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Association of Premenstrual Syndrome with Blood Pressure in Young Adult Women

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Abstract

Objective: The prevalence of hypertension in premenopausal women is increasing. There is substantial need for novel strategies to identify women who would benefit from increased screening and early interventions. Several mechanisms likely contributing to premenstrual syndrome (PMS) are also involved in hypertension, including renin–angiotensin–aldosterone system dysfunction and micronutrient deficiencies. However, it is unknown whether young women with PMS have elevated blood pressure.

Materials and Methods: We evaluated the association of blood pressure, PMS, and premenstrual symptoms in a cross-sectional study of 409 young women (mean age 21 years), conducted from 2006 to 2014. Our analysis included 78 cases (19%) who met established criteria for clinically significant PMS and 88 controls (22%) experiencing few symptoms. Blood pressure was measured during the mid-luteal phase. Lifestyle, diet, anthropometry, and other factors were measured by questionnaire and/or direct measurement.

Results: After adjustment for smoking, body mass index, and other factors, mean diastolic blood pressure in PMS cases was 72.3 versus 69.1 mm Hg in controls ($p = 0.02$). Diastolic blood pressure was also significantly higher in women reporting specific symptoms; for example, mean diastolic blood pressure in women reporting moderate or severe premenstrual nausea was 77.7 mm Hg compared with 71.0 mm Hg in women without nausea ($p = 0.007$). Systolic blood pressure did not vary by PMS status.

Conclusions: To our knowledge, this is among the first studies to suggest that diastolic blood pressure is elevated in young adult women experiencing PMS. Prospective studies are needed to determine whether PMS may be a useful sentinel for future hypertension risk in young women.

Keywords: premenstrual syndrome, menstrual cycle, blood pressure, diastolic pressure

Introduction

Women with hypertension are at significant increased risk for heart attack, stroke, and kidney disease.[1] Risk increases linearly with systolic and diastolic blood pressure, such that even small increases are associated with higher risk of morbidity and mortality. Hypertension is highly preventable with diet and lifestyle modification and pharmacological treatments.[2] However, despite extensive knowledge of etiology and the availability of effective treatments, the prevalence of hypertension in women aged 18–39 years has increased by nearly a third since the mid-1990s and is now more than 7%.[3,4]

There is a substantial need for novel strategies to identify premenopausal women at high risk for hypertension who would benefit from increased screening and early interventions. Numerous studies have evaluated pregnancy as a ''stress test'' for future cardiovascular health, suggesting that pregnancy-induced hypertensive disorders may predict risk of hypertension and cardiovascular disease (CVD).[5,6] However, because these conditions are rare and, by definition, limited only to women who have had a pregnancy, they have limited utility as a screening tool. Identifying more prevalent reproductive health conditions that are also associated with elevated blood pressure and hypertension risk may have greater public health impact.

Clinically significant premenstrual syndrome (PMS) is experienced by 8%–15% of premenopausal women.[7,8] Multiple mechanisms contributing to PMS have also been implicated in hypertension, such as renin–angiotensin–aldosterone system (RAAS) dysfunction and micronutrient deficiencies.[9–12] Thus, PMS may potentially be associated with higher blood pressure and future risk of hypertension. It is unknown whether young

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women with PMS have higher systolic and diastolic blood pressure than women without PMS.

To address this question, we evaluated the relationship of blood pressure with PMS status and specific premenstrual symptoms among young adult women. We also assessed whether differences in blood pressure may be attributed to adiposity, smoking, and other risk factors shared by PMS and hypertension.

Materials and Methods

Study population

Between 2006 and 2014, we conducted a cross-sectional study of dietary and lifestyle factors and reproductive health in 409 women.[13,14] Participants were recruited through advertisements posted around the University of Massachusetts, Amherst campus. Women were eligible if they were 18–30 years old; had cyclic menstrual bleeding; did not report a history of high blood pressure, elevated cholesterol, kidney or liver disease, bone disease, digestive disorders, rheumatological disease, multiple sclerosis, thyroid disease, hyperparathyroidism, cancer, type 1 or type 2 diabetes, or polycystic ovaries; and were not taking corticosteroids, anabolic steroids, anticonvulsants, cimetidine, or propranolol. Study measurements were completed in a single clinic visit scheduled for 5–7 days before the anticipated start date of each participant's next menses (*i.e.*, the mid-luteal phase). The date of next menses was subsequently reported and used to confirm the luteal phase timing of measurements. The study protocol was approved by the Institutional Review Board at the University of Massachusetts. All participants provided informed consent before enrollment in the study.

Assessment of PMS

Menstrual symptom experience was assessed with a questionnaire based on the Calendar of Premenstrual Experiences[15] and similar to that used in the Nurses' Health Study 2 Premenstrual Syndrome Sub-Study.[10,16] Participants were provided a list of 26 premenstrual symptoms including abdominal bloating, breast tenderness, dizziness, headache, hot flashes, palpitations, nausea, swelling in the extremities, acne, diarrhea or constipation, fatigue, abdominal cramping, lower back pain, food cravings, increased or decreased appetite, insomnia, confusion, forgetfulness, anxiety or nervousness, irritability, emotional hypersensitivity, mood swings, depression, a tendency to cry easily, angry outbursts, or increased desire to be alone. For each symptom, participants were asked whether they had experienced it ''most months of the year for at least several days before [their] menstrual period begins'' and to indicate the severity. We assigned point values as follows: none, 1; mild, 2; moderate, 3; severe, 4. Women then classified their overall symptom severity as minimal (no effect on normal activities), mild (noticeable, but not troublesome), moderate (interferes with normal activities), or severe (intolerable, prevents normal activities).

Additional questions asked about the timing of symptom occurrence during the menstrual cycle. To evaluate the impact of symptoms on interpersonal relationships and life activities, we asked participants to indicate whether their symptoms caused relationship problems with family or partner, relationship problems with friends or coworkers, poor work or school performance or attendance, and/or increased desire to be alone as a result of their symptoms. Response options were not a problem, mild, moderate or severe. We asked all participants about history of depression and bipolar disorder and current use of antidepressant medications. In 2008, we added the General Depression 20-item Sub-scale of the Inventory of Depression and Anxiety Symptoms to our study.[17]

We identified women meeting criteria for moderate-to-severe PMS, along with a control group of women who experienced few menstrual symptoms of no personal impact. Case criteria were based on the University of California at San Diego criteria.[15] They included (1) at least one physical/behavioral symptom and one affective menstrual symptom, (2) impact of symptoms on life activities and relationships of ''moderate'' or ''severe,'' or overall symptom severity rated as ''moderate'' or ''severe'' along with at least one affective symptoms rated as ''severe,'' (3) symptoms beginning within 14 days of the start of menses, (4) symptoms ending within 7 days of the start of menses, (5) symptoms absent in the week after menses, and (6) no evidence of a comorbid psychiatric disorder (defined as history of unipolar or bipolar depression, current antidepressant use, or depressive symptom score >50). Overall, 78 women (19%) met case criteria. Controls were women who reported (1) overall symptom severity of ''none'' or ''mild'' for all individual symptoms; (2) overall symptom severity of ''none,'' ''minimal,'' or ''mild''; (3) impact of symptoms on life activities and relationships of ''not a problem'' or ''mild'' for all items; (4) confirmed no previous clinical diagnosis of PMS; and (5) no evidence of a comorbid psychiatric disorder. Overall, 88 women (22%) met control criteria.

The validity of the classification method has been demonstrated previously.[13] In brief, among 41 women, we compared case and control classifications made by a retrospective questionnaire with those made based on daily symptom diaries as the gold standard. Sensitivity of the modified questionnaire to identify PMS cases was 73%, whereas positive predictive value was 80%. The specificity in identifying controls was 73%, whereas the negative predictive value was 100%.

Assessment of blood pressure and covariates

Blood pressure was measured with a standard sphygmomanometer after the participant had been sitting quietly for 10 minutes. We collected information on lifestyle and demographic factors by the self-reported questionnaire, including race/ethnicity, age at menarche, smoking status, and use of oral contraceptives (OCs). Weight and height were directly measured and used to calculate body mass index (BMI) (weight [kg]/height $[m]^2$). We asked the amount of time spent each week engaged in walking, jogging, running, bicycling, aerobics/dancing, tennis/racket sports, swimming, yoga/Pilates, and weight training, and then calculated total metabolic equivalent of task-hours per week of physical activity.[18] Frequency of intake of 131 food items and supplements in the previous 2 months was measured using a modified version of the Harvard food frequency questionnaire, which has been extensively validated.[19] Questionnaires were analyzed at Harvard University and used to assess intake of vitamin D, calcium, B vitamins, iron, alcohol, and other nutrients. Nutrient intakes were energy adjusted using the residual method.[20]

Statistical analysis

All data analyses were conducted using SAS v9.4 (Cary, NC). We compared demographic and lifestyle factors in PMS cases and controls using *t* tests and chi-squared tests. We then compared adjusted mean systolic and diastolic blood pressure in women meeting criteria for PMS versus control women, using PROC MIXED. In our main analyses, we controlled for factors significantly associated with blood pressure and/or PMS, including age (months, continuous), BMI (continuous), age at menarche (continuous), current OC use (yes vs. no), smoking status (ever vs. never), and enrollment date (three indicator variables, modeled as random effects). Additional covariates tested but not included in final models were physical activity, race/ethnicity, multivitamin use, and dietary intakes of calcium, vitamin D, sodium, potassium, iron, zinc, and alcohol. Finally, we assessed whether blood pressure was differently associated with specific premenstrual symptoms by comparing adjusted mean levels in women classifying each symptom as moderate or severe with levels in those reporting no or mild symptoms.

Results

The characteristics of PMS cases ($n=78$) and controls ($n=88$) are presented in Table 1. The mean age was 20.9 years, and the majority of participants reported white race. PMS cases had slightly earlier age at menarche than controls (12.2 vs. 12.8 years; $p<0.01$) and were more likely to have smoked ($p=0.05$). PMS cases and controls did not differ significantly in terms of BMI, physical activity, multivitamin use, or other characteristics.

Diastolic blood pressure, but not systolic blood pressure, differed significantly between PMS cases and controls (Table 2). After adjustment for BMI, smoking, OC use, and other factors, mean diastolic blood pressure was 71.5 mm Hg in cases versus 68.4 mm Hg in controls ($p=0.02$), a difference of 3.1 mm Hg (4.7%). Additional adjustment for race/ethnicity or for physical activity did not alter results. Results from a sensitivity analysis limited to never smokers ($n=64$ cases and 81 controls) were slightly stronger (mean diastolic blood pressure in cases versus controls is 72.8 vs. 68.9 mm Hg; $p=0.006$).

We evaluated how experience of individual symptoms was associated with blood pressure, comparing mean systolic and diastolic blood pressures between women reporting moderate or severe levels of each symptom and women classifying each symptom as absent or mild. Symptoms for which case versus control differences in either systolic or diastolic blood pressure were >3.0 mm Hg are shown in Table 3. Few symptoms were associated with significant differences in systolic blood pressure. Women reporting moderate or severe hot flashes or night sweats had 6.1 mm Hg higher systolic blood pressure than those without ($p=0.04$). Anxiety was also associated with higher systolic blood pressure (3.9 mm Hg difference: $p=0.03$). Diastolic blood pressure was significantly higher in women who reported premenstrual nausea, depression, acne, and abdominal bloating (all $p<0.05$). Women reporting moderate or severe premenstrual nausea had 6.7 mm Hg higher diastolic blood pressure than those with little or no nausea ($p=0.007$). Differences in diastolic blood pressure for women experiencing palpitations, forgetfulness, dizziness, and hot flashes or night sweats were also large but did not reach statistical significance.

Table 1. Characteristics of Premenstrual Syndrome Cases and Controls, University of Massachusetts Premenstrual Syndrome Study (2006–2014)

Characteristic	*PMS cases* n = *78*	*PMS controls* n = *88*	p *Value*
	Mean (SD)	*Mean (SD)*	
Age (years)	20.9 (2.5)	20.9 (1.7)	0.91
Body mass index (kg/m^2)	23.0 (3.3)	22.7 (3.1)	0.50
Age at menarche (years)	12.2 (1.3)	12.8 (1.5)	0.01
Physical activity (MET/week)	47.1 (42.0)	54.4 (44.2)	0.28
Alcohol intake (g/day)	5.9 (6.2)	6.1 (7.7)	0.88
	%	%	
White race	73.1	84.1	0.08
Ever smoking[a]	18.1	8.0	0.05
Current smoking	9.1	4.6	0.24
Current oral contraceptive use	52.6	54.6	0.80
Current antidepressant use	0.0[b]	1.1	0.35
Multivitamin use	37.2	46.6	0.22

[a]Ever smoking category includes current and former smoking.
[b]PMS case exclusion criterion.
PMS, premenstrual syndrome.

Discussion

Our results suggest that diastolic blood pressure is higher in young women who experience clinically significant PMS than in women experiencing few premenstrual symptoms. Mean diastolic blood pressure was 3.1 mm Hg higher in PMS cases versus controls, with greater differences observed for specific premenstrual symptoms, such as nausea (mean difference = 6.7 mm Hg). These relations persisted after adjustment for other factors associated with high blood pressure including BMI and smoking.

Diastolic blood pressure has been consistently recognized as a stronger predictor of future CVD risk than systolic pressure in women under age 50.[21–23] The magnitude of difference in diastolic blood pressure associated with PMS in our study is comparable with or greater than those observed for smoking, physical inactivity, and overweight in other studies of young adults.[24,25] For example, in 695 Greek women with a mean age of 21.8 years, diastolic blood pressure was 0.8 mm Hg higher in smokers versus nonsmokers, 1.8 mm Hg higher in physically inactive versus active women, and 5.2 points mm Hg higher in overweight versus normal weight women.[24]

A variety of mechanisms may underlie a relation between PMS and blood pressure. First, dysfunction of the RAAS alters the regulation of sodium balance, blood volume, and arterial constriction, and consequently impacts blood pressure.[26] Progesterone and estrogens directly impact RAAS function and may independently affect aldosterone secretion in premenopausal women.[27,28] Clinical studies of PMS suggest that RAAS dysfunction is also involved in premenstrual

Table 2. Unadjusted and Adjusted Mean Levels of Blood Pressure in Premenstrual Syndrome Cases ($N=78$) Compared with Controls ($N=88$); University of Massachusetts Premenstrual Syndrome Study (2006–2014)

	Unadjusted (mm Hg)			*Multivariable adjusted*[a] *(mm Hg)*			
	PMS cases	*Controls*	p	*PMS cases*	*Controls*	*Difference*[b]	p
Systolic	108.7	108.2	0.73	112.3	111.1	1.2	0.39
Diastolic	69.9	68.3	0.21	71.5	68.4	3.1	0.02

[a]Adjusted for age (months, continuous), body mass index (kg/m^2, continuous), age at menarche (years, continuous), current oral contraceptive use (yes vs. no), smoking status (ever vs. never), and enrollment date (three indicator variables).
[b]Difference in mean blood pressure between PMS cases and controls.

edema symptoms, including abdominal bloating, swelling of extremities, and breast tenderness.[29] Late luteal phase aldosterone levels and plasma renin activity appear higher in women with PMS than in symptom-free controls.[9] Medications acting on the RAAS, including diuretics (*e.g.*, spironolactone) and some progestins with antialdosterone properties (*e.g.*, drospirinone), are effective treatments for both somatic and affective symptoms associated with PMS in many women.[30,31]

Second, we recently observed higher luteal phase levels of several inflammatory factors in women with PMS versus controls,[13] providing some evidence that chronic inflammation may be implicated in menstrual symptom occurrence, as it is in hypertension.[32] Furthermore, high intake of several micronutrients has been inversely associated with the development of PMS, including B vitamins, vitamin D, calcium, and other minerals.[10–12,14] Many of these micronutrients also appear to be inversely associated with hypertension.[2,33,34] Additional studies examining whether vascular function, micronutrient deficiency, and/or inflammation are causally related to both PMS and blood pressure will be essential for understanding these relations.

A potential etiological relation of PMS and blood pressure was first proposed by Okeahialam in a case report describing the remission of refractory hypertension in two young women experiencing PMS after successful treatment of their menstrual symptoms.[35] Interestingly, the main symptoms reported were abdominal bloating, panic, palpitations, pain, insomnia, and dizziness; these are among the symptoms most strongly associated with diastolic and systolic blood pressure in our study. Subsequently, the same author observed luteal phase increases in systolic and diastolic pressure in 273 women with PMS but not in controls,[36] and a higher prevalence of PMS in 48 women with hypertension than in 33 controls.[37] Similarly, Stamatelopoulos et al. also reported significant luteal phase increases in peripheral and central systolic blood pressure in 21 PMS cases but no increase in 15 controls.[38] In contrast, a study of nine PMS cases and nine controls did not observe significant differences in systolic or diastolic pressure between groups, but reported late luteal

Table 3. Multivariable Adjusted Mean Levels of Blood Pressure Among Women Experiencing Specific Menstrual Symptoms; University of Massachusetts Premenstrual Syndrome Study (2006–2014)

	Systolic blood pressure (mm Hg)					*Diastolic blood pressure (mm Hg)*				
	Symptom severity					*Symptom severity*				
Symptom	*Moderate or severe*	*None or mild*	*Difference*[a]	p		*Symptom*	*Moderate or severe*	*None or mild*	*Difference*[a]	p
Hot flashes/night sweats	117.3	111.2	6.1	0.04		Palpitations	78.5	71.2	7.3	0.12
Dizziness	117.5	112.2	5.3	0.18		Nausea	77.7	71.0	6.7	0.007
Anxiety	115.1	111.2	3.9	0.03		Forgetfulness	77.9	71.2	6.7	0.15
Forgetfulness	115.9	112.3	3.6	0.48		Dizziness	77.4	71.2	6.2	0.09
						Hot flashes/night sweats	74.4	70.2	4.2	0.12
						Insomnia	74.9	70.8	4.1	0.10
						Depression	74.3	70.4	3.9	0.02
						Acne	73.5	70.3	3.2	0.02
						Abdominal cramping	72.8	69.7	3.1	0.02

Adjusted for age (months, continuous), body mass index (kg/m^2, continuous), age at menarche (years, continuous), current oral contraceptive use (yes vs. no), smoking status (ever vs. never), and enrollment date (three indicator variables).
[a]Difference in mean blood pressure between women reporting each symptom as ''moderate'' or ''severe'' versus ''none'' or ''mild.'' Results shown for symptoms with difference ≥3.0 mm Hg.

phase plasma volume, aldosterone levels, and renin activity to be significantly higher in PMS cases.[9]

Assessing relations of blood pressure with specific premenstrual symptoms may help clarify common physiologies. We saw the strongest associations between diastolic blood pressure and nausea, palpitations, forgetfulness, dizziness, hot flashes/night sweats, insomnia, and depression; for all of these symptoms, diastolic pressure was >5% higher in women classifying each as moderate/severe versus mild/none. Notably, these premenstrual symptoms are similar to vasomotor, cognitive, and psychological symptoms commonly experienced during the menopausal transition, many of which have also been associated with risk of hypertension and CVD.[39–42] A small number of studies have observed correlations between premenstrual symptoms and menopausal symptoms,[43–47] suggesting that women experiencing PMS in their younger reproductive years may be more likely to experience similar symptoms during the menopausal transition. Prospective studies assessing PMS in young women and following them through menopause and midlife are needed to address whether these conditions likely share an underlying etiology, and whether premenstrual vasomotor, cognitive, and physical symptoms may be related to future CVD risk through shared mechanisms.

Our study has several potential limitations. We assessed menstrual symptom occurrence *via* a retrospective questionnaire rather than with prospective symptom diaries, which are recommended for clinical studies of PMS.[8] However, our method has high sensitivity, specificity, and positive predictive value when validated against prospective methods.[13] In addition, because completion of a single questionnaire places lower burden on study participants than completion of multiple cycles of daily diaries, studies using a single questionnaire are less subject to selection bias and power issues related to differential dropout.[48] Previous studies using our questionnaire, including studies of PMS and blood pressure,[36,38] have demonstrated that our instrument is sensitive enough to identify risk factors for PMS.[13,14] Importantly, misclassification of PMS status would be expected to attenuate differences between cases and controls rather than exaggerate them. Misclassification is thus unlikely to account for the significant association we observed between PMS status and diastolic blood pressure, and true associations may be even stronger.

Our study is somewhat limited by our use of a single blood pressure measurement. However, this limitation is unlikely to explain the results for our study for several reasons. First, we timed all measurements for the mid-luteal phase of each participant's menstrual cycle, thus minimizing the impact of differences in cycle phase on results. Furthermore, any misclassification of true blood pressure status resulting from the use of a single measure rather than multiple measures would likely attenuate differences between PMS cases and controls, as opposed to exaggerate them.

As our study is cross-sectional, the temporal relation of menstrual symptom development versus blood pressure changes is unclear. Changes in behavior resulting from symptoms or PMS treatments could adversely impact blood pressure and lead to reverse causation. We controlled for many of these factors through multivariable adjustment (smoking, alcohol, and OCs) or restriction (antidepressant use) to minimize the impact of these treatment-related factors. It is important to note that prior studies did not adjust for BMI, smoking, and other factors,[9,35–38] our results thus contribute new information suggesting that associations of PMS and blood pressure are not explained by shared risk factors or treatment effects. We recommend that future studies consider using ambulatory blood pressure measurement to more comprehensively address questions of temporal concordance between premenstrual symptoms and elevated blood pressure.[49]

Conclusions

Our findings suggest that PMS is associated with higher diastolic blood pressure in young women. Additional studies evaluating whether women with PMS have a higher future risk of hypertension and CVD are warranted. Given the high prevalence of clinically significant PMS, a better understanding of whether PMS and hypertension are etiologically related, and whether PMS may serve a sentinel for future risk, could be useful for targeting screening and improving prevention.

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