ORIGINAL ARTICLE

Negative affect symptoms, anxiety sensitivity, and vasomotor symptoms during perimenopause

Marianna de B. **Jaeger**,[1] (iD) Camila S. **Miná**,[2] Sofia **Alves**,[3] Gabriela J. **Schuh**,[3] Maria C. **Wender**,[4] Gisele G. **Manfro**[1]

[1]Programa de Pós-Graduação em Psiquiatria e Ciências do Comportamento, Universidade Federal do Rio Grande do Sul (UFRGS), Porto Alegre, RS, Brazil. [2]Programa de Pós-Graduação em Neurociências, Instituto de Ciências Básicas da Saúde (ICBS), UFRGS, Porto Alegre, RS, Brazil. [3]Faculdade de Medicina, UFRGS, Porto Alegre, RS, Brazil. [4]Programa de Pós-Graduação em Ciências da Saúde: Ginecologia e Obstetrícia, UFRGS, Porto Alegre, RS, Brazil.

Objective: Vasomotor symptoms affect 60-80% of women during the menopausal transition. Anxiety, depression, and anxiety sensitivity can have an important role in the distressful experience of vasomotor symptoms. Our aim was to evaluate the prevalence and association of vasomotor and negative affect symptoms.
Methods: A cross-sectional study was conducted with 89 perimenopausal women aged 45-55 years. Broad psychiatric and clinical evaluations were carried out. The primary outcome was the vasomotor symptom problem rating and the main study factor was anxiety sensitivity. Linear regression analyses were conducted to examine the associations between the study factors and the primary outcome, and a multiple regression model was created to assess which variables were independently associated with vasomotor symptom problem rating.
Results: The prevalence of anxiety, depression, and vasomotor symptoms were 58, 62, and 73%, respectively. Negative affect symptoms were positively associated with vasomotor symptom problem rating. The association of anxiety sensitivity and vasomotor symptom problem rating remained significant after controlling for perimenopausal stage, thyrotropin, follicle-stimulating hormone levels, and psychotropic medication use (β = 0.314, p = 0.002).
Conclusion: A better understanding of the experience of vasomotor symptoms is needed, especially the role of negative affect symptoms and anxiety sensitivity. New strategies focusing on related thoughts and behaviors could improve the quality of life of perimenopausal women.

Keywords: Anxiety; depression; perimenopause

Introduction

Vasomotor symptoms (VMS) are characterized by hot flashes and night sweats (HF/NS) and are considered a major symptom of menopause, affecting 60-80% of women during the menopausal transition, especially in the late perimenopause and early postmenopausal years.[1] Perimenopause is a period with a high prevalence of negative affect symptoms: 46.9 and 56.3% of perimenopausal Brazilian women reported depression and anxiety symptoms, respectively.[2] Although the relationship between negative affect and VMS is not fully understood, these two factors have consistently been associated across investigations.[1] This association suggests that women with more depression, anxiety, and general negative mood are at increased risk for reporting VMS and are also more bothered by symptoms, regardless of their frequency. Alternatively, VMS may also have a negative impact on mood.[3] Regarding depression, a bidirectional association with VMS is largely supported by the literature.[4] However, the association between anxiety and VMS is still controversial, since there have been different results about the presence of a direct relationship between VMS severity and anxiety symptoms.[5] Two main questions remain unclear: whether anxiety precedes or is a consequence of HF, and whether anxiety can influence the perception or number of HF events.[6]

One possible explanation for the lack of consensus about the association between anxiety and VMS is the heterogeneity of anxiety and vasomotor measures. Moreover, measures that confound physical and psychological symptoms cannot distinguish between the somatic aspects of anxiety and VMS.[5] A study by Gibson et al.[3] evaluated the temporal associations between VMS and negative affect in the multi-site Study of Women's Health Across the Nation (SWAN). In their sample, negative

affect, adjusted by same-day VMS, was not associated with next-day VMS. In contrast, VMS, adjusted by same-day negative mood, was associated with next-day negative mood. In another longitudinal analysis from the SWAN study, Bromberger et al.[7] reported that although the association of frequent VMS with high levels of anxiety was significant for all women over a 10-year follow-up period, the odds were greater among those with high baseline anxiety. On the other hand, for women who did not have high baseline anxiety levels, VMS increased the odds of having high anxiety across the stages of the menopause transition. Moreover, the Penn Ovarian Aging cohort explored the differences between affective and somatic anxiety symptoms and found that the somatic symptom dimension increased the risk of HF more than 300% during the menopausal transition.[6] These findings could indicate the importance of concepts such as anxiety sensitivity (AS) in the relationship between anxiety-related sensations and the experience of HF.

AS is the personal tendency to react with fear to anxiety-related symptoms. It results from the belief that these symptoms and sensations have harmful somatic, social, or psychological consequences.[8] Empirically, AS is distinguishable from the tendency to experience more frequent anxiety symptoms (e.g., trait anxiety) and the propensity to negative affect (e.g., neuroticism). Although AS was initially conceptualized as a specific vulnerability factor for panic disorder, due to the prominence of fears in that disorder, it has since been established more broadly as an index of distress intolerance.[9]

Individuals with high AS are hypervigilant regarding internal stimuli and are more likely to misinterpret benign physical sensations as having harmful consequences: they worry that something might be seriously wrong when they have palpitations or when they blush or sweat in front of people. Women with high levels of AS report greater levels of anxiety, depression, and menstrual distress across the menstrual cycle than women with low levels of AS. Although it has been determined that AS plays an important role in the heightened reactions to hormonal changes exhibited by some women in menstrual distress, few studies have evaluated the specific association between AS and VMS.[10]

The aim of this study was to explore the association between negative affect (mainly anxiety and its components) and HF/NS in perimenopausal women. The primary objective was to evaluate the association between AS symptoms and the bothersomeness of VMS. Our hypothesis was that perimenopausal women with more negative affect symptoms, specifically AS symptoms, would have higher VMS problem ratings.

Methods

Procedures and participants

In this cross-sectional investigation, women between 45 and 55 years old in the menopausal transition were invited to participate in this study through Internet and newspaper announcements made between March and September, 2017. Menopausal transition was defined according to the Stages of Reproductive Aging Workshop criteria: menstruation within the past 12 months but a persistent difference of 7 days or more in the length of consecutive cycles or an interval of amenorrhea of 60 days or more.[11] The exclusion criteria were comorbid diagnosis of substance abuse or psychotic episode (past or present), untreated clinical diseases, menopause after surgery or chemotherapy, hormone replacement therapy, or oral contraceptive use.

Upon their visit to the hospital clinical research center, the participants had an extensive clinical, gynecological, and psychiatric evaluation. They also completed self-reported questionnaires regarding AS and their physical activity. Blood samples were collected by convenience for a complete blood count and to determine follicle-stimulating hormone (FSH) and thyrotropin (TSH) levels.

Measurements

Information on sociodemographic, clinical, and gynecological variables were collected using a structured questionnaire by trained psychiatrist and psychologist. The evaluated sociodemographic characteristics were age, self-reported race, educational level, employment, and socioeconomic class (according to 2016 Associação Brasileira de Empresas de Pesquisas criteria).[12] Clinical variables, smoking, weight profile, chronic disease, psychotropic medication use (antidepressants, antipsychotics, mood stabilizers, or anxiolytics), and family history of psychiatric disorders were assessed by the researchers. Gynecological information included the presence of premenstrual symptoms prior to perimenopause, family history of VMS, and perimenopausal stage (according to the date of the last period). Physical activity was evaluated using the International Physical Activity Questionnaire-Short Form, which assesses the intensity of different activities, including planned exercise and housework. This questionnaire was translated and validated for use in Brazil and has good reliability.[13]

Psychiatric disorders were assessed with the Mini-International Neuropsychiatric Interview (MINI), which consists of a structured and validated diagnosis interview based on DSM-IV and CID-10 psychiatric diagnostic criteria (adapted by the researches to DSM-5 criteria).[14] The instrument has been translated and validated for use in Brazil.[15]

The severity of anxiety and depression symptoms were evaluated using the Hamilton Anxiety Rating Scale (HAM-A) and the Hamilton Depression Scale (HAM-D), respectively. The HAM-A is a widely used 14-item clinical scale that measures somatic and psychic anxiety symptoms. Scores range from 0 to 56[16] and were classified as mild anxiety (14 to 17), moderate anxiety (18 to 24), and moderate to severe anxiety ($\geqslant$25 points).[17] It was translated and validated for use in Brazil, showing good psychometric properties.[18]

The HAM-D investigates how the patient has been feeling in the last seven days. We used the validated version of the scale. Scores range from 0 to 52 and are classified as follows: severe depression ($>$25), moderate depression (18-24), and mild depression (7-17).[19]

HF/NS frequency was measured with the Hot Flush Rating Scale, which records the number of HF/NS experienced in the previous week. The scale has good test-retest reliability (r = 0.8) and validity, with significant correlations based on daily diary recordings of HF (r = 0.97, p < 0.001) and NS (r = 0.94, p < 0.001). Scores were derived using factor analysis with good internal consistency (Cronbach's α = 0.9) and test-retest reliability (r = 0.8). The scale was translated and adapted for use in Brazil with good internal consistency (frequency-Cronbach's α = 0.739; problem-rating-Cronbach's α = 0.912). Problem rating, the primary outcome of this study, is determined by the mean of three items: To what extent do you regard your flashes/sweating as a problem?; How distressed do you feel about your HF?; and How much do your HF interfere with your daily routine? Each item is measured on a 10-point scale, with higher scores indicating more problematic HF.[20]

The Anxiety Sensitivity Index-Revised (ASI-R) was used to evaluate the level of AS, which was our main study factor. It consists of a Likert scale from 0 (agree very little) to 4 (agree very much). The sum of the responses for the 36 items represent the AS level, with higher scores indicating a more intense AS level.[21] The ASI-R has adequate criterion validity and excellent internal consistency (α = 0.95), with all 36 items showing adequate item-total correlations.

Data analysis

Frequencies and percentages were used to describe categorical variables. Median and percentiles (25 and 75) or means and standard deviation (SD) were used to describe numeric variables. According to the Shapiro-Wilk test, VMS problem rating did not have normal distribution. SPSS version 25.0 was used for all analyses.

The presence of any anxiety disorder (panic disorder, agoraphobia, social anxiety disorder, or generalized anxiety disorder) was an independent measure. To compare characteristics between patients with and without a diagnosed anxiety disorder, the χ^2 test was used for sociodemographic, gynecological, and clinical factors, while an independent-sample Mann-Whitney U test was used to compare factors related to VMS.

We used simple regressions to test the association between the dependent variable (VMS problem rating) and the independent variables. To assess which variables were independently associated with VMS problem rating, we constructed a multiple regression model, using the variance inflation factor to evaluate multicollinearity. Variables were chosen for the multiple regression model according to multicollinearity and clinical relevance.

The sample size calculation considered the probability of a type I error of 0.05 (bilateral) and a type II error of 0.2. Based on Freeman et al.,[22] a correlation coefficient of 0.3 was expected between anxiety and VMS regarding depressive symptoms, and a sample size of 85 women was considered to have sufficient power to detect differences. A significance level of 5% was accepted in all analyses and all tests were two-tailed.

Ethics statement

This study was approved by the ethics committee of Hospital de Clínicas de Porto Alegre, state of Rio Grande do Sul, Brazil. Written informed consent was obtained from all participants.

Results

Of the 240 women who sought enrollment in the study by e-mail, 92 were interviewed and 89 were considered eligible for participation (one was not perimenopausal, one could not finish the interview, and one was taking hormonal contraceptives). The sociodemographic, clinical, and gynecological characteristics of the sample are described in Table 1.

The results of the complete psychiatric evaluation are shown in Table 2. The prevalence of anxiety symptoms in our sample was 58.43%, and 39.3% were diagnosed with any anxiety disorder. A total of 61.79% of the women reported depressive symptoms.

Seventy-three percent of women reported VMS: 66.3% had HF and 52.8% had NS. The median frequency of VMS was 10 per week and the mean problem rating was 4.33 (Table 3). Women diagnosed with any anxiety disorder had more premenstrual symptoms (p = 0.046) and higher psychotropic medication use (p = 0.032), as well as higher scores in all components of the VMS problem rating scale (extent as a problem, distress, and interference with daily routine) compared to those without anxiety disorders.

Perimenopausal stage, complete blood count, AS Index, FSH and TSH levels, HAM-A and HAM-D scores, and number of diagnosed disorders (MINI) were significantly associated with VMS problem rating in the unadjusted analysis (Table 4). The frequency of VMS was also associated with problem rating (β = 0.505, p < 0.001), predicting 25.5% of the variance. Regarding the association between VMS problem rating and AS, the β was 0.254 and the p-value = 0.018. The association between AS and frequency of VMS was not statistically significant (β = -0.032, p = 0.768).

For the multivariate analysis, we excluded the HAM-A and HAM-D results and the number of diagnosed disorders (MINI) due to their collinearity with the AS Index, the main study factor. Since the literature indicates that psychotropic medications can interfere with both anxiety symptoms and VMS, we chose to include them, despite their non-significant correlation with VMS problem rating in our sample.[23] After adjustment, the association between VMS problem rating and AS symptoms remained statistically significant (β = 0.314, p = 0.002) after controlling for perimenopausal stage, psychotropic medication use, and FSH and TSH levels (Table 5). This model explained 26.9% of the VMS problem rating variance.

Discussion

In this sample of 89 perimenopausal women, the majority reported having VMS with HF/NS and considered the

Table 1 Characteristics of the sample and comparisons of women with and without anxiety diagnosis

Characteristics	Total	With anxiety diagnosis	Without anxiety diagnosis	p-value
Race				1.0
White	77 (86.5)	31 (40.3)	46 (59.7)	
Nonwhite	12 (13.5)	4 (33.3)	8 (66.7)	
Marital status				1.0
With a partner	62 (69.7)	24 (38.7)	38 (61.3)	
Without a partner	27 (30.3)	11 (40.7)	16 (59.3)	
Education, years				0.692
0-8	6 (6.7)	2 (33.3)	4 (66.7)	
9-11	33 (37.1)	15 (45.4)	18 (54.6)	
12 or more	50 (56.2)	18 (36.0)	32 (64.0)	
Paid employment				0.339
Yes	64 (71.9)	23 (35.9)	41 (64.1)	
No	25 (28.1)	12 (48.0)	13 (52.0)	
Sociodemographic class				0.367
A	13 (14.6)	3 (23.1)	10 (76.9)	
B1	18 (20.2)	10 (55.5)	8 (44.5)	
B2	27 (30.3)	10 (37.0)	17 (63.0)	
C1	21 (23.6)	7 (33.3)	14 (66.7)	
C2	9 (10.1)	5 (55.6)	4 (44.4)	
D-E	1 (1.1)	0 (0.0)	1 (1.0)	
Smoker				1.0
Yes	83 (93.3)	33 (39.8)	50 (60.2)	
No	6 (6.7)	2 (33.3)	4 (66.7)	
Physical activity (IPAQ) (n=83)				1.0
Active	69 (83.1)	27 (39.1)	42 (60.9)	
Sedentary	14 (16.9)	6 (42.9)	8 (57.1)	
Weight profile				0.290
Normal weight (BMI 18.5-24.9 kg/m^2)	24 (26.9)	9 (37.5)	15 (62.5)	
Overweight (BMI 25-29.9 kg/m^2)	33 (37.1)	10 (30.3)	23 (69.7)	
Obese (BMI $\geqslant$ 30)	32 (36.0)	16 (50.0)	16 (50.0)	
Chronic disease				0.829
Yes	50 (56.2)	19 (38.0)	31 (62.0)	
No	39 (43.8)	16 (41.0)	23 (59.0)	
Use of psychotropic medication				0.032
Yes	19 (21.3)	12 (63.2)	7 (38.8)	
No	70 (78.7)	23 (32.9)	47 (67.1)	
Premenstrual symptoms				0.046
Yes	54 (60.7)	26 (48.1)	28 (51.9)	
No	35 (39.3)	9 (25.7)	26 (74.3)	
Family history of vasomotor symptoms				0.368
Yes	58 (65.2)	25 (43.1)	33 (56.9)	
No	31 (34.8)	10 (32.3)	21 (67.7)	
Family history of psychiatric disorders				0.829
Yes	40 (44.9)	15 (37.5)	25 (62.5)	
No	49 (55.1)	20 (40.8)	29 (59.2)	
Perimenopausal stage				0.521
Early	39 (44.3)	14 (35.9)	25 (64.1)	
Late	49 (55.7)	21 (42.9)	28 (57.1)	

Data presented as n (%).
BMI = body mass index; IPAQ = International Physical Activity Questionnaire.

symptoms to be dysfunctional. In addition, more than half of the sample had depressive and anxiety symptoms. Furthermore, 39.3% were diagnosed with any anxiety disorder. Women with anxiety disorders described their VMS as more bothersome, more dysfunctional and distressful, and as having greater interference in their daily routine than women not diagnosed with any anxiety disorder. Higher VMS problem ratings were associated with perimenopausal stage, FSH and TSH values, depressive and anxious symptoms, number of diagnosed

Table 2 Assessment of psychiatric characteristics

Measurement	n (%)
Mini-International Neuropsychiatric Interview (n=89)	
Major depressive episode – current	22 (24.7)
Major depressive episode – previous	27 (30.3)
Persistent depression	9 (10.1)
Suicide risk	1 (1.1)
Bipolar disorder type I	2 (2.2)
Bipolar disorder type II	1 (1.1)
Panic disorder	5 (5.6)
Agoraphobia	14 (15.7)
Social anxiety disorder	17 (19.1)
Obsessive-compulsive disorder	2 (2.2)
Post-traumatic stress disorder	1 (1.1)
Compulsive eating disorder	3 (3.4)
Generalized anxiety disorder	32 (36.0)
Any anxiety disorder	35 (39.3)
Hamilton Anxiety Scale (n=89)	
No anxiety	37 (41.6)
Mild anxiety	14 (15.7)
Moderate anxiety	15 (16.9)
Moderate-severe anxiety	23 (25.8)
Hamilton Depression Scale (n=89)	
No depression	34 (38.2)
Mild depression	40 (44.9)
Moderate depression	12 (13.5)
Severe depression	3 (3.4)
Anxiety Sensitivity Index-Revised (n=86), median (percentiles 25/75)	14.0 (5.0/46.0)
Penn State Worry Questionnaire (n=85)	
Low worry	15 (17.6)
Moderate worry	49 (57.6)
Severe worry	21 (24.7)

Table 3 Vasomotor symptoms

	Total	With anxiety disorder	Without anxiety disorder	p-value
Hot flashes and night sweats	65 (73.0)	27 (41.5)	38 (58.5)	0.626
Hot flashes	59 (66.3)	24 (40.7)	35 (59.3)	0.820
Night sweats	47 (52.8)	21 (44.7)	26 (55.3)	0.288
Hot Flush Rating Scale, median (percentiles 25/75)				
Hot flash frequency (per week)	6.0 (0.0/21.0)	6.0 (0.0/21.0)	6.0 (0.0/21.0)	0.668
Night sweat frequency (per week)	1.0 (0.0/13.0)	3.0 (0.0/15.0)	0.0 (0.0/7.5)	0.202
Hot flash or night sweat frequency (per week)	10.0 (0.0/35.0)	10.0 (1.0/35.0)	10.0 (0.0/35.8)	0.983
Rating of extent as a problem	5.0 (1.0/8.0)	8.0 (1.0/9.0)	4.5 (1.0/8.0)	0.041
Rating of distress	5.0 (1.0/8.0)	7.0 (1.0/8.0)	3.5 (1.0/6.0)	0.015
Rating of interference with daily routine	2.0 (1.0/7.0)	5.0 (1.0/8.0)	1.0 (1.0/5.0)	0.019
Problem rating	4.3 (1.0/7.3)	6.3 (1.0/8.0)	3.7 (1.0/6.4)	0.016

Data presented as n (%), unless otherwise specified.

psychiatric disorders, and AS symptoms. An important finding was that the association of AS and VMS problem rating remained significant even when adjusted for perimenopausal stage, FSH, TSH, and psychotropic medication use. To our knowledge, few studies have explored the relationship between negative affect and VMS problem rating, focusing specifically on the role of AS.

Although the prevalence of major depression disorder and depressive symptoms in our sample was high, it is in agreement with the literature. In Brazilian studies with perimenopausal women, the prevalence of the diagnosis of depression has ranged from 18.7 to 34.3%, while the prevalence of depressive symptoms has been reported as 46.9%.[2,24,25] In a cross-sectional study of the SWAN cohort, 68.6% of perimenopausal women reported depressive symptoms. Likewise, the prevalence of anxiety disorders and symptoms in our study resemble the rates found by other studies. Veras et al.[24] found that 33.3% of peri- and postmenopausal Brazilian women were diagnosed with anxiety disorders according to the MINI, and the prevalence of anxiety symptoms reported by Polisseni et al.[2] was 56.3%. Other studies, however,

Table 4 Results of the simple regression of study factors and the primary outcome*

	Unstandardized coefficients		Standardized coefficients		
	B	SE	β	t	p-value
Perimenopausal stage	1.305	0.631	0.218	2.068	0.042
Complete blood count	2.050	0.912	0.235	2.247	0.027
Anxiety Sensitivity Index	0.025	0.011	0.254	2.406	0.018
Follicle-stimulating hormone	0.026	0.009	0.296	2.888	0.005
Thyrotropin	-0.972	0.302	-0.326	-3.216	0.002
Hamilton Anxiety Scale	0.141	0.028	0.480	5.109	0.000
Hamilton Depression Scale	0.145	0.045	0.325	3.211	0.002
Number of diagnoses – MINI	0.606	0.200	0.310	3.037	0.003
Penn State Worry Questionnaire	0.039	0.028	0.153	1.409	0.163
Psychotropic medication use	0.493	0.779	0.068	0.633	0.528

MINI = Mini-International Neuropsychiatric Interview; SE = standard error.
* Problem-rating of vasomotor symptoms.

Table 5 Results from the multiple regression of the study factors and the primary outcome*

	Unstandardized coefficients		Standardized coefficients		
	B	SE	β	t	p-value
(Constant)	3.563	1.140		3.126	0.002
Perimenopausal stage	0.803	0.621	0.134	1.292	0.200
Follicle-stimulating hormone	0.021	0.009	0.242	2.328	0.022
Thyrotropin	-0.993	0.299	-0.328	-3.325	0.001
Anxiety Sensitivity Index	0.031	0.010	0.314	3.185	0.002
Psychotropic medication use	-0.286	0.701	-0.040	-0.407	0.685

SE = standard error.
* Vasomotor symptom problem rating.

reported frequencies ranging from 9 to 21%, and these lower rates may be associated with broader inclusion criteria and the rating scales used.[26,27]

The women in our sample presented slightly higher AS levels than a nonclinical sample of undergraduate American and Canadian women (ASI-R = 12.8; SD = 10.5), but a lower mean total score than a sample of patients diagnosed with primary anxiety (ASI-R = 30.8; SD = 15.3).[21,28] Although we found no studies that applied the ASI-R to perimenopausal women, it can be inferred that our results are similar to nonclinical samples.

The prevalence of VMS in our sample was similar to that found by a cross-sectional Brazilian study.[29] In the SWAN cohort, 60-80% of women experienced VMS during the menopausal transition,[1] and in a cross-sectional study of women from Chile, Ecuador, Panama, and Spain, 58.5% of the sample reported VMS.[20] More than half of our sample reported HF and 52.8% complained of NS, rates similar to those found in a study of perimenopausal women from southern Brazil.[29] The frequency of HF/NS in our study was lower than that found by a large study with a sample of women from different countries, although the results are similar in terms of problem rating scores.[20] Several studies have also reported an association between depressive symptoms and VMS, but few have focused on HF/NS.[29-31] On the other hand, many anxiety studies have found an association with VMS severity and bothersomeness.[20,32,33] Our study showed high prevalence rates of generalized anxiety disorder and social anxiety disorder. The former is characterized by worry and fear of different situations, catastrophic thoughts, and body sensations, while the latter is characterized by hypervigilance to social and somatic clues. Both disorders are associated with higher AS, and thus with the bothersomeness of VMS.

In our sample, the VMS problem rating was associated with perimenopausal stage, FSH, and TSH. Longitudinal studies have also found an association between perimenopausal stage and VMS, reporting increased frequency and severity in the late perimenopausal stage.[32,34] In the adjusted analysis, however, perimenopausal stage was not associated with VMS problem rating, which was also reported by Freeman et al.[6] Several other studies have also reported an association between the frequency and severity of VMS and FSH levels.[1,34] Since VMS occur in the context of the reproductive hormone changes in the menopausal transition (declining estrogen levels and rising FSH levels, which stabilize in the late transition and postmenopause), it can be inferred that women with higher FSH levels would have more frequent and bothersome VMS.[35] Interestingly, we found a negative association between TSH and VMS problem rating. Very few studies have explored this association, and most reported that symptoms of thyroid function abnormalities could be very similar to those of menopause, including VMS.[36] Because of the numerous interactions between thyroid hormones and most body systems, as well as their major role in metabolism, the relationship between thyroid hormones and VMS requires further investigation.[34]

The hypothesis that women with higher levels of negative affect and, specifically, higher rates of AS, would be more bothered by VMS was confirmed in our study. Moreover, adjusting for biological variables (FSH and TSH),

perimenopausal stage, and psychotropic medication use, the association with AS remained significant. One possible explanation for our findings is that women with higher AS are more vigilant to symptoms such as palpitations, sweating, and blushing, which are common VMS, and are prone to interpret them as signs of a more serious condition. Also, women with higher AS might interpret VMS as having an extremely harmful social impact, since women have little control over the appearance and duration of HF.

These findings are consistent with Muslic et al.,[8] who showed that AS plays an important role in perimenopausal distress. Focusing on VMS, Hunter & Chilcot[37] developed and tested a cognitive behavioral model, and their study suggested that the level of symptom perception and somatic amplification could increase the likelihood of symptom detection, but could also increase the reporting of HF/NS due to a higher sensitivity and selective attention to small variations in thermoregulatory sensations.

Our findings must be interpreted in light of certain limitations. The cross-sectional design provides no information on the causal relationship between the factors. Furthermore, although our sample size had sufficient enough power to detect differences, it was not a large sample. Selection bias secondary to the means of enrollment could have determined that women with higher education and more concerned about their health were interviewed. In addition, the rate of psychiatric comorbidity was high, which might have interfered with the perception of VMS, possibly inflating the association between AS and VMS problem rating. However, our study also has a number of strengths. We conducted a broad psychiatric evaluation using trained clinicians, instead of using only self-report questionnaires. Not only was the severity of anxiety and depression symptoms evaluated, but depressive and anxiety disorders were diagnosed as well. Exploring the factors related to VMS problem rating provides important information for clinical purposes, making it possible to develop cost-effective non-pharmacological strategies, such as protocols for interventions based on psychoeducation and cognitive-behavioral techniques. Few studies have focused on the association between AS and VMS. Further studies with larger samples and longitudinal designs are needed to explore the relationship between negative affect and the bothersomeness of VMS, with a view to understanding the role of AS.

In short, based on our findings, it can be concluded that the evaluation of women seeking treatment for VMS should include assessment of negative affect symptoms. Moreover, the early identification of women with higher levels of AS and VMS would allow the development of new strategies targeting these symptoms, reducing the burden of psychological and somatic changes brought about by the menopausal transition.

Disclosure

The authors report no conflicts of interest.

References

1 Thurston RC, Joffe H. Vasomotor symptoms and menopause: findings from the study of women's health across the nation. Obstet Gynecol Clin North Am. 2011;38:489-501.
2 Polisseni ÁF, de Araújo DA, Polisseni F, Mourão Junior CA, Polisseni J, Fernandes ES, et al. [Depression and anxiety in menopausal women: associated factors]. Rev Bras Ginecol Obstet. 2009;31:28-34.
3 Gibson CJ, Thurston RC, Bromberger JT, Kamarck T, Matthews KA. Negative affect and vasomotor symptoms in the study of women's health across the nation daily hormone study. Menopause. 2011; 18:1270-7.
4 Worsley R, Bell R, Kulkarni J, Davis SR. The association between vasomotor symptoms and depression during perimenopause: a systematic review. Maturitas. 2014;77:111-7.
5 Bryant C, Judd FK, Hickey M. Anxiety during the menopausal transition: a systematic review. J Affect Disord. 2012;139:141-8.
6 Freeman EW, Sammel MD. Anxiety as a risk factor for menopausal hot flashes: evidence from the Penn ovarian aging cohort. Menopause. 2016;23:942-9.
7 Bromberger JT, Kravitz HM, Chang Y, Randolph JF Jr, Avis NE, Gold EB, et al. Does risk for anxiety increase during the menopausal transition? Study of women's health across the nation. Menopause. 2013;20:488-95.
8 Muslić L, Jokić-Begić N. The experience of perimenopausal distress: examining the role of anxiety and anxiety sensitivity. J Psychosom Obstet Gynaecol. 2016;37:26-33.
9 Otto MW, Eastman A, Lo S, Hearon BA, Bickel WK, Zvolensky M, et al. Anxiety sensitivity and working memory capacity: risk factors and targets for health behavior promotion. Clin Psychol Rev. 2016; 49:67-78.
10 Sigmon ST, Dorhofer DM, Rohan KJ, Boulard NE. The impact of anxiety sensitivity, bodily expectations, and cultural beliefs on menstrual symptom reporting: a test of the menstrual reactivity hypothesis. J Anxiety Disord. 2000;14:615-33.
11 Harlow SD, Gass M, Hall JE, Lobo R, Maki P, Rebar RW, et al. Executive summary of the stages of reproductive aging workshop + 10: addressing the unfinished agenda of staging reproductive aging. J Clin Endocrinol Metab. 2012;97:1159-68.
12 Associação Brasileira de Empresas de Pesquisa (ABEP). Critério Brasil 2019 [Internet]. [cited 2020 Jul 28]. http://www.abep.org/criterio-brasil
13 Craig CL, Marshall AL, Sjöström M, Bauman AE, Booth ML, Ainsworth BE, et al. International physical activity questionnaire: 12-country reliability and validity. Med Sci Sports Exerc. 2003;35:1381-95.
14 Sheehan DV, Lecrubier Y, Sheehan KH, Amorim P, Janavs J, Weiller E, et al. The Mini-International Neuropsychiatric Interview (M.I.N.I.): the development and validation of a structured diagnostic psychiatric interview for DSM-IV and ICD-10. J Clin Psychiatry. 1998;59 Suppl 20:22-33; quiz 34-57.
15 Amorim P. Mini International Neuropsychiatric Interview (MINI): validation of a short structured diagnostic psychiatric interview. Rev Bras Psiquiatr. 2000;22:106-15.
16 Shear MK, Bilt JV, Rucci P, Endicott J, Lydiard B, Otto MW, et al. Reliability and validity of a structured interview guide for the Hamilton anxiety rating scale (SIGH-A). Depress Anxiety. 2001;13:166-78.
17 Hamilton M. The assessment of anxiety states by rating. Br J Med Psychol. 1959;32:50-5.

18 DeSousa DA, Moreno AL, Gauer G, Manfro GG, Koller SH. Revisão sistemática de instrumentos para avaliação de ansiedade na população brasileira. Aval Psicol. 2013;12:397-410.

19 Freire MÁ, de Figueiredo VL, Gomide A, Jansen K, da Silva RA, Magalhães PV, et al. Hamilton scale: study of the psychometric characteristics in a sample from Southern Brazil. J Bras Psiquiatr. 2014;63:281-9.

20 Hunter MS, Gupta P, Chedraui P, Blümel JE, Tserotas K, Aguirre W, et al. The international menopause study of climate, altitude, temperature (IMS-CAT) and vasomotor symptoms. Climacteric. 2013; 16:8-16.

21 Escocard MRPG, Fioravanti-Bastos ACM, Landeira-Fernandez J. Anxiety sensitivity factor structure among Brazilian patients with anxiety disorders. J Psychopathol Behav Assess. 2008;31:246-55.

22 Freeman EW, Sammel MD, Liu L, Martin P. Psychometric properties of a menopausal symptom list. Menopause. 2003;10:258-65.

23 Jacob JA. Can nonhormonal treatments dial down the heat during menopause? JAMA. 2016;315:14-6.

24 Veras AB, Rassi A, Yukizaki LMG, Novo LD, Franco FS, Nardi AE. Impacto dos transtornos depressivos e ansiosos sobre as manifestações da menopausa. Rev Psiquiatr Rio Gd Sul. 2007;29:315-20.

25 Silva M-NM da, Brito LMO, Chein MB da C, Brito LGO, Navarro PA de AS. Depressão em mulheres climatéricas: análise de mulheres atendidas ambulatorialmente em um hospital universitário no Maranhão. Rev Psiquiatr Rio Gd Sul. 2008;30:150-4.

26 Li Y, Yu Q, Ma L, Sun Z, Yang X. Prevalence of depression and anxiety symptoms and their influence factors during menopausal transition and postmenopause in Beijing city. Maturitas. 2008;61:238-42.

27 Hantsoo L, Epperson CN. Anxiety disorders among women: a female lifespan approach. Focus (Am Psychiatr Publ). 2017;15:162-72.

28 Taylor S, Zvolensky MJ, Cox BJ, Deacon B, Heimberg RG, Ledley DR, et al. Robust dimensions of anxiety sensitivity: development and initial validation of the anxiety sensitivity index-3. Psychol Assess. 2007;19:176-88.

29 Oppermann K, Fuchs SC, Donato G, Bastos CA, Spritzer PM. Physical, psychological, and menopause-related symptoms and minor psychiatric disorders in a community-based sample of Brazilian premenopausal, perimenopausal, and postmenopausal women. Menopause. 2012;19:355-60.

30 Flores-Ramos M, Heinze G, Silvestri-Tomassoni R. Association between depressive symptoms and reproductive variables in a group of perimenopausal women attending a menopause clinic in México City. Arch Womens Ment Health. 2010;13:99-105.

31 Woods NF, Mitchell ES. Symptoms during the perimenopause: prevalence, severity, trajectory, and significance in women's lives. Am J Med. 2005;118 Suppl 12B:14-24.

32 Gold EB, Colvin A, Avis N, Bromberger J, Greendale GA, Powell L, et al. Longitudinal analysis of the association between vasomotor symptoms and race/ethnicity across the menopausal transition: study of women's health across the nation. Am J Public Health. 2006;96:1226-35.

33 Seritan AL, Iosif AM, Park JH, DeatherageHand D, Sweet RL, Gold EB. Self-reported anxiety, depressive, and vasomotor symptoms: a study of perimenopausal women presenting to a specialized midlife assessment center. Menopause. 2010;17:410-5.

34 Ziv-Gal A, Flaws JA. Factors that may influence the experience of hot flushes by healthy middle-aged women. J Womens Health (Larchmt). 2010;19:1905-14.

35 Santoro N, Randolph JF Jr. Reproductive hormones and the menopause transition. Obstet Gynecol Clin North Am. 2011;38:455-66.

36 Oi N, Ohi K. Comparison of the symptoms of menopause and symptoms of thyroid disease in Japanese women aged 35-59 years. Climacteric. 2013;16:555-60.

37 Hunter MS, Chilcot J. Testing a cognitive model of menopausal hot flushes and night sweats. J Psychosom Res. 2013;74:307-12.