Hormonal and Volume Dysregulation in Women With Premenstrual Syndrome

Rimma Rosenfeld, Dana Livne, Ori Nevo, Lior Dayan, Victor Milloul, Shahar Lavi, Giris Jacob

Abstract—Premenstrual syndrome (PMS) presents with emotional and physical symptoms. Although the emotional symptoms have been extensively studied, the pathophysiology of the fluid-retention symptoms is not currently known. We tested the hypothesis that the fluid regulatory mechanisms are disturbed in PMS. Nine regularly menstruating women with PMS were compared with 9 healthy age-matched women. Hemodynamic parameters and upright plasma volume shift (extrapolated from changes in hematocrit), plasma renin activity (PRA), and plasma aldosterone and sex hormones were measured at different times during the menstrual cycle. During the early follicular and the midluteal phases, the plasma volume shift, supine and upright PRA, and plasma aldosterone were similar in both groups, and none of the participants had edema. However, during the late luteal phase, ankle edema was present only in women with PMS, and their maximal plasma volume shift was lower compared with controls (11.7±1.3 versus 15.6±0.6; P=0.004). The area under the curve (estimates the amount of the total plasma shift during 30 minutes standing) was 300±28 and 406±16 in PMS and controls, respectively (P=0.01). PRA and aldosterone levels were higher during the late luteal phase in women with PMS compared with controls (supine PRA: 1.4±0.3 [PMS] versus 1.1±0.4 [control; P value not significant], upright PRA: 3.9±0.08 versus 1.6±0.3 ng/mL per hour [P=0.015], supine plasma aldosterone: 131±30 versus 68±17 pg/mL [P=0.09], and upright plasma aldosterone: 208±40 versus 102±16 pg/mL [P=0.03]). We, therefore, conclude that women with PMS have increased plasma fluid-regulatory hormones and disturbed fluid distribution only during their late luteal menstrual phase. (Hypertension. 2008;51:1225-1230.)

Key Words: premenstrual syndrome ■ aldosterone ■ renin ■ edema ■ sex hormones

Almost 75% of women experience premenstrual symptoms at some time during the reproductive phase of their lives, but only ~5% of the affected women perceive distressing or debilitating symptoms. Premenstrual syndrome (PMS) displays a cluster of nonspecific symptoms, which can be grouped into 2 classes. The first class is composed of psychological and behavioral symptoms, such as tension, irritability, mood swings, anxiety, and depression. The second class refers to the somatic aspect of the syndrome, which can be subdivided into 2 groups. The first subgroup relates to aberrations in volume homeostasis and includes somatic complaints, such as bloatedness, breast tenderness, abdominal swelling, and edema of extremities. The second subgroup is related to altered function of the autonomic nervous system and includes dizziness/lightheadedness, palpitations, and disorders of the gastrointestinal system.

Although there is a vast amount of knowledge about the psychological and psychiatric aspects of PMS, the pathophysiology of its somatic symptoms has been not fully investigated. The cyclic pattern of the symptoms of PMS recalls its relationship with the changing hormonal profile of the menstrual cycle. Symptoms start during the middle-to-late luteal phase and then subside after the onset of menstruation, thereby suggesting a role for ovarian hormones. Therefore, we hypothesized that the homeostatic mechanisms that control volume regulation are disturbed in PMS and account for the fluid-related somatic symptoms of the syndrome. Accordingly, the present study was undertaken to shed light on the mechanism of fluid retention in women with PMS.

Methods

Subjects
In response to an advertisement in local newspapers, 135 healthy women were interviewed for the study. Eleven women matched our stringent inclusion criteria for PMS, and 9 agreed to participate in the study. They were compared with 9 age-matched women without PMS. All of the participants met the following criteria: they had regular menstrual cycles, were aged between 20 and 45 years, and had a body mass index (BMI) within the reference range (19 to 25 kg/m²). The diagnosis of PMS was determined according to the Shortened Premenstrual Assessment Form, a questionnaire that classifies premenstrual symptoms (mood and physical) into 10 categories on a scale of 1 to 6.
Women were diagnosed as having PMS if they rated ≥5 of the premenstrual symptoms as severe (score of ≥5) in the subscales of Shortened Premenstrual Assessment Form (see Table 1). Women were diagnosed as not having PMS and were allocated into the control group if they rated all of the symptoms with a score of <2. Women completed the of Shortened Premenstrual Assessment Form ≥3 times before the study. None of the participants had any history of alcohol use, drug abuse, and smoking or used oral contraception within the 3 months before the start of the study.

All of the participants had normal physical and gynecologic examinations and had normal electrocardiograms, renal and thyroid function, and plasma levels of vitamin B12. The study was approved by the Rambam Institutional Ethics Review Board, and each volunteer read and signed a consent form before the enrollment.

Experimental Design
All of the investigational procedures were performed after overnight fasting in a partially darkened room of which the ambient temperature was ~24°C in the Recanati Autonomic Dysfunction Center. Each subject was studied at 3 different time points within 1 menstrual cycle: (1) early follicular (EF) phase, day 3 to 4 (low estrogen and low progesterone); (2) midluteal (ML) phase, day 21 to 22 (high estrogen and high progesterone); and (3) late luteal (LL) phase, days 26 to 27 (withdrawal phase of both hormones). Our selection of these specific time points was based on the knowledge that most premenstrual symptoms appear during the late luteal phase of the menstrual cycle and subside a few days after the menstruation begins (EF phase).

On each study day, subjects were placed in a rest supine posture, and a large (18-gauge) intravenous heparlock was inserted into an antecubital vein for blood sampling without a tourniquet. Blood was drawn for measurement of the plasma levels of the ovarian steroid hormones, estradiol (E2) and progesterone, and the gonadotropins, follicular stimulating hormone (FSH) and luteinizing hormone (LH). After 30 minutes at rest supine, cuff blood pressure and heart rate were measured (Datex), and blood was then drawn for the measurement of plasma renin activity (PRA), plasma aldosterone levels, hematocrit (Hct; Microcapillary reader and Micro MB centrifuge, IEC), and total plasma protein levels (Refractometer, Leica; for the extrapolation of acute plasma volume changes—“shift”). The identical parameters were reassessed simultaneously on the assumption of the upright posture (quiet standing with limited movement) after 5.0, 7.5, 10.0, 15.0, 20.0, and 30.0 minutes. Blood sampling for PRA and plasma aldosterone levels was done only at 30.0 minutes.

Acute plasma volume shift during quiet standing was estimated from quadruplicate microcapillary venous Hct measurements, corrected for trapped plasma (0.96) and whole-body Hct (0.91; 0.96×0.91=0.87). The Hct was measured after a 10-minute centrifugation at 11 500 rpm and read on a microcapillary tube reader. Acute dynamic percent changes (Δ) in plasma volume (PV) were calculated from Hct, where Hct1 was the baseline value and Hct2 was the test value using the following formula: dynamic ΔPV (%) = 100×(Hct1–Hct2)/Hct2×(1–Hct1). The percentage of change in total plasma protein (measured in triplicate by refractometry) was measured to further confirm the changes in PV shift using Hct values. 

Statistical Analysis
Results are expressed as means±SEMs. Paired and unpaired 2-sided t tests were used for comparisons between time points. Repeated-measures 1-way ANOVA was used to assess the effect of the time on the different study parameters. Repeated-measures 2-way ANOVA was used for the comparison between the groups and along the different time points. Nonlinear regression analysis (1-phase exponential decay, PV%=a×e kt+plateau) was used to calculate the area under the curve as a measure of the amount of plasma shift during standing in each participant. A 1-phase exponential association model was used to assess the changes in plasma total protein levels. Linear regression analysis was used to assess correlations between the various parameters. The selected level for statistical significance was P<0.05.

Results
The clinical, menstrual, and demographic characteristics of the 2 study groups are displayed in Table 2. Although the body weight and height were comparable between the 2 groups, the women with PMS tended to have higher BMI values than those women without PMS. The plasma levels of LH and FSH were significantly lower during the LL phase in women with PMS than those of the control group (Figure 1, top). The plasma levels of estrogen and progesterone were not

### Table 1. Summary of Results of the Short Premenstrual Assessment Form of Participants

<table>
<thead>
<tr>
<th>Symptoms</th>
<th>Control Subjects (n=9)</th>
<th>P</th>
<th>PMS Subjects (n=9)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tenderness or swelling of breast</td>
<td>1.8±0.3</td>
<td>0.001</td>
<td>4.7±0.5</td>
<td></td>
</tr>
<tr>
<td>Overwhelmed by daily demands</td>
<td>1.1±0.1</td>
<td>&lt;0.001</td>
<td>3.2±0.5</td>
<td></td>
</tr>
<tr>
<td>Feeling under stress</td>
<td>1.3±0.2</td>
<td>&lt;0.001</td>
<td>4.3±0.5</td>
<td></td>
</tr>
<tr>
<td>Irritability or bad temper</td>
<td>1.8±0.2</td>
<td>&lt;0.001</td>
<td>5.3±0.2</td>
<td></td>
</tr>
<tr>
<td>Feeling sad or blue</td>
<td>1.3±0.2</td>
<td>&lt;0.001</td>
<td>3.9±0.5</td>
<td></td>
</tr>
<tr>
<td>Backaches, joint and muscle pain</td>
<td>1.4±0.2</td>
<td>0.012</td>
<td>3.2±0.6</td>
<td></td>
</tr>
<tr>
<td>Weight gain</td>
<td>1.8±0.3</td>
<td>&lt;0.001</td>
<td>5±0.3</td>
<td></td>
</tr>
<tr>
<td>Abdominal heaviness, discomfort, or pain</td>
<td>1.3±0.2</td>
<td>&lt;0.001</td>
<td>4.9±0.4</td>
<td></td>
</tr>
<tr>
<td>Edema, swelling, or water retention</td>
<td>1±0</td>
<td>&lt;0.001</td>
<td>4.3±0.6</td>
<td></td>
</tr>
<tr>
<td>Feeling bloated</td>
<td>1±0</td>
<td>&lt;0.001</td>
<td>4.9±0.6</td>
<td></td>
</tr>
</tbody>
</table>

### Table 2. General Characteristics of Participants

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Control Subjects (n=9)</th>
<th>P</th>
<th>PMS Subjects (n=9)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>30±2.5</td>
<td>ns</td>
<td>30±2.0</td>
<td></td>
</tr>
<tr>
<td>Age range</td>
<td>21 to 43</td>
<td>NA</td>
<td>21 to 40</td>
<td></td>
</tr>
<tr>
<td>Menstrual cycle length, d</td>
<td>29.7±0.3</td>
<td>0.07</td>
<td>28.2±0.5</td>
<td></td>
</tr>
<tr>
<td>Time to menstruate, d*</td>
<td>3.7±0.2</td>
<td>0.003</td>
<td>2.7±0.2</td>
<td></td>
</tr>
<tr>
<td>Height, m</td>
<td>1.62±0.01</td>
<td>ns</td>
<td>1.69±0.01</td>
<td></td>
</tr>
<tr>
<td>Weight, kg</td>
<td>63.8±4</td>
<td>ns</td>
<td>60±2.3</td>
<td></td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>24.4±1.5</td>
<td>0.055</td>
<td>21±0.7</td>
<td></td>
</tr>
<tr>
<td>Systolic BP, supine, mm Hg</td>
<td>106±2</td>
<td>ns</td>
<td>103±2</td>
<td></td>
</tr>
<tr>
<td>Diastolic BP, supine, mm Hg</td>
<td>62±2</td>
<td>ns</td>
<td>61±1</td>
<td></td>
</tr>
<tr>
<td>Heart rate, supine, bpm</td>
<td>60±2</td>
<td>ns</td>
<td>62±3</td>
<td></td>
</tr>
<tr>
<td>Systolic BP, upright, mm Hg</td>
<td>105±3</td>
<td>ns</td>
<td>108±3</td>
<td></td>
</tr>
<tr>
<td>Diastolic BP, upright, mm Hg</td>
<td>66±3</td>
<td>ns</td>
<td>67±3</td>
<td></td>
</tr>
<tr>
<td>Heart rate, upright, bpm</td>
<td>75±2</td>
<td>ns</td>
<td>79±3</td>
<td></td>
</tr>
<tr>
<td>Hct corrected</td>
<td>0.298±0.012</td>
<td>ns</td>
<td>0.302±0.004</td>
<td></td>
</tr>
<tr>
<td>Total protein, g/dL</td>
<td>6.83±0.11</td>
<td>ns</td>
<td>6.68±0.11</td>
<td></td>
</tr>
</tbody>
</table>

Menstrual cycle length was calculated over 3 consecutive cycles. Hemodynamic, Hct, and total plasma protein data are reported from the EF menstrual phase. ns indicates not significant; NA, not applicable.

*Time to menstruate indicates the number of days until the appearance of the cycle, after the LL phase study.
significantly different between the 2 groups (Figure 1, bottom).

Ankle edema and breast tenderness were reported in all of the women with PMS during the LL phase of the menstrual cycle. During the EF phase and the ML phase, the dynamic PV%, supine and upright PRA, and plasma aldosterone levels were similar in both groups. However, during the LL phase, the women with PMS demonstrated significantly smaller plasma shifts as extrapolated from changes in both Hct and total plasma protein levels than the women without PMS (Figure 2). Maximal decrease in PV (PV%) was significantly lower in the PMS women compared with the control group (11.1±1.3% versus 15.6±0.6%; \( P = 0.004 \)). Also, the area under the curve (an estimate of the amount of the total plasma shift during 30 minutes standing) was 300±28 mL and 406±23 mL (\( P = 0.02 \)) in the PMS and control group, respectively. The correlation between plasma shift calculated from the changes in corrected Hct and total protein was linear in both groups (\( R^2 = 0.97; \ P < 0.001 \)).

Plasma aldosterone levels and PRA were higher only during the LL phase in women with PMS compared with those of the control group (Figure 3, bottom): supine PRA: 1.4±0.3 ng/mL per hour versus 1.1±0.4 ng/mL per hour (\( P \) value not significant); upright PRA: 3.9±0.8 ng/mL per hour versus 1.6±0.4 ng/mL per hour (\( P = 0.02 \)); supine plasma aldosterone levels: 131±30 pg/mL versus 67±17 pg/mL (\( P = 0.09 \)); and upright plasma aldosterone levels: 208±40 pg/mL versus 101±16 pg/mL (\( P = 0.03 \)), respectively.

**Discussion**

This study is the first to systematically investigate the basis of the somatic symptoms that are associated with fluid retention in women with PMS. These women, who were selected using stringent criteria, reveal that their fluid retention-related symptoms, namely, ankle edema, bloatedness, and breast swelling, during the LL phase of their menstrual cycles, are associated with elevated levels of plasma aldosterone and PRA. This was also associated with a reduced fluid shift from the intravascular compartment to the surrounding tissues during orthostatic stress.

Although the plasma levels of estrogen and progesterone were comparable, a delay in their physiological withdrawal (withdrawal phase) was evident in the women with PMS during the LL menstrual phase. This was associated with low plasma levels of LH and FSH.

The number of women who experience ≥1 premenstrual symptom is high. Indeed, many women responded to our
advertisement, yet only a few actually fulfilled our stringent criteria for PMS. Because an abundance of literature and an absence of consensus on the epidemiology of PMS exist, different selection criteria are often used when diagnosing PMS. The selection criteria used in the present study were chosen from those studies that considered mainly physical symptoms, namely, the Shortened Premenstrual Assessment Form. We avoided using behavioral and mood symptoms that are often used by psychiatrists and that are described in the fourth edition of the Diagnostic and Statistical Manual of Mental Disorders. Only patients with severe symptoms were enrolled in the PMS group to demonstrate eventual mechanical differences compared with normal.

During the LL phase, the plasma levels of LH and FSH were significantly lower in the PMS group compared with the controls. This occurs in the setting of nonsignificant changes in the plasma levels of E2 and progesterone during the LL phase in the PMS women. The delay in the physiological withdrawal of these ovarian hormones could be enough to cause an ongoing negative feedback on LH and FSH release. Although the selection of study time points was intentionally similar, a delay in the appearance of the menstruation in the PMS group was seen (see Table 2). A delay in the lag time between plasma levels of ovarian hormones and gonadotropins in PMS has also been reported by others. Whether this delay may be the result of a flaw in the study design or a PMS-dependent aberration in hormonal regulation remains to be investigated.

Obviously, ovarian hormones play a fundamental role in the pathogenesis of PMS, but their contribution remains unclear. Frank claims that high plasma E2 levels and a disturbed balance between plasma E2 and progesterone levels could contribute to the onset of the symptoms in PMS. Several bodies of evidence also suggest that progesterone (or its metabolite, allopregnanolone), during the LL (withdrawal) phase, contributes to the pathophysiology of PMS. Symptoms in women with PMS could be associated with either high or low plasma levels of progesterone. The plasma levels of the sex hormones in our PMS group were unquestionably disturbed, reinforcing the notion that these hormones have a crucial role in the pathophysiology of PMS. Our study, however, was not appropriately designed to resolve the potential role of these hormones in the pathophysiology of PMS.

Ankle edema and swelling of breast during the LL phase in PMS women indicate the presence of excessive fluids in the extravascular compartment. High plasma levels of progesterone, and possibly estrogen, are involved in increasing capillary permeability (ie, leaking), allowing the augmented crossing of fluid and albumin into the interstitial space. As reported previously, the presence of peripheral arterial vasodilation during the luteal phase could also contribute to the genesis of this edema. In addition, a decrease in the baseline-corrected Hct was present in both groups during the LL phase (data not shown). These results suggested that PV increased by ~3% in the 2 groups. Because we were unable to find data in the published medical literature to support the notion that long-term changes in the Hct do not reflect changes in intravascular volume, we decided not comment further, because they would be without basis and would, thus, be speculative. Nevertheless, increased capillary permeability and hydrostatic pressure (peripheral vasodilation) and possibly expanded intravascular volume are all possible causes for the presence of edema.

Reduced plasma shift on standing during the LL menstrual phase was prominent in the women with PMS. The plasma shift that occurs on standing depends on the constituents of the Starling forces, ie, the balance among interstitial and capillary hydrostatic pressure, oncotic pressure, and the capillary filtration coefficient. Therefore, the presence of interstitial edema during the LL phase in women with PMS increases the interstitial hydrostatic pressure, which, in turn, could oppose further fluid shifting during orthostatic stress.

The present study shows that women with PMS have exaggerated increases in PRA and plasma aldosterone levels during the LL phase of their menstrual cycles compared with those of healthy control subjects. This could help to explain the pathophysiology of the fluid retention, ie, edema in these women. Plasma levels of both fluid regulatory hormones positively and significantly correlated with plasma levels of progesterone (r = 0.5, P = 0.000 and r = .35, P = 0.02 for PRA and aldosterone, respectively) but less so with plasma estrogen levels. This may suggest the possibility of a link between progesterone and the hormone-fluid status in these women with PMS. The mechanism leading to the increase in PRA and the plasma levels of aldosterone, however, is not completely understood. At least in part, it may be a compensatory response to the vasodilator effect of estrogen, and the natriuretic action of progesterone. Progesterone could stimulate the release of aldosterone by affecting directly the cells of the zona glomerulosa in the adrenals.

Without doubt, salt and fluid retention during the luteal phase are present in women with PMS. Healthy regularly menstruating women (without PMS) have increased PRA and plasma levels of aldosterone during their LL phase without the development of edema. A paucity of data exists on PRA in women with PMS. Davidson et al found that PRA in women with PMS was comparable with that found in women without PMS. During the luteal phase, urinary aldosterone and the potassium:sodium ratio are elevated in women with PMS; plasma aldosterone levels, however, were similar with those of the women without PMS. It has been reported that the administration of the aldosterone receptor antagonist, spironolactone, may alleviate fluid-related somatic symptoms in women with PMS.

Limitations
Our study was designed to explore the pathophysiology of fluid retention–related symptoms of PMS and not its mood related symptoms. Our stringent selection criteria may have amplified the differences between the 2 studied groups, thereby overlooking the majority of women who have milder forms of PMS who may have a different pathophysiology.

The women with PMS in our study were not obese, but the values of their BMI tended to be in the higher range of
normal values. It has been reported that the BMI could affect plasma sex hormones in women with PMS. Therefore, we correlated the between-individual values of BMI and the corresponding plasma levels of progesterone, estrogen, and aldosterone, as well as PRA, during the luteal phase. We did not find any significant correlation between the tested parameters (all values of $R^2$ were $<0.15$, and the $P$ values did not reach any significance). It is doubtful that these differences in BMI, of which the values were within the reference range, could affect the hormonal profile of our study subjects. The cyclic changes of the measured parameters in this complex analysis could have been better demonstrated by repeating the same study during a subsequent menstrual cycle.

Perspectives
The pathophysiology of edema-related symptoms in women with PMS during their late luteal phase, at least in part, is because of increased fluid-regulatory hormone concentrations. This provides a rationale for treating these women with aldosterone receptor antagonists, such as spironolactone and eplerenone. Such treatment modality needs to be commenced only at the onset of symptoms during the LL phase of their menstrual cycle. Because female sex hormones adversely affect the regulatory mechanisms of volume homeostasis, this relationship warrants further investigation in other conditions in which volume regulation is disturbed, such as in hypertension or cyclic edema.

Acknowledgments
This work is part of a doctoral thesis of R.R. We thank Prof Arieh Bomzon for his help in editing the final version of the article.

Sources of Funding
This work was supported by the Yahel Foundation (Israel) and in part by the Chronic Fatigue and Immune Dysfunction Syndrome, association of America (United States).

Disclosures
None

References


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Hypertension. 2008;51:1225-1230; originally published online February 7, 2008; doi: 10.1161/HYPERTENSIONAHA.107.107136
Hypertension is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0194-911X. Online ISSN: 1524-4563

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