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The influence of the menstrual cycle on reactivity to a CO₂ challenge among women with and without premenstrual symptoms

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Abstract

Clinically significant premenstrual symptoms (PMS) is conceptualized as a depressive disorder in DSM-5, however, it may share pathophysiological processes with anxiety- and fear-related disorders. Specifically, women with PMS panic at higher rates during biological challenge procedures. It is unclear if this increased interoceptive sensitivity is a general vulnerability or specific to the premenstrual phase. The current study examined the role of menstrual cycle phase on reactivity to a CO₂ challenge among women with ($n = 11$) and without ($n = 26$) clinically significant PMS ($N = 37$). During the late follicular phase (days 6–12), women with and without PMS responded similarly to the CO₂ challenge, whereas during the premenstrual phase (within 5 days before menses), women with PMS reported significantly more intense panic symptoms in response to the challenge than women without PMS. Vulnerability to panic in women with PMS may be specific to the premenstrual phase. Potential psychological and neurobiological mechanisms underlying this phenomenon are discussed.

Keywords

CO₂ challenge; menstrual cycle; panic; PMS

Approximately 50–80% of women report that they experience increased psychological symptoms (e.g., anxiety, sadness) and/or physical symptoms (e.g., muscle aches, headaches) from the late follicular phase when estradiol is rising and progesterone is low and stable (i.e., 6 – 12 days following the beginning of menses) as compared to the premenstrual phase

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when estradiol and progesterone are decreasing (1 to 5 days prior to menses; Gonda et al., 2008). However, only 13%–19% of women report impairment related to these symptoms (Angst, Sellaro, Merikangas, & Endicott, 2001; Spitzer, Williams, Kroenke, R., & McMurray, 2000), and only about 2%–8% meet DSM-5 criteria for premenstrual dysphoric disorder (PMDD; Halbreich, Borenstein, Pearlstein, & Kahn, 2003).

Despite the conceptualization of PMDD as a depressive disorder in DSM-5, several lines of evidence suggest that PMDD may share pathophysiologic features with anxiety disorders as well. First, PMDD is frequently comorbid with both anxiety and depressive disorders (Kim et al., 2004). Moreover, prospective reports of premenstrual symptoms among women with PMDD suggest that anxious mood is endorsed just as often, or even more frequently, than depressed mood (Pearlstein, Yonkers, Fayyad, & Gillespie, 2005). In addition, women with clinically significant premenstrual syndrome (PMS) and PMDD show heightened sensitivity to bodily sensations (Kent et al., 2001). For example, equally intense levels of arousal and fear are experienced by patients with PMDD and panic disorder in response to a biological challenge with carbon dioxide (CO₂) enriched air (Kent et al., 2001), whereas healthy controls and patients with major depression react less intensely (Harrison et al., 1989; Kent et al., 2001; Le Mellédo et al., 1999). Even in a nonclinical sample, retrospectively reported premenstrual symptoms were associated with more panic in response to a CO₂ challenge above and beyond other psychological vulnerability factors that predict panic reactions to a CO₂ challenge (Nillni, Rohan, Bernstein, & Zvolensky, 2010).

Given that PMS is characterized by cyclical periods of distress and impairment, one might also expect that individuals with PMS would be more reactive to a biological challenge during specific phases of the menstrual cycle, such as the premenstrual phase. However, to our knowledge, only one study has examined the influence of menstrual cycle phase on reactivity to biological challenge among women with PMDD. Specifically, Le Mellédo and colleagues (1999) reported a trend for women with PMDD to show greater anxiety and increased heart rate in response to a cholecystikinin (CCK)-4 injection during the premenstrual phase (i.e., 1 to 5 days prior to menses) as compared to the late follicular phase (days 7 to 10 after onset of menses). Although preliminary, this study suggests that challenge induced panic in women with PMDD may be specific to the premenstrual phase. However, given the limited literature in this area and the marginally significant findings, more research on this topic is warranted.

Thus, the current study aims to clarify and extend the existing literature by examining the role of menstrual cycle phase (late follicular vs. premenstrual) on panic reactions to a CO₂ challenge among women with and without clinically significant PMS. Based on the extant literature, we hypothesized that women with clinically significant PMS would evidence increased CO₂-induced panic symptoms in comparison to healthy controls during the premenstrual phase. We also expected that women with PMS would demonstrate within group increases in CO₂-induced panic symptoms during the premenstrual phase compared to the late follicular phase of the menstrual cycle.

Method

Participants

Participants providing data for this study were part of a larger study examining panic reactivity across the menstrual cycle (Nillni, Rohan, & Zvolensky, 2012). Thirty-seven women with normal menstrual cycles were recruited from a northeastern community via newspaper advertisements and flyers. Participants who responded to advertisements were invited to the laboratory for a screening visit. Exclusion criteria for the original study included: a) use of hormonal birth control, b) postmenopausal or perimenopausal status (e.g., hot flashes, irregular periods), c) pregnancy or trying to become pregnant, d) any current anxiety disorder, alcohol or substance dependence, or psychosis as ascertained by the *Structured Clinical Interview for DSM-IV Axis I Disorders-Non Patient Version* (SCID-NP; First, Spitzer, Gibbon, & Williams, 1994), e) current suicidal intent, f) contraindicated medical conditions (e.g., cardiovascular or seizure disorder, asthma), and g) current use of anxiolytic medication (e.g., beta blockers, benzodiazepines). This study was approved by the IRB and all participants provided informed consent.

Measures

A *Medical Screening Questionnaire* (MSQ) was administered to assess inclusion/exclusion criteria. The MSQ assessed medical conditions, current medications, and presence of a regular menstrual cycle (i.e., average cycle length of 25–35 days that did not regularly vary in length month-to-month by > 7 days).

The *Anxiety Sensitivity Index–3* (ASI-3; Taylor et al., 2007) is an 18-item self-report measure of the degree to which individuals are concerned about possible negative consequences of anxiety symptoms (e.g., “It scares me when my heart beats rapidly”). Internal consistency in the current sample was good ($\alpha = .77$).

The *Positive and Negative Affect Schedule – Negative Affect Scale* (N-PANAS; Watson, Clark, & Tellegen, 1988) is a 10-item self-report scale used to assess their general affect during the past year. Internal consistency in the current sample was excellent ($\alpha = .89$).

The *Daily Record Severity of Problems* (DRSP; Endicott & Harrison, 1997; Endicott, Nee, & Harrison, 2006) is a 14-item questionnaire that assesses a range of premenstrual symptoms (e.g., “felt angry, irritable”) and impairment. Participants rated each symptom daily for at least one menstrual cycle on a 6-point Likert scale from 1 (“not at all”) to 6 (“extreme”); a daily severity score was calculated by summing all items. The DRSP has shown good reliability and validity as a measure of premenstrual symptoms and impairment (Endicott et al., 2006). Late follicular and premenstrual phase DRSP scores were calculated as the average of all available premenstrual and late follicular day total scores. Following the method described in papers by Borenstein and colleagues (Borenstein, Dean, Leifke, Korner, & Yonkers, 2007), as well as Nillni and colleagues (2013), clinically significant PMS was diagnosed if: 1) at least one symptom on the DRSP was 5 during the premenstrual phase (1 to 5 days prior to menses), and 2) the mean premenstrual phase score was greater than the late follicular phase (6 to 12 days following menses) score.

The *Diagnostic Sensations Questionnaire (DSQ)* (Sanderson, Rapee, & Barlow, 1988, 1989) is a 16-item self-report measure of DSM-IV-TR panic symptoms, including both physical (e.g., “pounding of racing heart”) and cognitive (e.g., “fear of losing control”) symptoms. Participants rated the intensity of each panic symptom on a 9-point Likert scale (0 = “not at all noticed” to 8 = “very strongly felt”). The DSQ mean severity score, calculated as the average of all DSQ items, was used as the primary outcome measure of panic symptoms during the CO₂ challenge. Internal consistency in the current sample was excellent ($\alpha = .86$).

Procedure

Screening Visit—Participants who responded to advertisements were invited to the laboratory for a screening visit. Interested participants were administered the MSQ and SCID-NP. Those meeting eligibility criteria also completed the PANAS-N, ASI-3 during this visit.

Randomization and Menstrual Cycle Phase Confirmation—Randomization, ovulation testing, and saliva sampling procedures are described fully in Nillni, Rohan, and Zvolensky (2012). In brief, eligible participants attended laboratory visits during both the premenstrual phase, a time when estradiol and progesterone levels are declining, and the late follicular phase, a time when estradiol is rising and progesterone is low and stable. The order of visits was counterbalanced. The late follicular laboratory visit was scheduled 6–12 days after menses. The premenstrual laboratory visit was scheduled 12–14 days following detection of the luteinizing hormone (LH) surge using a home ovulation test kit. As an additional check to ensure that data was collected during the premenstrual phase, participants were instructed to notify study staff of the first day of their next menstrual period.

Participants also provided saliva samples at each visit for progesterone assay. All samples were assayed for salivary progesterone in duplicate using a highly-sensitive enzyme immunoassay (Cat. No. 1–1502 Salimetrics LLC, State College PA). The test used 50 μ L of saliva per determination, has a lower limit of sensitivity of 5.0 pg/mL, standard curve range from 10 pg/mL to 2430 pg/mL, an average intra-assay coefficient of variation of 6.2%, and an inter-assay coefficient of variation of 7.6 %. Method accuracy determined by spike recovery averaged 99.6 % and linearity determined by serial dilution averaged 91.8 %. Correlation between serum and saliva samples is significant for females ($r = 0.87$, $p < .001$) in previous studies (Salimetrics LLC, 2010). Given that women have varying progesterone levels that naturally decline during the premenstrual phase (Rubinow et al., 1988), confirmation of menstrual cycle phase was determined using information from day count, ovulation testing, and progesterone assay in combination. Data from laboratory visits that did not meet menstrual cycle verification were not included in analyses.

CO₂ Challenge Procedure—Participants were seated in a 9×10 ft experiment room and given an overview of the CO₂ challenge procedure, including the physiological effects of breathing CO₂-enriched air (e.g., dizziness, racing heart). The CO₂ was stored in a 101-cm cylinder located in an adjacent control room and fed through a 5×5 cm hole via aerosol

tubing to the positive pressure C-PAP mask worn by participants. Participants were instructed to sit quietly for an adaptation period during which they breathed regular room air through the mask. This was followed 10 minutes later by a single 3-minute 10% CO₂-enriched air presentation (10% CO₂, 21% O₂, 69% NO₂). Although participants knew they would receive CO₂ enriched air, they were not told when administration would begin. Participants completed the DSQ preceding and immediately following the CO₂ challenge.

Data Analytic Strategy

Demographic characteristics were compared between the PMS and no PMS groups using independent samples t-tests and chi-square analyses. Then, a series of $2 \times 2 \times 2$ repeated measures ANOVAs were conducted to examine the interactive effects of PMS group (PMS vs. no PMS status), menstrual cycle phase (premenstrual vs. late follicular), and challenge time (pre-challenge vs. post-challenge) on panic symptoms (DSQ mean severity) in response to the CO₂ challenge. Both the ASI-3 and the N-PANAS were included in the model as covariates given a large body of research documenting their association with panic responding during a CO₂ challenge (Spira, Zvolensky, Eifert, & Feldner, 2004; Vujanovic et al., 2006).

Results

The PMS and no PMS groups did not significantly differ on any demographic variables with the exception of race; there were more minority individuals in the PMS group than the no PMS group. A total of two women in the clinically significant PMS group met criteria for PMDD. See Table 1 for participant demographics.

Zero-order correlations between the ASI-3 and the N-PANAS, and between DRSP and DSQ scores in the premenstrual and late follicular cycle phases for the sample as a whole were examined. The ASI-3 and N-PANAS were significantly correlated at .61, suggesting that they are measuring similar constructs. The correlation between premenstrual DRSP and DSQ severity scores was significant ($r = .421$), while the correlation between follicular DRSP and DSQ severity scores was not significant ($r = -.033$).

Despite literature documenting the effects of anxiety sensitivity and pre-challenge negative affect on response to CO₂ challenge, there were no significant associations between ASI-3 and N-PANAS scores and response to the CO₂ challenge as measured by DSQ mean severity scores. Nonetheless, ASI-3 and N-PANAS scores were included in the final analyses given their associations with challenge responding in previous studies (Spira et al., 2004; Vujanovic et al., 2006). However, it should be noted that results did not differ with and without inclusion of these covariates.

Despite unequal sample sizes between the groups, examination of Levene's test revealed that the homogeneity of variances assumption has been satisfied. There was a main effect for challenge time (pre-challenge vs. post-challenge) regardless of menstrual cycle phase ($F(1, 33) = 33.00, p < .001, \eta^2 = .37$), whereby women reported significantly more panic symptoms post-challenge ($M = 3.64, SE = 0.27$) than pre-challenge ($M = 0.49, SE = 0.08$). In addition, analyses revealed a significant PMS group $\times$ phase $\times$ challenge time interaction

($F(1, 33) = 9.80, p < .01, \eta^2 = .23$). Results were similar for total number of panic symptoms, mean intensity of cognitive symptoms of panic, and mean intensity of physical symptoms of panic.

In order to decompose this 3-way interaction, PMS group $\times$ phase was examined within the pre-challenge and post-challenge time epochs. The PMS group $\times$ phase interaction was not significant at pre-challenge, suggesting that both groups experienced similar levels of panic symptoms prior to the CO₂ challenge during both the premenstrual and late follicular cycle phases. There was, however, a significant PMS group $\times$ phase interaction at post-challenge ($F(1, 33) = 8.21, p < .01, \eta^2 = .20$). During the premenstrual phase, women in the PMS group reported more panic symptoms following the CO₂ challenge procedure ($M = 4.51, SE = .51$) than women in the no PMS group [$(M = 2.94, SE = .33): F(1, 33) = 6.39, p < .05, \eta^2 = .16$]. This group difference was not observed in the late follicular phase. Additionally, both the PMS and no PMS groups evidenced significant within group phase differences in post-challenge panic symptoms between menstrual phases. The PMS group reported more symptoms in the premenstrual phase ($M = 4.51, SE = .51$) as compared to the late follicular phase [$M = 3.53, SE = .53; (F(1, 33) = 4.43, p < .05, \eta^2 = .12)$]. The no PMS group reported more symptoms in the late follicular phase ($M = 2.94, SE = .33$) as compared to the premenstrual phase [$M = 3.57, SE = .34; (F(1, 33) = 4.34, p < .05, \eta^2 = .12)$]. See Figure 1.

Discussion

The current study found that women with clinically significant PMS reported more panic symptoms in response to a CO₂ challenge than women without PMS, but only during the premenstrual phase. Notably, both groups of women responded similarly to the challenge when assessed in the late follicular phase. These findings align with past work (Le Mellédo et al., 1999), suggesting that women with clinically significant PMS may only experience interoceptive extra-sensitivity during the phase of the menstrual cycle (i.e., the premenstrual phase) to which they are particularly vulnerable to PMS symptoms. These findings do not support the notion that individuals with PMS have a general vulnerability to challenge-induced panic, as do individuals with PD or PTSD (Muhtz, Yassouridis, Daneshi, Braun, & Kellner, 2011). Unlike the Le Melledo et al. (1999) study, however, the current study did not find that women with clinically significant PMS reported greater reactivity to biological challenge than healthy controls in the late follicular phase. Differences in the nature of the biological challenge (CO₂ inhalation vs. CCK-4 injection) and in the severity of PMS symptoms in the disordered group (PMDD vs. clinically significant PMS) may have contributed to the differences in results.

Contrary to expectation, the no PMS group experienced fewer panic symptoms in response to the challenge in the premenstrual phase than in the late follicular phase. Post-hoc exploratory analyses were conducted in order to rule out potential confounds that may have contributed to this finding. Randomization order did not significantly differ between PMS and no PMS groups, and randomization order did not impact challenge responding for either group. Likewise, the day of challenge during the premenstrual phase did not predict panic symptoms for either group.

There are several psychological and neurobiological possibilities as to why individuals with clinically significant PMS may be more likely to panic during the premenstrual phase of the menstrual cycle. First, PMS and anxiety disorders may share similar psychological vulnerability factors such as anxiety sensitivity (AS) – the fear of physiological symptoms of anxiety (McNally, 2002). AS predicts increased panic responding to biological challenge agents (Spira et al., 2004) and has been associated with increased reports of premenstrual distress. (Sigmon et al., 2000) Given that women with PMS experience frequent intense physical and psychological symptoms, they may have learned to worry about interoceptive stimuli during the premenstrual phase. In line with learning models of panic etiology and maintenance (Barlow, 2002), these recurrent opportunities may increase development of maladaptive coping strategies (e.g., avoidance), which may ultimately contribute to increased anxiety during this phase.

Underlying neurobiological mechanisms related to the menstrual cycle, and more specifically, fluctuating levels of estrogen and progesterone, may also possibly explain the different patterns of panic reactivity to the CO₂ challenge observed across the menstrual cycle in groups with and without PMS. Although levels of estrogen and progesterone do not consistently predict PMS symptoms (Hsiao, Liu, & Hsiao, 2004) or differentiate individuals with PMS vs. no PMS (Rubinow, Schmidt, & Roca, 1998), these hormones may have downstream effects that influence PMS symptoms. For example, neuroactive steroid metabolites of progesterone, allopregnanolone and its equipotent stereoisomer, pregnanolone (together termed ALLO) exert potent anxiolytic effects via positive modulation of the effects of gamma-amino-butyric acid (GABA) at GABA_A receptors. These effects are potentially mediated in the amygdala (Agis-Balboa et al., 2006). For example, women with PMDD demonstrate increased amygdala reactivity to negative stimuli in the premenstrual phase (but not the late follicular phase) as compared to healthy women (Protopopescu et al., 2008). Studies comparing absolute levels of ALLO between women with and without PMS or PMDD have been mixed (Crowley & Girdler, 2014), potentially due to differences in menstrual cycle phase of assessment, timing of blood draw following placement of the intravenous line, or differences in assay methodology. Other research suggests that falling levels of progesterone (and thus, ALLO) during the premenstrual phase are associated with increased anxiety (Halbreich, Endicott, Goldstein, & Nee, 1986), particularly under conditions of stress or in women with underlying psychological or neurobiological vulnerabilities (Smith, Ruderman, Frye, Homanics, & Yuan, 2006). Thus, low levels of ALLO, a potential reduction in the efficiency of progesterone conversion to ALLO during stress (Girdler, Straneva, Light, Pedersen, & Morrow, 2001), or differences in GABA_A receptor sensitivity (Crowley & Girdler, 2014) may contribute to PMS and PMDD, and increase panic reactivity in women with PMS during the premenstrual phase. The women without PMS thus may have experienced more sustained benefits of ALLO during the mid-luteal phase, when levels of progesterone, the precursor for ALLO, are highest.

In the current study, women without PMS also reported a surprising within group increase in panic reactivity in the late follicular phase compared to the premenstrual phase. This relative increase in panic reactivity may be attributable to late follicular phase increases in estrogen. For example, estrogen upregulates the expression of 5HT₂ receptors (Frokjaer et al., 2010) and downregulates expression of neuropeptide Y (NPY), which may directly increase

amygdalar reactivity as well as diminish frontal lobe inhibition of amygdala-mediated cardiovascular and behavioral reactions to physiological stress. (Rasmusson & Shalev, 2014) This also may be true for women in the PMS group, who responded similarly to the women in the no PMS group in the late follicular phase. However, additional pathological mechanisms present in the latter group, such as deficiencies in the production of ALLO, may have further increased panic reactivity during the premenstrual phase in the PMS group. Therefore, investigation of a range of neurobiological factors downstream from progesterone and estrogen will be needed in the future to understand differences in menstrual phase-related patterns of stress reactivity among women with and without PMS. Importantly, there are likely to be both inter-individual, as well as diagnostic group differences in the precise mechanisms involved.

Several study limitations should be noted. The study sample was small and results should be considered preliminary. However, effect sizes were large, which strengthen our confidence in the study results. The study sample also consisted mainly of highly educated Caucasian women, and was a clinically less severe sample (i.e., only 2 women met criteria for PMDD). Therefore, future studies using a larger and more diverse group of women, as well as those with more severe premenstrual symptoms are needed in order to understand the generalizability of these results. On the other hand, the study was strengthened by using a repeated measures design, hormone assays to verify menstrual cycle phase, and a carefully controlled biological challenge to assess stress reactivity.

In summary, this study suggests that PMS may share pathophysiologic features with anxiety disorders, although these vulnerability pathways may be particularly relevant during the premenstrual phase. Clinically, these findings may suggest that targeting pharmacological and/or psychological treatment during the premenstrual phase may be most useful. Future research which disentangles both the psychological and/or neurobiological mechanisms involved in the pathogenesis of PMS is warranted.

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Figure 1.

The interaction between PMS Group, menstrual cycle phase (late follicular and premenstrual), and CO₂ challenge time (pre-challenge and post-challenge) on panic symptoms severity. η^2 = eta square effect sizes for the differences in panic symptoms severity between PMS groups in the premenstrual phase and within group differences between menstrual cycle phases.

Table 1

Demographic Characteristics of the PMS group and No PMS group

		Total Sample (<i>n</i> =37)	PMS Group (<i>n</i> =11)	No PMS Group (<i>n</i> =26)
<i>Age</i> M (SD)	<i>t</i> (35) = 1.03	26.4 (9.5)	23.91 (7.81)	27.42 (10.10)
<i>Ethnicity</i> n (%)	$\chi^2 = 5.00$			
Hispanic		2 (5%)	2 (18%)	0 (0%)
Non-Hispanic		35 (95%)	9 (81%)	26 (100%)
<i>Race</i> n (%)	$\chi^2 = 8.43^*$			
Caucasian		32 (86%)	7 (64%)	25 (96%)
African American		1 (3%)	1 (9%)	0 (0%)
Asian		2 (5%)	1 (9%)	1 (4%)
American Indian		2 (5%)	2 (18%)	0 (0%)
<i>Education</i> n (%)	$\chi^2 = 3.04$			
Completed high school		1 (3%)	0 (0%)	1 (4%)
Some college		20 (54%)	7 (64%)	13 (50%)
2 or 4 year degree		12 (32%)	4 (36%)	8 (31%)
Graduate school		3 (8%)	0 (0%)	3 (12%)
<i>Marital Status</i> n (%)	$\chi^2 = 1.39$			
Single		26 (70%)	9 (82%)	17 (65%)
Married		9 (24%)	2 (18%)	7 (27%)
Living Together		1 (3%)	0 (0%)	1 (4%)
Divorced		1 (3%)	0 (0%)	1 (4%)
<i>Any current Axis I diagnosis</i> n (%)	$\chi^2 = 4.40$			
No		33 (89%)	8 (73%)	25 (96%)
Yes		4 (11%)	3 (27%)	1 (4%)
<i>ASI-3</i> M (SD)	<i>t</i> (35) = -1.07	11.43 (6.84)	13.27 (8.09)	10.65 (6.25)
<i>N-PANAS</i> M (SD)	<i>t</i> (35) = -1.34	20.84 (7.57)	23.36 (10.3)	19.77 (5.99)
<i>F Prog, pg/mL</i> M (SD)	<i>t</i> (35) = -1.06	92.45 (43.51)	104.10 (40.19)	87.52 (44.67)
<i>P Prog, pg/mL</i> M (SD)	<i>t</i> (35) = -.740	153.64 (103.27)	173.08 (109.77)	145.41 (101.49)

Note. ASI-3 = Anxiety Sensitivity Index-3; N-PANAS = Positive and Negative Affect Schedule – Negative Affect Scale; F Prog = progesterone levels in the late follicular phase; P Prog = progesterone levels in the premenstrual phase.