Perimenstrual Symptom Exacerbation in Borderline Personality Disorder: Evidence from Multilevel Models and the Carolina Premenstrual Assessment Scoring System

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Abstract

Background. Individuals with BPD suffer from a constellation of rapidly shifting emotional, interpersonal, and behavioral symptoms. Fluctuations in ovarian hormones across the menstrual cycle may contribute to symptom expression and instability among females with this disorder.

Methods. 15 healthy, unmedicated females without dysmenorrhea meeting criteria for BPD reported daily emotional and behavioral symptoms across 35 days. Urine LH surge and salivary progesterone were used to confirm ovulation and verify cycle phase. Cyclical worsening of symptoms was evaluated using (1) phase contrasts in multilevel models and (2) the Carolina Premenstrual Assessment Scoring System (C-PASS), a standardized tool for evaluating clinically significant cycle effects on symptoms.

Results. Despite low cross-sectional perceptions of perimenstrual symptom change at baseline, all symptoms showed marked perimenstrual worsening in prospective ratings, with secondary worsening of certain symptoms in the midluteal and follicular phases. The ovulatory phase was associated with the lowest symptoms. 14 of 15 participants met C-PASS criteria for clinically significant (>=30%) perimenstrual symptom exacerbation.

Conclusions. Females with BPD may be at elevated risk for perimenstrual worsening of emotional symptoms. Experimental work is needed to determine the pathophysiology of perimenstrual exacerbation in BPD.

Perimenstrual Symptom Exacerbation in Borderline Personality Disorder: Evidence from Multilevel Models and the Carolina Premenstrual Assessment Scoring System

Individuals with borderline personality disorder (BPD) suffer from a chronic and disabling combination of emotional, cognitive, and behavioral psychiatric symptoms. Diagnostic criteria for BPD (at least five of which must be met for diagnosis) highlight instability and flux in a variety of domains, including unstable and intense moods, reactive and uncontrolled anger (exacerbated by a tendency to ruminate on angry experiences (Baer & Sauer, 2011; Peters et al, 2017), changing identities, frequent feelings of emptiness, turbulence in interpersonal relationships, fear of abandonment, a tendency to become paranoid or dissociate during times of stress, and damaging impulsive behaviors. Recurrent self-injurious thoughts and behaviors are also a criterion of BPD, with suicide often the tragic outcome of BPD; longitudinal studies indicate that up to 10% of individuals with BPD die by suicide (Paris & Zweig-Frank 2001). Individuals with BPD are heavy utilizers of psychiatric treatment including therapy, hospitalizations, and pharmacology (Bender et al, 2001). Although treatment can be beneficial for BPD, treatment is often extremely challenging (Aviram et al, 2006), and quality of life often remains low following treatment despite improved functioning (Linehan *et al.* 2006).

Research on the biology of BPD has generally focused on trait-level factors, whereas relatively little research examines biological influences on the *instability* characteristic of BPD. Given that the ovarian steroid hormones estradiol (E2) and progesterone (P4) regulate nearly every brain system implicated in emotional disorders (Schiller *et al.* 2016), the rapid changes in ovarian hormones that occur across the monthly female menstrual cycle could represent one source of fluctuating biological vulnerability to BPD symptoms. The present study uses a longitudinal design and standardized diagnostic system to describe, in both relative and absolute terms, the impact of the menstrual cycle on symptoms in a sample of unmedicated females with BPD.

The prototypical menstrual cycle is 28 days and can be divided into two halves: The

follicular phase from menses to ovulation, characterized by low P4 and increasing E2 that peaks prior to ovulation, and the *luteal phase* from ovulation to the next menses, characterized by high levels of P4 and a secondary slower and generally lower peak in E2. E2 and P4 fall precipitously prior to and during the first few days of menses, and the cycle begins again. Among patients with the severe cyclical mood diagnosis of DSM-5 premenstrual dysphoric disorder (PMDD), symptoms peak in the perimenstrual window (Epperson *et al.* 2012, Hartlage *et al.* 2002) suggesting the most pronounced symptoms occur during the precipitous withdrawal from E2 and P4 prior to and during menses, a finding that dovetails with preclinical findings that ovarian steroid withdrawal precipitates anxious and depressive phenotypes (Stoffel & Craft 2004; Smith *et al.* 2006).

Although most females do not show clinically significant cyclical changes in emotional (Schwartz *et al.* 2012; Ben Dor *et al.* 2013; Hengartner *et al.* 2017) or cognitive (Schmidt *et al.* 2013; Leeners *et al.* 2017) symptoms, experimental work clearly demonstrates that a subset of females do suffer from an *abnormal sensitivity to normal ovarian steroid changes.* This ***hormone sensitivity*** manifests as emotional, cognitive, and behavioral changes appearing only or primarily in the context of normative ovarian steroid changes, such as the midluteal and perimenstrual cycle phases, as in PMDD (Schmidt *et al.* 1998); during pregnancy and postpartum (Bloch *et al.* 2000); and during the menopause transition (Schmidt *et al.* 2015; Gordon *et al.* 2016). The content of emotional symptoms most commonly observed in these *reproductive mood disorders* overlaps to a greater degree with BPD than with major depressive disorder: Reproductive mood disorders in general are often characterized by *high arousal negative affect* and *interpersonal* symptoms like anger and irritability and interpersonal sensitivity, with depressive symptoms being less common (Freeman *et al.* 2011; Eisenlohr-Moul *et al.* 2017a; Putnam *et al.* 2017); While having a mood or anxiety disorder as a female does not in itself equate to greater risk of perimenstrual symptom exacerbation (Stein *et al.* 1989; Hartlage *et al.* 2004), perimenstrual exacerbations may be more prevalent in a disorder such as

BPD that is already characterized by instability in this particular set of symptoms.

Little prospective evidence is available to evaluate the hypothesis that females with BPD are at high risk for cyclical symptom exacerbation. Only one study has examined the impact of the menstrual cycle in patients with BPD (Ziv, 1995; N=14). This study reported no evidence of reliable symptom changes from the premenstrual to postmenstrual phases of the cycle; however, most participants were taking psychotropic medications which may have interfered with cyclicity of symptoms. Also, hormonal markers were not used to make precise cycle phase delineations, and no LH surge testing was done to confirm ovulation, which is critical given that anovulatory cycles in women with PMDD are asymptomatic (Hammarbäck *et al.* 1991). In a more recent study, undergraduates blinded to the purpose of the study were recruited to achieve a flat distribution of BPD features (*N*=40) and were followed across four weeks. Among only individuals with elevated trait BPD features, daily BPD symptoms were highest at visits when P4 was higher-than-usual and E2 was lower-than-usual, a hormonal profile often found in the midluteal and perimenstrual phases (Eisenlohr-Moul *et al.* 2015). These findings suggest the possibility of heightened risk for psychiatric hormone sensitivity and related cycle effects in BPD; however, generalizability is limited given the nonclinical sample.

The present study aims to move this line of research forward by examining the prospective impact of ovulatory, hormonally normal menstrual cycles on daily self-reported psychiatric symptoms in a sample of community-recruited, unmedicated females with BPD (*N* = 15) who were *not* recruited for perceived premenstrual symptoms. In addition to examining the significance and size of contrasts between cycle phases, we utilize a standardized diagnostic system, the Carolina Premenstrual Assessment Scoring System (C-PASS; Eisenlohr-Moul *et al.* 2017b), to describe, in absolute terms, the clinical significance of perimenstrual symptom exacerbation in this sample of females with BPD.

Hypotheses

Given the evidence above, it was hypothesized that females with BPD would show a

similar *pattern* of symptom change as is observed in PMDD, where symptoms begin to increase in the midluteal phase, peak before and during menses ("perimenstrually"), and are reduced following menses, leading to lower symptoms in the follicular and ovulatory phases. Since BPD is a chronic disorder, we hypothesized cyclical *exacerbation* (midluteal and perimenstrual symptom exacerbation, follicular phase return to moderate symptoms) following this pattern rather than the typical luteal phase confinement of symptoms (luteal phase symptom appearance – full symptom remission in follicular phase) indicative of PMDD. We examined the following predictions related to our hypotheses:

(1) Given that the perimenstrual window corresponds to the greatest hormone withdrawal and the maximum symptoms in PMDD, we predicted symptoms in women with BPD would be at their worst during the perimenstrual phase relative to all other phases (i.e., midluteal, follicular, ovulatory).

(2) Given that symptoms in PMDD generally *begin* during the midluteal phase, when P4 rises and begins to fluctuate, we predicted symptoms would be worse during the midluteal phase than in the follicular and ovulatory phases.

(3) Given that the follicular phase is generally asymptomatic in PMDD, we predicted participants with BPD would show their normal baseline levels of symptoms during the follicular and ovulatory phases, and these two phases would not differ from one another.

(4) Given overlapping risk factors and similar core symptom content in PMDD and BPD, we predicted a majority (>50%) of the sample would meet the C-PASS diagnostic criterion of *premenstrual elevation* (worsening of at least 30% premenstrually vs. postmenstrually) on at least one emotional symptom.

Methods

Procedure

Participants were recruited from the community using email listservs, flyers, and social media advertisements that *did not refer to the menstrual cycle*. Interested individuals were

directed to an online screening survey, including the *Personality Diagnostic Questionnaire—Borderline Personality Disorder Subscale* (PDQ; Hyler *et al.* 1992) and eligibility questions. Exclusionary criteria were self-reported dysmenorrhea in the 3 months, current pregnancy or breastfeeding, psychotropic medication or oral contraceptive (OC) use, illicit drug use, and history of chronic medical condition, schizophrenia or manic episodes. Menstrual cycles between 25-35 days were required.

Individuals were contacted for follow-up phone screening if they met exclusion criteria and had a PDQ score endorsing 5 out of 9 BPD criteria. The phone screen included an additional interview version of the PDQ. Participants providing examples meeting SCID-PD (First *et al.* 1997) criteria on at least 5 symptoms were invited to the laboratory for a SCID-PD (BPD section) interview with a clinical psychologist for which they were paid $15. If they met SCID-PD criteria for BPD during, they completed self-report questionnaires and were instructed in study procedures. Participants completed online daily surveys for 35 days starting on their next menstrual period start day, daily urine ovulation testing, and passive drool saliva samples on 8 days across the cycle. Participants received $100 for participation of the longitudinal sampling study. All procedures were approved by the university institutional review board. The data were collected 2015-2016.

Participants

310 potential participants were screened online; 112 were eligible for phone screening (exclusion due to insufficient PDQ severity (*n*=143), hormone use (*n*=42), irregular cycles (*n*=6), or medical conditions (*n*=7)). Of those, 43 individuals completed the PDQ phone interview; 31 were invited for an initial visit (exclusion due to insufficient PDQ examples (*n*=8), OC use (*n*=2), pregnancy/nursing (*n*=2)). Of those, 18 completed the initial visit. Seventeen met SCID-BPD criteria and enrolled. One participant was noncompliant and one did not ovulate; the final sample included 15 medically healthy, unmedicated females with BPD. Demographics and

clinical characteristics are provided in Table 1. All participants reported a lifetime history of psychotherapy; 1 was currently in psychotherapy.

Baseline Measures

In addition to the SCID-II for BPD, participants completed several questionnaires during their baseline visit: a) demographics, b) the borderline subscale of the *Personality Assessment Inventory* (Morey 2014), c) the *Childhood Trauma Questionnaire* (Bernstein & Fink 1998), d) the *Beck Depression Inventory* (Beck & Steer 1987) and the state form of the *State-Trait Anxiety Inventory* (Spielberger 1983), and e) items from the *Premenstrual Assessment Form* (Halbreich *et al.* 1982) to assess perceptions of menstrually-related symptom change. Participants were asked to rate their typical degree of premenstrual symptom exacerbation for depressed mood, hopelessness, worthlessness or guilt, anxiety, anger, irritability, and interpersonal conflicts on a scale where 1=no change, 2=mild change, 3=moderate change, and 4=severe change. .

Daily Measures

The present study utilized standardized methods, developed for the study of PMDD. As part of their online daily surveys, participants completed the *Daily Record of Severity of Problems* (DRSP; Endicott *et al.* 2006), a list of hormone-sensitive psychiatric symptoms developed to reliably detect menstrually-related changes (e.g. premenstrual exacerbation) in psychiatric symptoms. The presence and degree of cyclical symptom change can be determined with the C-PASS, a standardized system for scoring the daily DRSP ratings (Eisenlohr-Moul *et al.* 2017b). In the present study, we chose to focus on the core emotional symptoms typically studied in relation to the menstrual cycle, including the following nine DRSP outcomes: depression, anxiety, anhedonia, hopelessness, emotional overwhelm, rejection sensitivity, anger/irritability, interpersonal conflict, physical symptoms (average of the items measuring breast tenderness, breast swelling, bloating, joint or muscle pain). Response ratings range from 1=not at all to 6=extreme.

In addition to the nine DRSP outcomes, the present study also examined three

processes known to play a key role in BPD symptom expression: a) daily shame with two items from the shame subscale of the *State Shame and Guilt Scale* (Marschall *et al.* 1994) b) daily felt invalidation with two items created for the purposes of this study, and c) daily anger rumination was measured with two items from the *Anger Rumination Scale* (Sukhodolsky *et al.* 2001). Each of these items were rated from 1=not at all to 5=extremely.

Ovulation Testing and Salivary P4

Participants completed home urine tests for the luteinizing hormone (LH) surge each morning using the Clearblue ovulation testing kit. The day after the positive LH test was considered the day of ovulation. Participants also provided saliva samples for hormone assays on 8 days across the cycle: days 2, 3, 8, and 9 following menstrual onset and days 2, 3, 8, and 9 following a positive LH surge test. Participants collected 5 mL of saliva in polypropylene vials (passive drool) each afternoon between 4pm and 6pm, froze the samples in their home freezer in a temperature stability pouch and returned them to the lab after study completion. P4 was assayed in saliva using standard RIA methods (Gandara et al. 2007) and demonstrated the expected cyclical trajectory.

Menstrual Cycle Phase Coding

The determination of the cycle phases *ovulatory*, *midluteal*, *perimenstrual*, and *midluteal* phase was based on several sources of information: (1) forward and backward count as described elsewhere (Edler *et al.* 2007), (2) day of positive LH surge, and (3) exponential P4 rise following ovulation. First, the ovulatory phase was determined using backward count (days -15 to -12), and was validated using the LH surge ovulation test and the presence of a substantial postovulatory rise in P4 following the ovulatory phase. Next, the perimenstrual phase was determined using backward and forward count (days -4 to +3, where day +1 is menses onset and there is no day 0), and was further validated by time since positive LH surge (14 +/- 2 days). The midluteal phase was defined as the days falling between the ovulatory and perimenstrual phases, and was validated by the presence of elevated P4. The follicular phase

was defined as the days falling between the perimenstrual and ovulatory phases, and was validated by the presence of low P4.

Data Analysis and Power

To improve interpretability and isolate the within-person component of the outcome, each outcome was person-standardized (as in Edler *et al.* 2007; Klump *et al.* 2013). To test the first three predictions, multilevel models evaluated the impact of cycle phase (coded as a categorical variable, with alternating reference phases). SAS PROC MIXED was utilized to account for the nested structure of observations (i.e., random intercept) as well as the autocorrelation of today's rating with yesterday's rating. Random effects of cycle phase contrasts were not included as they did not improve model fit; this indicates that the impact of the menstrual cycle on symptoms were roughly uniform in this sample. Person-standardized dependent variables result in contrast estimates representing the average number of person-standard deviations by which the two phases differed on that outcome. 5-day rolling averages of each person-standardized variable were utilized for smoother graphical depictions.

To determine power for phase contrasts, we calculated the design effect to determine the smallest detectible effect size (Snijders 2005). Each participant provided up to 35 daily surveys (lower-level *N* was 490), and symptoms generally showed low intraclass correlations (i.e., a high degree of flux within a given person, average ICC for DRSP items = .18). Calculations indicated power for these models was adequate to detect conventionally small-to-medium sized, clinically significant contrasts between cycle phases (smallest detectible effect size, was, on average, f^2 of .10). That is, the present study was powered to detect significant phase contrasts that accounted for at least 10% of the variance in the daily outcome.

To test hypothesis 4, we evaluated whether each participant met the C-PASS diagnostic criterion of *premenstrual elevation* (over baseline) on at least one emotional symptom (Eisenlohr-Moul *et al.* 2017b). In contrast to PMDD, which requires luteal phase elevation *and* full remission of symptoms in the follicular phase, cycle-related symptom *exacerbation* can be

diagnosed when at least one core emotional symptom demonstrates a 30% *premenstrual* week elevation of symptoms relative to the postmenstrual week. We used the validated C-PASS percent change calculation method [(premenstrual week average – postmenstrual week average/range of scale ever used by a given woman)*100] to determine the presence of clinically significant premenstrual symptom exacerbation using a >= 30% cutoff (Eisenlohr-Moul *et al.* 2017b).

Results

Descriptives

Table 1 provides demographic and clinical characteristics. The sample was diverse with regard to age and race. Participants reported high BPD symptoms on the PAI-BOR, generally moderate depression on the BDI, moderate anxiety on the STAI, and many participants reported significant experiences of childhood trauma; these characteristics are consistent with typical profiles of comorbidity and adverse childhood experiences in BPD. Proportions of the sample meeting each SCID criterion are also listed in Table 1. On the MAF, participants cross-sectionally reported an average perception of *mild* premenstrual exacerbation of emotional symptoms (*Mean* = 2.18, *SD* = .73) that was similar across domains (Range of Means = 1.97 to 2.50).

Menstrual Cycle Phase Contrasts

Next, menstrual cycle phase contrasts were performed to describe the general pattern of cyclical symptom change. We also sought to test the prediction that people with BPD demonstrate perimenstrual and, to a lesser extent, midluteal worsening of symptoms. Results of multilevel models contrasting symptom levels across different phases are presented in Table 2. All symptoms demonstrated strong cyclical changes; Figures 1-3 depict patterns of symptom change across cycle day and cycle phase observed in several exemplar symptoms. Graphs by day and by cycle phase are provided for each individual outcome in Supplement 1. Graphs include smoothed person-standardized P4 values to improve interpretability relative to the

normative luteal P4 rise and fall.

As predicted, the perimenstrual phase was associated with significantly higher symptoms relative to the other three phases, with the largest contrasts generally emerging between the perimenstrual and ovulatory phases. This was true for all symptoms except depression, shame, anhedonia, and hopelessness, which were higher in the perimenstrual phase than in the ovulatory and midluteal phases but, contrary to our expectations, showed no difference between the perimenstrual and follicular phases; thus, it appears that perimenstrual worsening of depressive symptoms persisted into the follicular phase. As predicted, the midluteal phase was also associated with worsening of some symptoms relative to the follicular and ovulatory phases, specifically for higher-arousal symptoms of anxiety, anger/irritability, and interpersonal conflict. Additional models controlled for person-standardized physical symptoms; no substantive changes were found, suggesting the results presented above are not an artifact resulting from perimenstrual physical pain (e.g., dysmenorrhea) in females with BPD.

C-PASS Diagnosis of Cyclical Exacerbation in Each Participant

In contrast to the previous analyses, which focused on describing the patterns of symptom exacerbation across the entire menstrual cycle, the next set of analyses used standardized diagnostic procedures to define, in more absolute terms, the percentage of individuals in this sample showing *clinically significant* cyclical symptom exacerbation. Results of individual diagnostic analyses revealed 11 of 15 participants (73%) showed >= 30% premenstrual elevation in symptoms relative to the post-menstrual week on at least one of the eight DRSP emotional symptoms.

It is possible exclusion of the first three days of menses omitted the most symptomatic days; similar analyses were conducted replacing the pre- and post-menstrual means with perimenstrual and follicular means (as described in the contrast analyses), respectively; this did not alter the 73% outcome. Finally, given that participants demonstrated follicular exacerbation of depressive symptoms, we also conducted similar analyses replacing the C-PASS pre-

menstrual and postmenstrual means with those from the perimenstrual and *ovulatory* phases (as defined in the contrast analyses), respectively. The number of participants showing significant cyclical exacerbation of symptoms from the ovulatory to the perimenstrual phase was to 14 out of 15 (93%), with all but 1 showing exacerbation of at least one emotional symptom.

Discussion

Summary

The purpose of the present study was to describe menstrual cycle-related patterns of symptom exacerbation in unmedicated individuals with BPD. Despite cross-sectionally reporting only mild premenstrual symptom changes, evaluation of daily ratings unequivocally demonstrated perimenstrual worsening of all symptoms, including depression, anxiety, anhedonia, rejection sensitivity, feelings of overwhelm, anger, conflict, anger rumination, feelings of invalidation, and shame. Additionally, some symptoms showed secondary exacerbations in the midluteal phase (anxiety, anger, conflict) or the follicular phase (depression, anhedonia, hopelessness, shame). Critically, although participants also demonstrated perimenstrual physical symptoms, this did not account for perimenstrual exacerbation of emotional symptoms. C-PASS diagnostic procedures indicated that the phase contrasts observed were not only significant, but could be categorized as clinically significant perimenstrual exacerbation in 14 of 15 cases.

Inspection of symptoms across the cycle (Figures and Supplement 1) leads to the following insights: First, all symptoms generally show lowest levels in the ovulatory phase. Second, in the midluteal phase, high-arousal symptoms of anxiety, anger, and interpersonal conflict worsen but are not yet accompanied by exacerbation of other symptoms. Third, in the perimenstrual phase, all symptoms become exacerbated, with continued heightening high-arousal symptoms, but also increased experiences of physical discomfort, felt invalidation, shame, rejection sensitivity, anger rumination, emotional overwhelm, depression, anhedonia, and hopelessness. Finally, although high-arousal symptoms return to baseline by the follicular

phase, low-arousal, depressive emotions such as depression, hopelessness, shame, and anhedonia continue to be exacerbated in the follicular phase before returning to their lower baseline at ovulation and the midluteal phase.

Although it may be premature to comment on the specific biological mechanisms of perimenstrual exacerbation in BPD, this study does allow us to compare and contrast the patterns observed in this sample with BPD with the patterns typically observed in PMDD, a disorder for which the pathophysiology of cyclic symptom change is relatively understood. Given their identical timing, the pathophysiology of perimenstrual worsening of high-arousal symptoms (e.g., anger/irritability) in BPD may have a shared pathophysiology with PMDD—that is, an abnormal dysphoric response to luteal fluctuations in the GABAergic neurosteroid metabolites of P4 (Martinez *et al.* 2013; Schiller *et al.* 2014). However, regarding depressive symptom worsening, the premenstrual exacerbation into the follicular phase observed here is not necessarily consistent with a shared pathophysiology with PMDD. This profile may suggest females with BPD also have *additional* sensitivity to withdrawal from—or low levels of—ovarian steroids in the follicular phase. It is also possible the emergence of PMDD during puberty interacts with environmental BPD risk factors to precipitate the development of BPD, especially when emotion regulation skills are insufficient to prevent PMDD symptoms from persisting into the follicular phase (Dawson *et al.* in press).

Several lines of research indicate that the predictors and characteristics of BPD overlap with those of hormone sensitivity. First, traumatic stress exposure and extreme stress vulnerability have been identified as being both particularly relevant to the etiology of BPD (Lynam & Widiger 2001; Ball & Links 2009) and relevant to the pathophysiology of psychiatric hormone sensitivity across the lifespan (Gollenberg *et al.* 2010; Gordon *et al.* 2015; Nillni *et al.* 2015; Eisenlohr-Moul *et al.* 2016). Second, indices of impulsivity, a core feature of BPD (Peters *et al.* 2013), have been found to predict sensitivity to perimenstrual hormone withdrawal in rodents (Löfgren *et al.* 2009) and in humans (Martel et al., in press). Finally, several extreme

behavioral manifestations of emotion-related impulsivity have been found to show perimenstrual exacerbation across the menstrual cycle, including binge eating in bulimia (Edler *et al.* 2007; Klump *et al.* 2013), substance use and abuse (Terner & de Wit 2006), and suicide attempts (Saunders & Hawton 2006). The finding that elevated hopelessness persists into the follicular phase in BPD is particularly consistent with evidence for greater risk of suicide attempt and more lethal attempts in the perimenstrual and follicular phases (Saunders & Hawton 2006).

Clinical Implications

Despite the development of useful psychotherapies for BPD, such as dialectical behavior therapy (DBT; Linehan 2014) and mentalization-based therapy (Bateman & Fonagy 2004), quality of life often remains low following treatment (Linehan *et al.* 2006). Studies like the present one point to the potential benefits of identifying and stabilizing biological sources of instability in BPD and dangerous associated phenomena such as recurrent suicidal behavior (Glenn *et al.* 2017). Future studies are needed to determine whether experimental stabilization of ovarian steroids might benefit females with BPD. Of note, most of the people in this study reported only mild premenstrual symptom change cross-sectionally; some females with BPD may underestimate the role of the cycle in their symptoms. Greater cycle awareness in the context of psychosocial treatment may also support targeted skills use to improve stability, and the standard DBT diary card could be a natural method of tracking the impact of the cycle. Finally, the dramatic perimenstrual exacerbation of hopelessness observed here combines with previous work (Saunders & Hawton 2006) to highlight the potential role of the perimenstrual phase in elevated acute risk for suicide among this chronically-at-risk population.

Limitations and Strengths

The present study has key limitations, including the small clinical sample. However, the repeated measures of symptoms within each woman ensured sufficient power to detect the large observed effects of the menstrual cycle. Also, the lack of a control group simply means that we cannot estimate the extent to which people with BPD differ from people without BPD in

the size of their phase contrasts. This concern is mitigated by the use of a standardized prospective diagnostic protocol (the C-PASS; Eisenlohr-Moul *et al.* 2017b) to document clinically significant symptom exacerbation. Nevertheless, the missing clinical control group means that we cannot conclude that the symptom exacerbations demonstrated here are due to factors specific to BPD rather than transdiagnostic factors such as trauma exposure (Eisenlohr-Moul *et al.* 2016). More work is needed to determine the extent to which this risk for cyclicity in BPD differs from risk for other clinical disorders. Another constraint on generalizability is that women were excluded on the basis of taking OCs; since some women discontinue OCs due to progestin sensitivity that leads to adverse mood effects, women with BPD who do not take OCs could be more likely exhibit hormone change sensitivity.

Despite study limitations, it has notable strengths that address methodological limitations of previous work: First, self-selection due to premenstrual mood concerns was reduced due to blinding potential participants to the study purpose. Second, participants were not taking medications that might interfere with symptom cyclicity. Third, the community-recruited, demographically diverse clinical sample improves generalizability. Fourth, use of electronic daily diaries (in contrast to typical pencil and paper diaries) ensured more accurate and time-verified ratings. Fifth, use of both LH surge detection and salivary P4 to ensure ovulatory cycles and characterize phases enhanced precision. Finally, the present study examined all pairwise comparisons between phases to more precisely describe the nature of cyclical symptom change in BPD.

Conclusions

People with BPD suffer intense fluctuations in painful emotional and behavioral symptoms. The present work supports the hypothesis that females with BPD may be at high risk of psychiatric hormone sensitivity, leading to perimenstrual symptom exacerbation, with secondary worsening in the midluteal (high arousal symptoms) and follicular (low arousal symptoms) phases. Patterns of symptom change suggest shared pathophysiology with PMDD

with regard to midluteal and perimenstrual high-arousal symptoms (e.g., possible abnormal sensitivity to changes in P4-derived GABAergic neurosteroids), but also suggest potentially divergent pathophysiology with regard to depression (e.g., additional deleterious effects of ovarian steroid withdrawal or deprivation in the follicular phase). Experimental studies are needed for the dual purposes of investigating the therapeutic potential of hormone stabilization while probing the pathophysiologic relevance of steroid changes to cyclical worsening of BPD. Finally, studies should evaluate whether PMDD is a developmental risk factor for the emergence of BPD.

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Table 1. Sample Descriptive Information (*N* = 15)

Variable	Mean (SD); n (%)	Range
General Characteristics		
Age	32.16 (8.64)	19-44
African American Race	5 (33%)	-
Hispanic Ethnicity	1 (6%)	-
Education Level		
Trade School	1 (6%)	-
Some College	7 (47%)	-
College Grad	7 (47%)	-
Marital Status		-
Married	2 (15%)	-
Living with Partner	5 (33%)	-
Divorced	3 (20%)	-
Never Married	5 (33%)	-
Average Cycle Length in Days	28.97 (1.32)	26-35
Age at Menarche in Years	11.24 (1.08)	10-14
% with Biological Children	4 (26%)	-
Clinical Characteristics		
Trauma Exposure		
Childhood Trauma Questionnaire (CTQ)	43.00 (12.08)	28-64
% Significant Childhood Physical Abuse (>=8)	7 (47%)	-
% Significant Childhood Sexual Abuse (>=8)	4 (27%)	-
% Significant Childhood Physical Neglect (>=8)	7 (47%)	-
% Significant Childhood Emotional Abuse (>=10)	7 (47%)	-
% Significant Childhood Emotional Neglect (>=15)	5 (33%)	-
Borderline Symptom Assessments		
PAI-BOR Score	44.23 (9.84)	29-53
Number of SCID-BPD Criteria Met	6.89 (1.26)	5-8
% Meeting Fear of Abandonment Criterion	10 (67%)	-
% Meeting Affective Lability Criterion	15 (100%)	-
% Meeting Identity Disturbance Criterion	8 (53%)	-
% Meeting Interpersonal Disturbances Criterion	14 (93%)	-
% Meeting Emptiness Criterion	11 (73%)	-
% Meeting Anger Criterion	10 (67%)	-
% Meeting Paranoia/Dissociation Criterion	8 (53%)	-
% Meeting Self-Harm Criterion	6 (40%)	-
% Meeting Impulsivity Criterion	11 (73%)	-
Comorbidity Assessments		
Depression (BDI)	13.66 (4.37)	2-29
% Minimal (0-13)	5 (33%)	-
% Mild (14-19)	5 (33%)	-
% Moderate (20-28)	3 (30%)	-
% Severe (29-63)	2 (13%)	-
Anxiety (STAI-T)	45.36 (8.86)	29-56

Note. CTQ = Childhood Trauma Questionnaire. STAI=State-Trait Anxiety Inventory (Trait Form). BDI = Beck Depression Inventory. PAI-BOR = Personality Assessment Inventory – Borderline Subscale. SCID-BPD = Structured Clinical Interview for Personality Disorders – Borderline Personality Disorder Module.

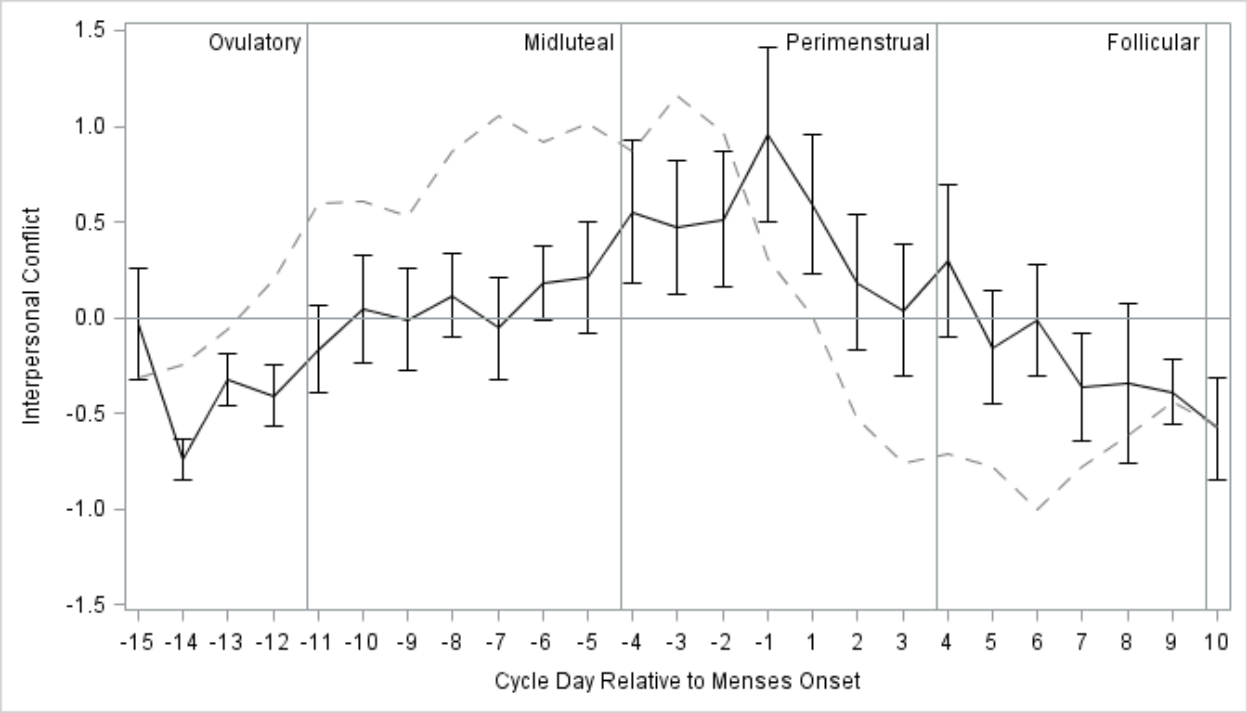
Table 2

Multilevel Model Results: Within-Person Menstrual Cycle Phase Contrasts for Intrapersonal and Interpersonal Symptoms

	Within-Person Phase Contrasts (Standardized Fixed Effects)					
	Perimenstrual Phase (Falling E/P)			Midluteal Phase (High Stable E/P)		Follicular Phase (Low Stable E/P)
	v. Follicular (Low Stable E/P)	v. Midluteal (High Stable E/P)	v. Ovulatory (Rising E/Low P)	v. Ovulatory (Rising E/Low P)	v. Follicular (Low E/P)	v. Ovulatory (Rising E/Low P)
Core Cyclical Emotional Symptoms (DRSP)						
Depression	-.12 (.35)	**-.51*** (.14)**	**-.51** (.17)**	-.01 (.17)	**.39** (.14)**	**-.39** (.15)**
Hopelessness	-.12 (.12)	**-.44** (.14)**	**-.71*** (.16)**	-.26 (.17)	**.32* (.13)**	**.59*** (.16)**
Anxiety	**-.61*** (.13)**	**-.34* (.15)**	**-.70*** (.17)**	**-.37* (.18)**	-.28 (.14)	-.09 (.17)
Rejection Sens	**-.26* (.12)**	**-.33* (.14)**	**-.40* (.16)**	-.07 (.17)	.07 (.13)	-.13 (.15)
Anger/Irritability	**-.51*** (.13)**	**-.24* (.11)**	**-.76*** (.17)**	**-.52** (.18)**	**-.27* (.13)**	-.24 (.17)
Interpersonal Conflict	**-.71*** (.13)**	**-.33* (.14)**	**-.77*** (.17)**	**-.44* (.18)**	**-.37* (.14)**	-.07 (.16)
Additional Symptoms						
Anhedonia	-.12 (.13)	**-.35* (.15)**	**-.34* (.17)**	.004 (.19)	.22 (.14)	-.22 (.17)
Overwhelmed, Can't Cope	**-.50*** (.12)**	**-.36* (.14)**	**-.70*** (.17)**	-.35 (.16)	.14 (.13)	.21 (.16)
Shame	-.22 (.12)	**-.28* (.12)**	**-.54** (.16)**	-.26 (.17)	**.49*** (.13)**	**-.76*** (.16)**
Felt Invalidation	**-.60*** (.13)**	**-.45** (.15)**	**-.53** (.17)**	-.07 (.18	-.15 (.14)	-.08 (.18)
Anger Rumination	**-.54*** (.13)**	**-.42** (.15)**	**-.50** (.17)**	-.07 (.18)	-.12 (.14)	.04 (.17)
Physical Symptoms	**-.36** (.13)**	**-.39* (.15)**	**-.79*** (.17)**	**-.41* (.18)**	-.01 (.14)	**-.43* (.17)**

Note. *$p < .05$; **$p < .01$ *** $p < .001$. Outcomes have been person-standardized to represent the number of standard deviations away from one's mean (0); therefore, estimates reflect the average number of personal standard deviations by which the two phases differ. DRSP=Daily Record of Severity of Problems.

PANEL A



PANEL B

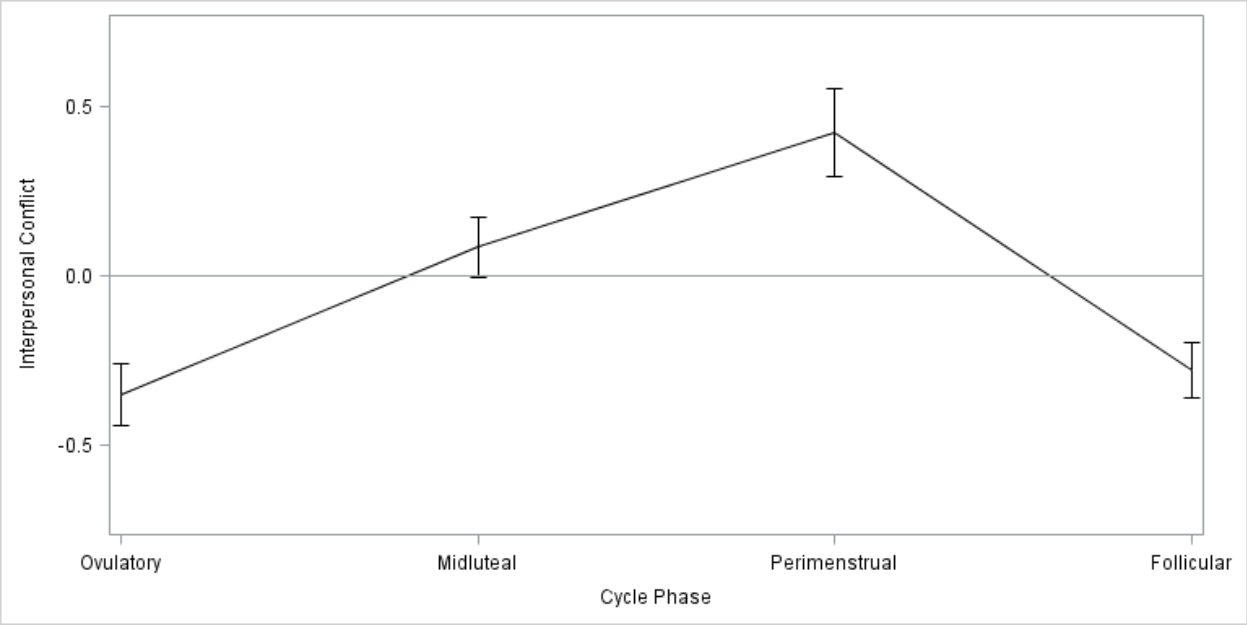
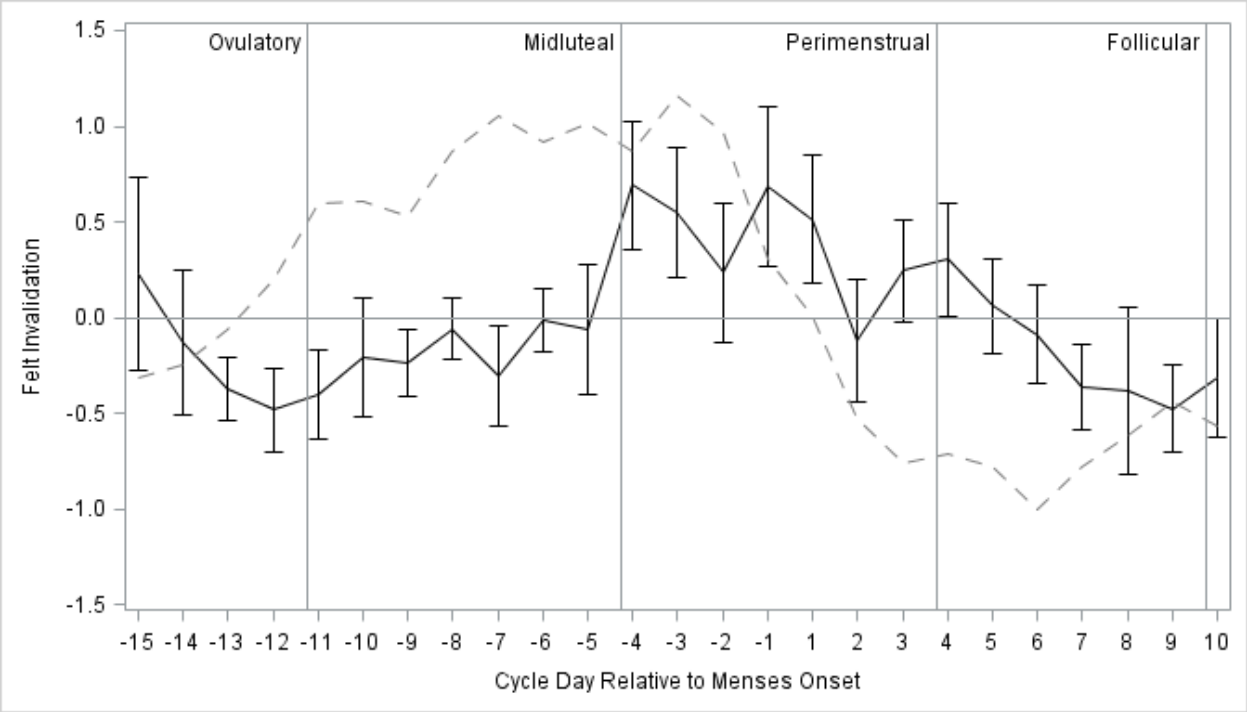


Figure 1. Person-Standardized Progesterone (dashed line) and Interpersonal Conflict Across Menstrual Cycle Day (Panel A) and Person-Standardized Interpersonal Conflict Across Cycle Phase (Panel B) in 15 People with BPD.

PANEL A



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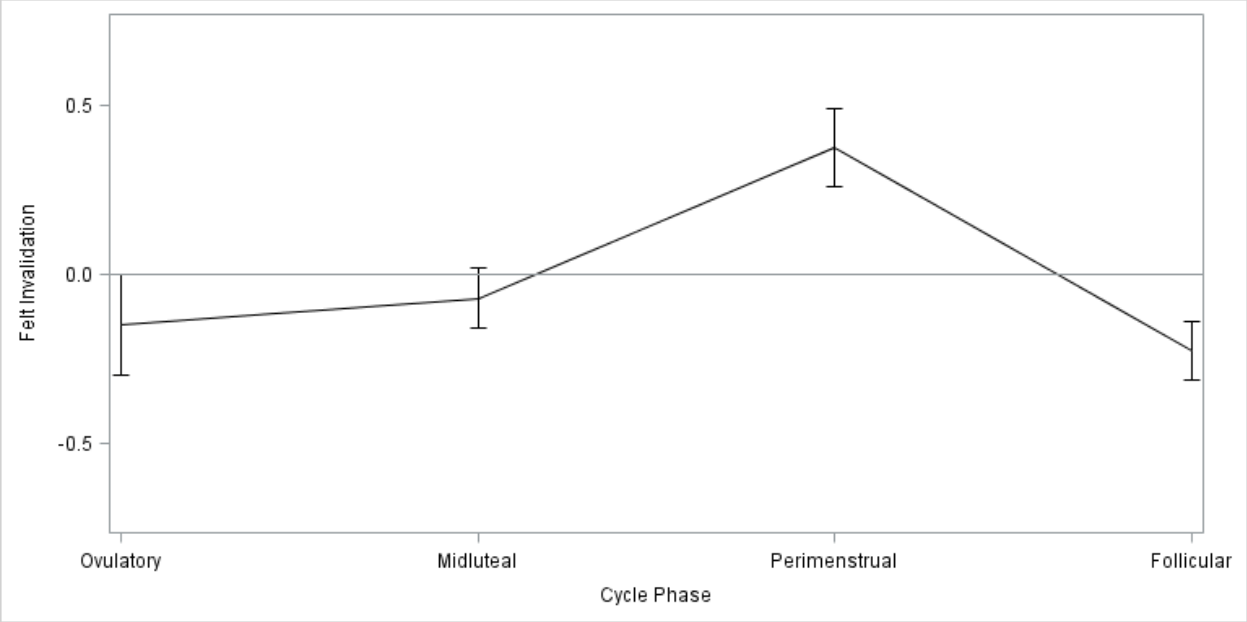
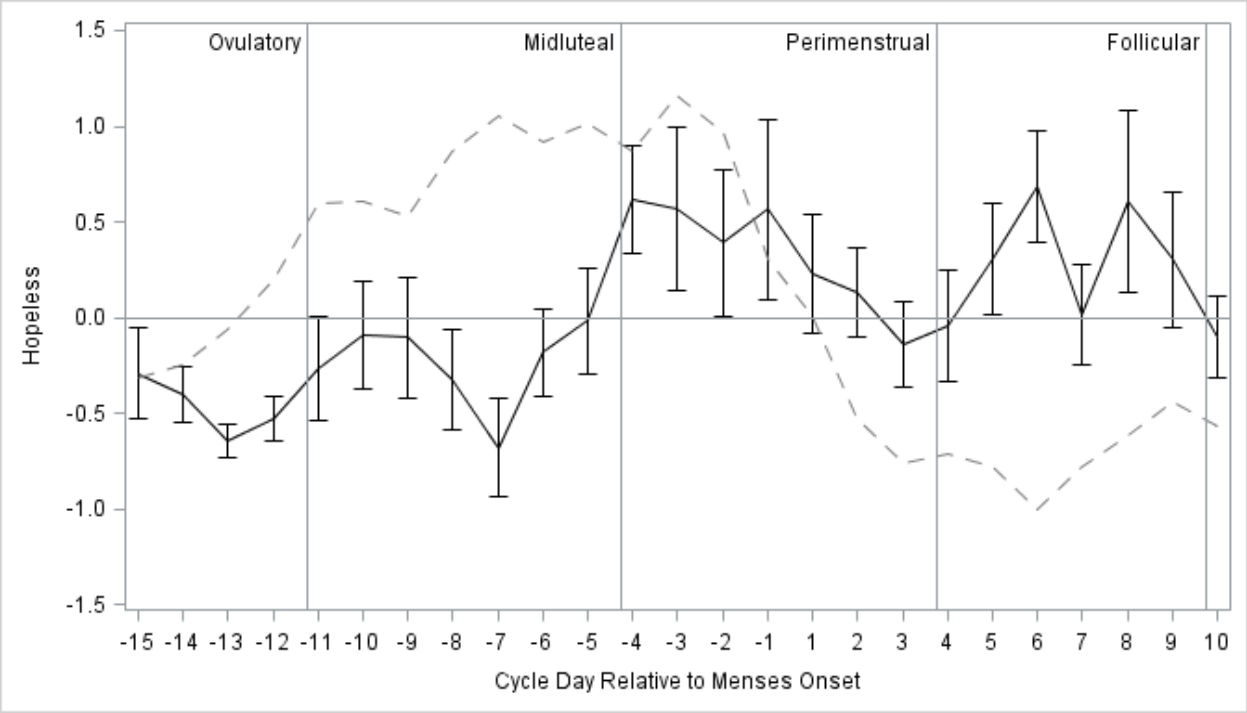


Figure 2. Person-Standardized Progesterone (dashed line) and Felt Invalidation Across Menstrual Cycle Day (Panel A) and Person-Standardized Felt Invalidation Across Cycle Phase (Panel B) in 15 People with BPD.

PANEL A



PANEL B

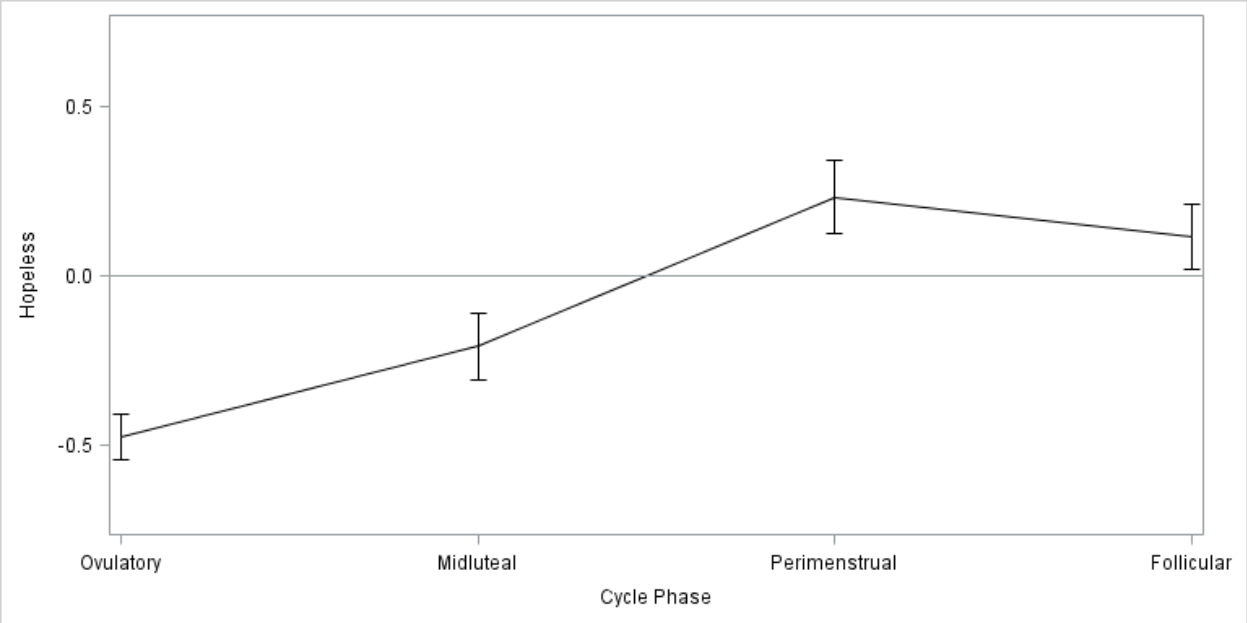


Figure 3. Person-Standardized Progesterone (dashed line) and Hopelessness Across Menstrual Cycle Day (Panel A) and Person-Standardized Hopelessness Across Cycle Phase (Panel B) in 15 People with BPD.