are present in 13.9% of premenopausal women, peaking 1 year (55.7%) and then decreasing 5 years (28.9%) after menopause onset.[7] These figures may vary and depend on potential confounders and methodological issues: VMS intensity inclusion criteria (severe or any degree), hormone therapy (HT) use, surgical menopause, method of follow-up into the postmenopausal stage, and so on. Therefore,

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NIH considers that more research is required to better define the natural history of menopausal symptoms to design and implement appropriate public health policies.[1]

Previous reports suggest that climacteric symptoms among Latin American women are more severe than in other populations. The multicentric Collaborative Group for Research of the Climacteric in Latin America (REDLINC) Study IV[8] found that the Menopause Rating Scale (MRS) scores were higher than those reported for European and North American women. A similar trend has been reported by the Study of Women's Health Across the Nation in which Hispanic and Afro-descendant women in the United States present increased VMS.[9] The aim of the present research was to determine VMS prevalence, duration, and impact on quality of life in middle-aged Latin American women using a validated menopausal tool.

METHODS

Participants

Previously, a cross-sectional study was carried out to assess quality of life and sexuality among healthy Hispanic middle-aged women (40-59 y) from 18 Latin American cities (22 healthcare centers) with a population of at least 500,000 inhabitants. Methodological aspects and details of the original study have been previously published elsewhere.[8,10] Women of black or indigenous origin, unable to understand the survey, or with psychological or physical incapacity imposing difficulties during the interview were excluded. Healthy status was defined, according to the National Center for Health Statistics, as the capability of performing daily routine activities.[11] The present study aims to specifically present data related to VMS.

Women fulfilling the inclusion criteria were informed about the research and its purposes and were requested to fill out the MRS and a general data questionnaire after giving consent of participation according to the Declaration of Helsinki.[12] Research protocol of the original study (REDLINC IV) and this secondary subanalysis were reviewed and approved by the bioethics committee of the PROSAM Foundation, Santiago de Chile, Chile. A minimal sample size of 380 participants per center was calculated (EPI-INFO 6.04 statistical software), considering that each center covered an estimated population of 50,000 women[13] and assuming that 50% of the surveyed population would present VMS[7] with a 5% desired precision and a 95% CI.

Variables included in the general questionnaire

General data

An itemized questionnaire was constructed to record all data and validated in 50 women before implementation at the Latin American centers affiliated with REDLINC that were participating in the REDLINC IV study. It was originally intended to assess quality of life and sexuality in middle-aged women and to determine factors related to their impairment.

Female variables

Female data included the following: age (in years), educational level (total years), parity, menopause status (premenopausal, perimenopausal, and postmenopausal), years of postmenopause status, surgical menopause (yes/no), partner status (yes/no), marital status, sexual status last 4 weeks (active or inactive), and accessed healthcare system (free-minimal cost or paid). Lifestyle and other personal factors included in this section were as follows: smoking habit, church attendance, and history of sexual abuse (rape). Medical care and drug use included psychiatric consultation (yes/no) and current use of psychotropic drugs, contraceptives, and HT/alternative therapies for menopause. A code number was assigned to each participating REDLINC center according to location (high altitude: >2,500 meters above sea level) and temperature (hot: maximal mean daily temperature >30°C). Insufficient educational level was defined if women had achieved 12 years or less of study.[14]

Menopause status definitions

Menopause status was defined using the criteria of the Stages of Reproductive Aging Workshop: premenopausal (women having regular menses), perimenopausal (irregularities >7 d from their normal cycle), and postmenopausal (no more menses in the last 12 mo). The latter phase was divided as early (1-4 y since menopause) and late postmenopause (≥5 y).[15] Surgical menopause was defined if women had a hysterectomy with bilateral oophorectomy. Premature menopause was defined as that occurring before 40 years of age.[16]

MRS

The MRS is a health-related quality of life instrument translated and validated in several languages including Spanish.[17-19] The present study used the Spanish version.[20] The tool assesses the presence and intensity of 11 items or symptoms and is divided into three subscales: (1) somatic: hot flushes, heart discomfort, sleeping problems, and muscle and joint problems (items 1-3 and 11, respectively); (2) psychological: depressive mood, irritability, anxiety, and physical and mental exhaustion (items 4-7, respectively); and (3) urogenital: sexual problems, bladder problems, and vaginal dryness (items 8-10, respectively). Each item can be graded by the participant from 0 (not present) to 4 (1, mild; 2, moderate; 3, severe; 4, very severe). For a particular individual, the total subscale score is the sum of each graded item contained in that subscale. Total MRS score is the sum of scores obtained for each subscale. Items can individually be presented as scores (mean and SDs) or percentages (and corresponding CIs). Scores above 8 (vasomotor), 6 (psychological), 3 (urogenital), and 16 (total MRS) were defined as severe scores and are indicative of severe quality of life compromise.[21] Item 1 of the MRS was used to identify women with VMS (those presenting hot flushes and/or sweating episodes). Because few studies report the outcomes for the isolated symptoms (hot flushes and/or night sweats), no attempt was made to individualize VMS. The MRS is a tool validated for measuring menopausal symptom severity (VMS included) and not number of hot flushes. Hence, daily hot flush quantification was not performed; instead, for comparison purposes, women with VMS were divided

TABLE 1. *Sociodemographic characteristics of women according to the presence of vasomotor symptoms*

Characteristics	Without vasomotor symptoms (n = 3,806 women)	With vasomotor symptoms (any degree) (n = 4,567 women)	*P*
Age, y	47.8 ± 5.9[a]	50.3 ± 5 4	0.0001
Educational level, y	12.2 ± 4.3	11.2 ± 4.5	0.0001
Parity	2.4 ± 1.5	2.7 ± 1.7	0.0001
Premenopausal	43.9 (42.3-45.5)	21.6 (20.4-22.8)	0.0001
Perimenopausal	17.8 (16.6-19.0)	21.3 (20.1-22.5)	0.0001
Postmenopausal	38.3 (36.8-39.9)	57.2 (55.7-58.6)	0.0001
Surgical menopause	10.6 (9.7-11.6)	16.9 (15.9-18.1)	0.0001
Currently with a partner	81.2 (79.9-82.4)	80.3 (79.1-81.4)	NS
Sexually active	79.4 (78.1-80.7)	74.8 (73.5-76.0)	0.0001
Free healthcare access	54.1 (52.5-55.7)	57.9 (56.4-59.3)	0.0004
Current smoker	18.4 (17.2-19.7)	16.6 (15.5-17.7)	0.03
Church assistance	54.2 (52.6-55.8)	60.9 (59.5-62.3)	0.0001
History of rape	4.1 (3.5-4.8)	4.6 (4.0-5.3)	NS
Receiving psychiatric consultation	10.2 (9.2-11.2)	12.7 (11.8-13.7)	0.0003
Psychotropic drug use	7.8 (6.9-8.7)	8.3 (7.5-9.1)	NS
HT use	13.4 (12.3-14.5)	15.8 (14.7-16.9)	0.002
Contraceptive use	8.5 (7.7-9.5)	4.0 (3.4-4.6)	0.0001
Alternative therapy use	5.0 (4.3-5.7)	9.9 (9.0-10.8)	0.0001
Living at high altitude (>2,500 meters)	34.3 (32.8-35.9)	29.9 (28.6-31.2)	0.0001
Living in cities with temperatures >30°C	44.4 (42.8-46.0)	46.3 (44.8-47.7)	NS

NS, nonsignificant; HT, hormone therapy.
[a]Data are presented as mean ± SD or percentages (95% CIs).

into two groups: "any degree" (MRS item 1 scores: ≥1) and "bothersome or severe" symptoms (MRS item 1: scores ≥3).[22]

Statistical analysis

Analysis was performed using EPI-INFO statistical software (versions 6.04 and 3.5.1; Centers for Disease Control and Prevention, Atlanta, GA; World Health Organization, Basel, Switzerland). Data are presented as mean ± SDs or percentages (95% CIs). Means were compared using analysis of variance, Student's *t* test, or Mann-Whitney *U* test, according to homogeneity of the measured variance as determined with the Bartlett test. Percentages were compared using the χ^2 test. Logistic regression analysis using two independent models was performed for the simultaneous assessment of several variables influencing the prevalence of bothersome/severe VMS (first model) and their duration into the late postmenopausal stage (second model). Regression models were generated from significant variables provided from univariate analysis. Interactions between significant variables found during regression model construction were also considered for the final model. For the first model, VMS score (MRS item 1) was recoded into a binary variable (dependant): bothersome, 1 (scores 3 or more), and not bothersome, 0 (scores <3). For the second model, same recoding was used; however, only late postmenopausal women were included in the analysis.

Independent variables to be entered in each regression model were as follows: hot climate city (yes/no), high-altitude city location (yes/no), access to free health care (yes/no), older age (median, ≥50 y), nulliparity (yes/no), low schooling (≤12 y), severe MRS scores (total and subscale: yes/no), having a partner (yes/no), sexually active (yes/no), perimenopause-postmenopause status (yes/no), surgical menopause (yes/no), current smoking (yes/no), medication use (contraceptives, HT/alternatives for the menopause, psychiatric drugs), history of rape (yes/no), church attendance (yes/no), and if currently consulting a psychiatrist (yes/no). Entry of variables into the model was considered, with a 20% significance level and the stepwise procedure being performed. Adequacy of the regression model was demonstrated with the Hosmer-Lemeshow goodness-of-fit test. A *P* value of less than 0.05 was considered statistically significant.

RESULTS

During the study period, a total of 8,394 women fulfilling the inclusion criteria were requested to participate. Because of incomplete data, 21 participants were excluded, leaving 8,373 complete surveys for statistical analysis. For the whole sample, mean (SD) age and educational level was 49.1 (5.7) and 11.6 (4.4) years, respectively. Thirty-percent lived at high altitude, 56.2% had free healthcare access, 17.4% smoked, 14.7% used HT, 54.4% were married, 80.7% currently had a partner, and 48.8% were postmenopausal. Women with VMS (any degree), as compared with those without, were older, were less educated, had higher parity, were predominantly perimenopausal-postmenopausal, were less sexually active, more frequently consulted a psychiatrist, used HT or alternatives, and lived in high altitude cities (Table 1). Rate of women currently having a partner, using psychiatric drugs, or having a history of sexual abuse did not differ among groups.

Of all women studied, 54.5% presented VMS of any degree, with 9.6% presenting severe/bothersome ones (Table 2). VMS rate (any degree) significantly increased from one menopausal stage to the next, with a peak observed among early postmenopausal women (68.5%) and a further decrease in late postmenopausal ones (60.6%). More than half (63.6%) of women with 10 to 15 years of menopause onset still presented VMS. Premenopausal women presented severe VMS in 5.5%, with a two-fold increased observed among perimenopausal women.

A total of 1,230 women (14.7%) were HT users at the time of the survey (Table 3). HT use was similar among

TABLE 2. *Prevalence of vasomotor symptoms (any degree/bothersome) according to menopausal stage*

Reproductive stage (STRAW)	n	Vasomotor symptom (any degree), % (95% CI)	Vasomotor symptom (bothersome), % (95% CI)
Premenopausal	2,655	37.1 (35.3-39.0)	5.5 (4.7-6.5)
Perimenopausal	1,648	58.9 (56.5-61.3)[a]	10.8 (9.4-12.4)[a]
Early postmenopause	1,821	68.5 (66.3-70.7)[a]	12.3 (10.8-13.9)[NS]
Late postmenopause	2,249	60.6 (58.5-62.6)[a]	11.5 (10.2-12.9)[NS]
Total	8,373	54.5 (53.5-55.6)	9.6 (9.0-10.3)

STRAW, Stages of Reproductive Aging Workshop; NS, nonsignificant.
[a]$P < 0.0001$ or NS as compared with the prior menopausal stage.

TABLE 3. *Prevalence of vasomotor symptoms (any degree) according to menopausal stage and HT use*

	Non-HT use		HT use		
Reproductive stage (STRAW)	n	With vasomotor symptom[a], % (95% CI)	*n*	With vasomotor symptom[a], % (95% CI)	*P*
Premenopausal (n = 2,655)	2,553	36.3 (34.5-38.3)	102	55.9 (45.7-65.7)	0.0001
Perimenopausal (n = 1,648)	1,477	58.5 (55.9-61.0)	171	62.6 (54.9-69.8)	NS
Early postmenopause (n = 1,821)	1,391	71.4 (68.9-73.7)	430	59.3 (54.5-64.0)	0.0001
Late postmenopause (n = 2,249)	1,722	61.6 (59.3-63.9)	527	57.3 (52.9-61.6)	NS
All (n = 8,373)	7,143	53.8 (52.7-55.0)	1,230	58.6 (55.8-61.4)	0.001

HT, hormone therapy; STRAW, Stages of Reproductive Aging Workshop; NS, nonsignificant.
[a]Any degree.

women with lower (≤12 y) and higher education (>12 y; 14.4% vs 15.2%, respectively; nonsignificant [NS]). Interestingly VMS prevalence (any degree) was higher among HT users (58.6% vs 53.8%, $P = 0.001$). When HT-using women were stratified according to menopausal stage, VMS prevalence was found significantly higher in premenopausal women and lower in early postmenopausal ones (55.9% vs 36.3% and 59.3% vs 71.4%, respectively; $P = 0.0001$). Among non–HT users, VMS prevalence significantly increased from one menopausal stage to the next, peaking in early postmenopausal women (71.4%) and further decreasing in late postmenopausal ones (61.6%). This trend was not observed for HT users. When symptom severity was taken into account, results differed. The rate of women with severe symptoms were similar among HT users and non–HT users (8.8% vs 9.8%, respectively, NS), although early postmenopausal HT users displayed severe VMS in a lesser extent than did non–HT users (6.7% vs 14.0%, respectively; $P = 0.0001$). Premenopausal HT users displayed severe VMS at a higher rate compared with non–HT users (15.7% vs 5.1%, $P = 0.0001$). HT use was significantly higher among women with surgical menopause as compared with natural menopausal women (29.2% vs 12.3%, respectively; $P = 0.0001$; data not shown on table).

VMS prevalence (any degree) was significantly higher among surgically postmenopausal women, regardless of HT use (Table 4). When surgically postmenopausal women were compared, non–HT users displayed a higher prevalence of severe VMS (16.1% vs 9.0%, $P = 0.0001$). Prevalence and severity of VMS did not differ among women with or without premature menopause. The risk of concomitantly presenting other menopausal symptoms among women with or without VMS is presented in Table 5. Heart discomfort, depressive mood, sleeping problems, and sexual problems were more strongly related to VMS of any degree.

Because women with VMS concomitantly present other symptoms at high rates, quality of life impairment also increases. Severity of VMS and the risk of severe quality of life impairment (higher total and subscale MRS scores) are depicted in Table 6. One can observe that the presence of VMS (any degree) increases three to five times the risk of presenting higher total, somatic, psychological, and urogenital MRS scores and hence severely impairing quality of life. This effect was even higher among women presenting severe VMS.

Risk factors for severe VMS obtained after logistic regression analysis are presented in Table 7. Severe psychological and urogenital MRS scores, lower educational level, natural perimenopause-postmenopause status, nulliparity, surgical menopause, and living at high altitude were significant risk factors for presenting severe VMS. HT use was related to a lower risk. Age, oral contraceptive use, alternative menopausal therapies, psychotropic drug use, psychiatric consultation, tobacco use, and living in hot temperature were not related to more intense VMS. The second regression model found that women with severe psychological/urogenital MRS scores (odds ratio [OR], 3.65 [95% CI, 2.68-4.97] and OR, 2.50 [95% CI, 1.84-3.4], respectively), a history of psychiatric consultation (OR, 1.48; 95% CI, 1.05-2.09), and surgical menopause (OR, 1.42; 95% CI, 1.07-1.89) were factors related to bothersome VMS persisting into the late postmenopausal phase. No significant interactions were found during regression analysis.

DISCUSSION

Overall, VMS prevalence was high (54.5%) in the present Latin American series, with high rates observed among premenopausal and late postmenopausal women (37.1% and 60.6%). Moreover, 60% or more of our studied women still present VMS 12 years after menopause onset. Despite the fact that comparisons between populations are not feasible, our

TABLE 4. *Prevalence of vasomotor symptoms (any degree/bothersome) according to HT use and type of menopause*

	Menopause					
	Non-HT use			HT use		
Vasomotor symptoms	Natural	Surgical	*P*	Natural	Surgical	*P*
% Any degree (95% CI)	52.3 (51.1-53.5)	65.6 (62.2-68.8)	0.0001	55.8 (52.4-59.1)	65.8 (60.5-70.7)	0.001
% Bothersome (95% CI)	8.9 (8.2-9.7)	16.1 (13.8-18.9)	0.0001	8.8 (7.2-10.9)	9.0 (6.3-12.6)	NS
n	6,310	833		886	344	

HT, hormone therapy; NS, nonsignificant.

TABLE 5. *Risk of concomitantly presenting other menopausal symptoms among women without and with vasomotor symptoms*

Menopausal symptoms (MRS)	Without vasomotor symptoms, % (95% CI)	With vasomotor symptoms (any degree), % (95% CI)	OR (95% CI)
Heart discomfort (item 2)	23.1 (21.7-24.4)	61.1 (59.7-62.5)	5.24 (4.75-5.78)
Depressive mood (item 4)	42.2 (40.6-43.8)	75.7 (74.4-76.9)	4.26 (3.87-4.68)
Sleeping problems (item 3)	40.9 (39.3-42.5)	74.1 (72.8-75.4)	4.14 (3.77-4.55)
Sexual problems (item 8)	28.8 (27.3-30.2)	61.5 (60.1-62.9)	3.96 (3.60-4.35)
Anxiety (item 6)	36.0 (34.5-37.5)	68.8 (67.5-70.2)	3.93 (3.58-4.31)
Physical and mental exhaustion (item 7)	48.5 (46.9-50.1)	78.3 (77.1-79.5)	3.84 (3.48-4.23)
Vaginal dryness (item 10)	29.0 (27.6-30.5)	60.0 (58.6-61.4)	3.67 (3.34-4.03)
Irritability (item 5)	49.7 (48.1-51.3)	77.0 (75.7-78.2)	3.38 (3.08-3.72)
Muscle and joint problems (item 11)	47.8 (46.2-49.4)	75.6 (74.4-76.9)	3.39 (3.08-3.73)
Bladder problems (item 9)	27.5 (26.1-29.0)	54.2 (52.7-55.6)	3.11 (2.84-3.42)

OR, odds ratio; MRS, Menopause Rating Scale.

results seem to indicate that VMS prevalence among Latin American women is higher than those recently reported for other ethnic groups[7] and is in agreement with other reports drawn from Hispanic female populations.[8,9] Using the MRS, a similar VMS prevalence (56%) has previously been reported among Ecuadorian middle-aged women.[23] One study found that Hispanic women living in the United States display more intense menopausal symptoms when compared with white women.[24] This difference persisted even after adjustment for socioeconomic level, therefore suggesting that ethnicity could be an independent risk factor predicting symptom intensity. We have recently reported data suggesting that severity of menopausal symptoms observed among Latin American women could be related to their indigenous origin.[25] Ethnic associations between VMS presence and specific estrogenic receptor polymorphisms have been reported. Indeed, African American (CYP1B1 rs1056836 GC genotype) and Chinese women (CYP1A1 rs2606345 AC genotype) present a lower risk for severe VMS.[26] Although this may seem an interesting approach for our population, more research is required in this regard.

Study design and the characteristics and selection of the population studied (ie, inclusion of HT users, naturally postmenopausal women) are factors influencing reported VMS prevalence. Highlighting this is a recent meta-analysis[7] that initially identified a total of 410 studies, of which only 10 fulfilled the inclusion criteria: 6 reporting VMS by years since menopause and 4 based on Stages of Reproductive Aging Workshop staging. Of the 10 included, 1 reported on ethnic groups, 3 on symptom severity, and 7 using different symptom assessing time intervals. Hence, future VMS research should rely on a unified protocol to adequately compare different ethnic groups.[27]

In correlation with a Swedish study,[28] late postmenopausal women of our series displayed a high VMS prevalence (60.6%). This rate did not differ among participating centers, despite the fact that HT use was similar among early and late postmenopausal women (23.6% vs 23.4%, respectively; NS). A recent report[29] of 205 women followed for 13 years seems to also support the fact that the average duration of bothersome VMS is 5 years, substantially longer than previously reported. Women who are HT/contraceptive users and those presenting VMS at study initiation were not included. Moreover, women studied were older, were physically more active, had better health, and had a higher educational level than those declining participation, hence displaying a lower risk of presenting VMS as that reported in other series.[30,31] Despite the limitations of the study of Col et al,[29] it does, however, highlight the fact that VMS duration is longer than that perceived by the medical community.[32,33] The relevance of a longer VMS duration seems to relate to their negative impact on female quality of life, increased cardiovascular[5] and osteoporosis risk,[4] and a higher risk of aortic calcifications, especially among HT users.[34] As pointed out by the NIH, there is no doubt that more research is warranted to clarify the natural history of VMS.[1]

VMS are a main reason for HT use among postmenopausal women.[35] Contrary to the expected, HT users of our series presented VMS in a higher rate than did nonusers. Nevertheless, this trend has been reported by others in the United

TABLE 6. *Severity of vasomotor symptoms and risk of severe quality of life impairment*

		Risk of severe quality of life impairment (MRS total and per subscale)			
Vasomotor symptoms	n	Somatic[a], OR (95% CI)	Psychological, OR (95% CI)	Urogenital, OR (95% CI)	Total MRS[a], OR (95% CI)
Absent	3,806	1.00	1.00	1.00	1.00
Any degree	4,567	3.4 (2.7-4.1)	3.4 (3.1-3.8)	3.6 (3.2-4.0)	4.7 (4.1-5.3)
Bothersome	807	24.6 (19.6-30.9)	12.8 (10.7-15.2)	8.6 (7.2-10.2)	20.0 (16.6-24.1)
P^b		0.0001	0.0001	0.0001	0.0001

OR, odds ratio; MRS, Menopause Rating Scale.
[a]Scores of item 1 (vasomotor symptoms) were excluded.
[b]*P* value as calculated with χ^2 test within each group.

TABLE 7. *Risk factors related to presenting bothersome vasomotor symptoms: logistic regression analysis*[a]

Risk factor	OR	95% CI
Severe psychological symptoms (MRS)	4.29	3.60-5.10
Severe urogenital problems (MRS)	2.12	1.79-2.52
Schooling ≤12 y	1.83	1.54-2.18
Natural perimenopause-postmenopause	1.57	1.28-1.92
Nulliparity	1.47	1.09-1.97
Surgical menopause	1.36	1.11-1.66
Living at high altitude (>2,500 meters)	1.21	1.03-1.42
HT use	0.74	0.59-0.93

OR, odds ratio; HT, hormone therapy; MRS, Menopause Rating Scale.
[a]Adequacy of the regression model was demonstrated with the Hosmer-Lemeshow goodness-of-fit test.

States,[36,37] Brazil,[38] and Korea[39] and could be explained by the incomplete efficacy of HT in relieving symptoms or the intermittent nature of its use. One study found that women take HT before ever reporting VMS, and those taking HT in fact had more severe or prolonged VMS.[40] Fentiman et al[41] reported that more than 70% of women with severe VMS had used HT. A possible explanation for the higher VMS prevalence seen among HT users of our series could be related to the fact that users were more likely to be surgically menopausal, a group displaying a higher prevalence of symptoms.

Women of our series with VMS concomitantly present a high rate of other menopausal symptoms. Indeed, heart discomfort, depressive mood, sleeping problems, and sexual problems were more strongly related to VMS. These associations have been previously reported for postmenopausal[42,43] and premenopausal women,[44] suggesting that these symptoms may have a similar etiopathological origin. The relation between high core body temperature and poor sleeping quality[45] seems to support this fact for both situations: low estradiol and high gonadotropin levels.[45] Low estradiol levels affect not only the hypothalamic temperature regulating center but also serotonergic and noradrenergic pathways.[46] Hence, it is of no surprise that women with VMS concomitantly present a higher rate of psychological symptoms and that drugs modulating neurotransmission, such as selective serotonin reuptake inhibitors and serotonin-noradrenaline reuptake inhibitors, are useful for treating the so-called menopausal "missed symptoms": mood changes, sleep disturbances, and somatic complaints.[47] The presence of VMS should therefore be considered a marker of impaired quality of life. Women with VMS in our series had five times the risk of having impaired quality of life, defined as higher MRS scores (total and subscales); if VMS were severe, this risk was even higher. Williams et al[48] have reported that hot flushes affect work (46.0%), social activities (44.4%), leisure activities (47.6%), sleep (82.0%), mood (68.6%), concentration (69.0%), sexual activity (40.9%), total energy level (63.3%), and overall quality of life (69.3%). The latter is consistent with our results and point out to the fact that VMS should be treated and seen as a relevant indicator of female health.

Women in our series with severe psychological symptoms were more likely to present severe VMS. Supporting this is the fact that women with moderate/severe depressive symptoms are almost twice as likely to report VMS.[49] Contrarily, those experiencing severe VMS report anxiety and/or depressive symptoms more frequently.[42,50] Interestingly, hot flushes and depressive symptoms both occur early in the menopausal transition in women who had not previously presented with these symptoms; depressive symptoms more probably precede hot flushes.[51] Therefore, depressed mood in the premenopausal phase may be seen as a predictive marker of subsequent severe VMS presentation.

Another factor relating to more severe VMS in our series was the presence of severe urogenital symptoms. However, this association may only reflect the fact that both symptoms share the same etiological cause (hormonal imbalance). Indeed, VMS and vaginal dryness are directly related to follicle-stimulating hormone levels.[52] The French GAZEL study found that perimenopausal women were more likely to report hot flushes than premenopausal women.[43] Perimenopause-postmenopause status in our series also related to more bothersome VMS; however, this was not as strong as the presence of severe psychological/urogenital symptoms perhaps because nearly 40% of our premenopausal women also presented VMS. A stronger association between menopause status and VMS has been reported for Australian women.[53] Consistent with the findings of others,[54-56] our series found that surgical menopause was related to more severe VMS, explaining why HT use among surgically menopausal women was two times higher.

Lower education in our series was related to severe VMS. This association has been reported by others[57] and may also apply to other ethnic groups.[58,59] The lower educational level among Latin American women may relate to lower socioeconomic status, which correlates to an earlier menopause onset,[60] obesity, and unhealthy lifestyles,[61] all which favor more intense menopausal symptoms.

More than one third of the women in our study lived at high altitude, a factor also related to more intense VMS. A possible explanation for this may be the fact that women who live in high altitude display lower oxygen saturation levels once they reach menopause, thus correlating with lower plasma estradiol levels and more intense symptoms.[62] Few studies have related VMS with high altitude. Slovenian women living in the valleys as compared with high altitude reported similar VMS frequency.[63] Contrary to this, Chedraui et al[23] have reported that Ecuadorian women who live in high altitude present with hot flushes more frequently than those living on the coast, yet symptom severity was higher for the latter.

Consistent with several studies demonstrating the effectiveness of HT in treating VMS,[3] the present series found HT use as a factor related to less intense VMS. Climate and smoking habit were not related to more intense VMS in the present study. Women in warmer temperatures report fewer hot flushes, and the difference between the hottest and coldest temperatures was also a significant predictor.[64] Conversely, others have reported a direct relation between warmer climate and more intense hot flushes.[23] A direct relation between hot flushes and the number of cigarettes smoked has been

reported.[65] This was not the case in our series, perhaps because of the fact that smoking habit is low among middle-aged Latin American women.[59]

Very few studies have assessed the risk factors for severe VMS persisting 5 years after menopause onset. Col et al[29] found that less physical activity, earlier VMS onset, and depressed mood related to a longer duration of severe VMS. The present series found that surgical menopause, a history of psychiatric consultation, and severe psychological/urogenital symptoms related to severe VMS persisting into the late postmenopausal phase. Our findings correlate with those of Col et al in relation to depressive symptoms.

Finally, as for the limitations of the present study, one can mention its cross-sectional–observational design; hence, the causal nature of each relationship cannot be assumed. Ideally, a study should be longitudinal; however, this requires follow-up and increases costs. Second, several variables were not taken into account such as physical activity and body composition, factors known to increase VMS prevalence. Daily hot flush quantification was not performed; however, this was not within the aims of the study. Despite the limitations outlined, several strengths can be identified: large sample size, the use of a validated menopausal symptom assessing tool, and the inclusion of women with surgical menopause and/or HT use. Despite the size of the sample studied, one must bear in mind that findings cannot be totally extrapolated to the whole or any Latin American population. This may be seen as another drawback; however, the data are indeed a useful reference tool that will aid in the designing of future studies.

CONCLUSIONS

VMS prevalence was high in this middle-aged Latin American series, with high VMS rates seen among premenopausal and late postmenopausal women. Several factors relating to VMS severity and duration were identified. In light of the fact that VMS related to severe quality of life impairment, dissemination of these results to the medical and general community should be encouraged to improve health care of middle-aged Latin American women.

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APPENDIX 1

List of Participating Countries (City) and Investigators

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