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Cyclical Exacerbation of Suicidal Ideation in Female Outpatients: Prospective Evidence From Daily Ratings in a Transdiagnostic Sample

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Abstract

Suicide is a leading cause of death among females of reproductive age. The menstrual cycle is a plausible yet understudied trigger for acute suicide risk. Cross-sectional studies have demonstrated a greater frequency of suicide attempts and deaths in the weeks before and after the onset of menses compared to other cycle phases. Here, using prospective daily ratings, we examine the relationship between the cycle and suicidal ideation (SI) and related symptoms known to show a cyclical change in some patients (depression, hopelessness, guilt, rejection sensitivity, interpersonal conflict, anxiety, mood swings, and anger/irritability). Thirty-eight naturally cycling outpatients recruited for past-month SI reported SI severity and other symptoms across an average of 40 days. Participants were excluded for hormone use, pregnancy, irregular cycles, serious medical illness, and body mass index >29.9 or <18. Intraclass correlations ranged from .29 to .46, highlighting that most symptom variance lies within-person. Cyclical worsening of symptoms

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The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national and institutional committees on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008. The original research described in this manuscript was conducted in compliance with APA ethical standards in the treatment of participants, with the approval of the University of North Carolina Institutional Review Boards (Study 16–2078). The manuscript has been preposted online prior to peer review at https://osf.io/6hfxk. Preliminary results from this study were also shared at the 2019 meeting of the International Academy of Suicide Research and American Foundation for Suicide Prevention and the 2020 meeting of the Association for Behavioral and Cognitive Therapies. Power analyses for determining sample size, the handling of missing data, all data exclusions, and all manipulations are reported. Materials and analysis code for this study are available by emailing the corresponding author. Data were analyzed using SAS OnDemand for Academics and R. The design and analyses of this secondary data analysis were not preregistered.

was evaluated using phase contrasts in multilevel models. Most symptoms, including SI, were significantly worse in the perimenstrual phase than in all other phases. Additionally, anger/irritability was higher in the midluteal than in the midfollicular phase, and several symptoms of depression were higher in the midfollicular than in the periovulatory phase. Otherwise, symptoms did not significantly differ between the midluteal, midfollicular, and periovulatory phases. Cycle phase predictors accounted for 25% of the within-person variance in SI. Females with SI may be at risk for perimenstrual worsening of SI and related symptoms. These findings highlight the importance of assessing the cycle phase for improved prediction of suicide risk.

General Scientific Summary

Previous cross-sectional research has suggested that suicidal behaviors are more prevalent in the weeks before and after the onset of menses compared to other menstrual cycle phases. Using prospective daily ratings of symptoms, this study supports the hypothesis that females with chronic suicidal ideation are at risk for perimenstrual worsening of affective symptoms and suicidal ideation.

Keywords

menstrual cycle; suicide; premenstrual symptoms; hormones

Suicide is a leading cause of death among females1 of reproductive age in the United States each year (2nd leading cause of death for ages 15–24, 3rd leading cause of death for ages 25–34, 4th leading cause of death ages 35–44; Heron, 2021). Decades of research have provided clues about who is at risk for suicidal thoughts and behaviors across their lifetime, focusing largely on comparing groups based on demographic variables (e.g., age and gender) and discrete diagnostic categories (e.g., Borderline Personality Disorder and Major Depressive Disorder; Glenn et al., 2017). However, few studies examine factors that influence suicide risk across psychiatric diagnoses (Glenn et al., 2018). Fewer still clarify when at-risk individuals will consider suicide or make an attempt over short intervals, due to the challenges of applying intensive methods to describe patterns in high-risk behaviors (Glenn et al., 2018; Kleiman et al., 2017). Recent studies have begun to demonstrate high intraindividual variability in suicidal ideation (SI) over short periods of time (e.g., hours) and have called for studies describing patterns in variability in SI over weeks and months to help clinicians and patients better predict periods of acute risk (Kleiman et al., 2017). In sum, there is an urgent need to identify *transdiagnostic, time-varying* predictors of risk that may be more useful for predicting and preventing suicide in routine clinical care.

A growing body of research points to the menstrual cycle as one promising yet understudied time-varying, transdiagnostic predictor of acute suicide risk. Suicide risk increases following the pubertal transition and the onset of regular menstrual cycles (Nock et al., 2013; Ortin & Miranda, 2020) and cross-sectional studies have demonstrated increased risk for suicide in the weeks surrounding menses (Saunders & Hawton, 2006). However, to date, there are no prospective, longitudinal studies examining the association between the menstrual cycle and fluctuations in SI or suicidal behavior. In this article, we present the results of a study designed to evaluate the association of the menstrual cycle with day-to-day severity of SI

and related affective symptoms in a transdiagnostic sample of naturally cycling outpatients with affective disorders who report past-month SI.

During puberty, levels of the ovarian steroid hormones 17β-estradiol (E2; estrogen) and progesterone (P4) rise and begin to fluctuate systematically over the course of the monthly menstrual cycle. In the typical cycle, P4 levels remain low throughout the follicular phase, while E2 levels are low in the early follicular phase (the week following the onset of menstrual bleeding) and begin to rise steadily about 8 days after the onset of menstrual bleeding. They continue to rise until ovulation, the start of the luteal phase (approximately 14 days prior to next menses). Following a brief decline in E2, both E2 and P4 rise during the early luteal phase, a trend that continues through the late luteal phase until a rapid decline just before the next onset of menstrual bleeding.

While these hormone fluctuations follow a predictable cyclical pattern in ovulating adults, *affective responses to hormone changes vary significantly between individuals in a dimensional manner, with some individuals showing larger cyclical changes in symptoms than others*. Experimental studies using hormone manipulations demonstrate that a subset of individuals shows an abnormal affective and behavioral reaction to normal hormone changes when compared to controls; that is, they are *hormone-sensitive* (Schmidt et al., 2017). While the etiology and prevalence of hormone sensitivity are not known, there appears to be some overlap in factors that predict hormone sensitivity and risk for suicide. Exposure to traumatic events (Eisenlohr-Moul, Rubinow, et al., 2016), symptoms or diagnosis of borderline personality disorder (BPD; Eisenlohr-Moul et al., 2015, 2018), and trait impulsivity (Roberts et al., 2018) appear to correlate with both lifetime suicidal thoughts and behaviors and greater changes in affective symptoms across the cycle. While not all female psychiatric patients experience this hormone sensitivity, individuals with a history of SI and suicidal behaviors may be particularly likely to experience changes in mood or behavior across the menstrual cycle due to shared underlying risk factors.

Hormone sensitivity has been most comprehensively characterized in individuals with Premenstrual Dysphoric Disorder (PMDD). Roughly 5.5% of ovulating adults meet criteria for PMDD, which is characterized by a pattern of significant psychiatric symptoms that occur only in the luteal phase (i.e., the time from the day after ovulation until the day before the next menstrual onset) of the menstrual cycle (according to The Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition [DSM-5] criteria for PMDD; Gehlert et al., 2009). While decades of research seeking to understand cyclical fluctuations in symptoms have been fruitful, prior studies have generally excluded individuals with comorbid conditions and psychiatric symptoms that do not neatly remit following menses. Preliminary research has begun to indicate that far more individuals are affected by perimenstrual exacerbation of psychological symptoms without total symptom remission following menses (the end of the luteal phase). As the within-person longitudinal multilevel modeling techniques have been applied to examine cyclical fluctuations in symptoms across diagnoses, it has become more apparent that many females with chronic affective and behavioral disorders likely experience cyclical exacerbation of their persistent symptoms. For example, roughly 60% of female with a depressive disorder demonstrate a clinically significant perimenstrual worsening of at least one symptom (i.e., consistent with the degree

of change observed in PMDD despite a lack of follicular remission; Hartlage et al., 2004). Limited prospective research has begun to indicate that many other psychiatric disorders and symptoms are worsened by the cycle for some individuals, including posttraumatic stress disorder (perimenstrual worsening; Nillni et al., 2015), borderline personality disorder (perimenstrual and midluteal symptom worsening; Eisenlohr-Moul et al., 2018), and eating disorder symptoms (midluteal worsening; Klump et al., 2013). Despite this evidence that the menstrual cycle and ovarian hormones may contribute to predictable, acute changes in emotion and behavior across the cycle for many individuals, *no prospective studies have examined whether females with ongoing SI report increased SI intensity in the weeks before and after menstrual onset compared to other phases of the cycle*.

Additional preliminary evidence for the existence of such cyclical SI fluctuations is derived from a small body of cross-sectional studies linking the weeks before and after the onset of menses to a greater risk of suicide attempt and death relative to other cycle phases (Baca-Garcia et al., 2010; Dogra et al., 2007; Saunders & Hawton, 2006; Zengin et al., 2015). A systematic review of these cross-sectional studies found increased hospitalization for SI and suicide attempts in the late luteal and early follicular (perimenstrual) phases (Saunders & Hawton, 2006). The majority of reviewed studies examining suicide attempts (15 of 23) found a positive association between the perimenstrual phase and attempts; the same pattern of effects was found for all studies of ideation. Since the publication of this review, several additional studies have found suicidal behavior to be associated with the perimenstrual phase of the cycle (Baca-Garcia et al., 2010; Dogra et al., 2007; Zengin et al., 2015). These cross-sectional findings suggest that the perimenstrual phase may be a time of elevated risk for suicide.

Despite cross-sectional evidence for the hypothesis that the perimenstrual weeks are a time of elevated suicide risk in ovulating individuals, methodological flaws limit confidence in these findings, and thus limit their impact on clinical practice and treatment development. First, the cross-sectional nature of the findings is a massive limitation that leaves open several alternative explanations, including altered timing of menstrual onset due to suicide attempt. Furthermore, many studies relied on retrospective self-report of last menstruation to determine cycle phase, despite research documenting limited accuracy in recall of last menses (Baca-García et al., 2000). Studies of suicide death and cycle phase used visual examinations of endometrial tissue to determine cycle phase, a method limited by the autolysis of endometrial tissue shortly after death (Dogra et al., 2007; Saunders & Hawton, 2006). As lysed cells may be easily mistaken for menstruum, several studies had poor inter-rater agreement while others elected to exclude large proportions of samples due to large time lapses between death and autopsy. Overall, while menstrual cycle changes have been associated with suicide risk, methodological limitations have reduced the impact of these findings.

In the present study, 38 naturally cycling psychiatric outpatients recruited for past-month SI (but not recruited for cyclical changes in emotion, behavior, or suicidality) completed 1–2 months of daily ratings before being randomized as part of a mechanistic experiment. Our primary goal was a descriptive test of within-person associations between the phases of the menstrual cycle and SI severity. For completeness, and to increase comparability with

prior studies of cyclical fluctuations in mood and behavior, we also present exploratory descriptive tests of cycle associations with the eight core affective symptoms of DSM-5 PMDD (depression, hopelessness, worthlessness/guilt, anxiety, mood swings, rejection sensitivity, anger/irritability, and interpersonal conflict).

Based on the work described above, our first hypothesis was that daily SI severity, as well as the severity of each affective symptom, would be highest in the perimenstrual phase (perimenstrual > midfollicular, periovulatory, midluteal). Our second hypothesis was that SI severity and the severity of each affective symptom would be lowest in the periovulatory phase (midluteal, midfollicular > periovulatory), given that the ovulatory phase consistently emerges as the least symptomatic in prospective studies of cyclical exacerbation (Owens & Eisenlohr-Moul, 2018), and cross-sectional studies of suicidal thoughts and behaviors across the cycle (Saunders & Hawton, 2006).

Method

Recruitment and Screening

This study utilized baseline data from a crossover mechanistic trial examining the effects of hormone stabilization on daily SI severity (for details, see ClinicalTrials.Gov Identifier: NCT03720847). Participants were recruited via advertisements on social media and flyers stating, “Seeking participants for a study on the Biology of Depression, Stress, and Suicidal Thoughts,” which routed individuals to an initial online eligibility survey. These advertisements did not refer to women, female sex, hormones, or the menstrual cycle; social media ads were shown to female 18–45 years living within 30 miles of the university. Those who passed the online screen were screened via phone. During the recruitment process, the study’s later experimental trial was not framed as a treatment; instead, it was described as “a hormone experiment to help scientists better understand whether specific hormone changes might impact suicidal thoughts in some people.”

At a 4-hr enrollment visit in the laboratory, the participants completed demographic and baseline questionnaires, the Structured Clinical Interview for DSM-5 (SCID-5; First et al., 2016) and the Columbia Suicide Severity Rating Scale (C-SSRS; Posner et al., 2011), reviewed the purpose of the larger study, and received instructions for completing surveys. Following the enrollment, participants completed 1–2 months of daily symptom ratings before moving into the experimental portion of the study; these baseline ratings are used in the present study.

Participants were 38 female outpatients who reported past-month SI. Inclusion criteria were past-month SI, ongoing treatment by a mental health provider (at least once every 3 months), ages 18–45, and regular menstrual cycles (25–35 days). Exclusionary criteria were a history of manic episodes, psychosis, or current (past year) substance use disorder of moderate or greater severity, pregnancy, breastfeeding, or trying to get pregnant, medications affecting hormone levels or function (e.g., hormonal birth control), and history of serious medical illness. Most outpatients with suicidality take psychotropic medications; therefore, to increase feasibility and generalizability, stable medication use was not exclusionary. Several additional inclusion and exclusion criteria were applied to ensure safety in the

hormone administration phase of the clinical trial. Participants were required to have no known genetic risk for thrombotic events (e.g., Factor V Leiden) and were required to be in the normal weight range (BMI = 18–29 kg/m^2) as responses to doses of hormones vary by BMI and risk for thromboembolic events with hormone use increases at higher weight ranges. Participants were also excluded if they reported a suicide attempt in the past year, to reduce the possibility of imminent risk during the clinical trial, given that the effects of hormone administration on acute suicide risk were unknown at the start of this trial.

Measures

Each evening, participants received a text message from the study team with a survey link, which inquired about menstrual bleeding ("Did you experience menstrual bleeding today?," "Was today the first day of your menstrual period?"), as well as symptom items.

Daily SI Severity—Daily SI severity was measured using seven items primarily adapted from the Adult Suicidal Ideation Questionnaire (ASIQ; Reynolds, 1991) to capture daily experiences of both passive and active SI ("I wished I were dead," "I thought that life was not worth living," "I thought others would be better off if I were dead," "I thought about killing myself," "I thought about killing myself, but would not do it," "I thought that if things did not get better, I would kill myself," and "I wished I could go to sleep and not wake up"). Participants were asked to rate each item's highest level across the prior 24 hr on the same rating scale used in the Daily Record of Severity of Problems (DRSP) from 1 = *not at all* to 5 = *extremely*. A daily average of all seven items was utilized for analysis. Utilizing equations from Shrout and Lane (2012), we observed excellent between-person reliability (RKF =.99) and adequate reliability of within-person change (R_C = .85) for this daily composite scale.

Daily Affective Symptoms—The DRSP (Endicott et al., 2006) is a 24-item measure used for diagnosis and study of reproductive mood disorders that measures all 11 symptom domains from DSM-5 PMDD. Participants are instructed to indicate the degree to which symptoms are experienced each day from 1 to 6 (1 = *not at all*, 2 = *minimal*, 3 = *mild*, 4 = *moderate*, 5 = *severe*, 6 = *extreme*). For this study, the first eight items were included. These items represent the required "core affective symptoms" of the disorder and are the most commonly reported cyclical affective symptoms among females with cyclical exacerbation of an underlying chronic disorder or PMDD (Pearlstein et al., 2005). These items include: (a) felt depressed, sad, "down," or "blue," (b) felt hopeless, (c) felt worthless or guilty, (d) felt anxious, tense, "keyed up," or "on edge," (e) had mood swings (e.g., suddenly felt sad or tearful), (f) was more sensitive to rejection or my feelings were easily hurt, (g) felt angry, irritable, and (h) had conflicts or problems with people.

In descriptive analyses, we utilized the RMCORR package in R to estimate repeated measures correlations among the nine daily outcomes; we observed conventionally moderate-to-strong within-person correlations among daily symptoms (r's ranging from .23 to .74; see Figure S1 in the online supplemental materials). Therefore, shared daily variance in negative affect may drive each of the effects presented in this article to some extent. However, we have chosen to present them as unique outcomes in the present study given

that (a) prior work in related samples (e.g., BPD; Eisenlohr-Moul et al., 2015, 2018) has suggested potentially distinct patterns of individual symptoms across the cycle, which we wished to describe here, and (b) the limited size of the sample precludes more complex models that parse shared and unique outcome variance.

Menstrual Cycle Phase Coding

Determination of each of the four cycle phases (periovulatory, midluteal, perimenstrual, and midfollicular) was based on forward and backward count (Edler et al., 2007; Schmalenberger et al., 2021). First, the periovulatory phase was identified as Days −15 to −12, counting backward from the last day before the subsequent menses (i.e., from Day −1, where menstrual onset is Day 1 and there is no Day 0). Next, the perimenstrual phase was identified with both backward and forward count as Days −3 to +2, where, again, Day +1 is menses onset, and there is no Day 0. The midluteal and midfollicular phases were subsequently determined with the midluteal phase defined as all days between the periovulatory and next perimenstrual phase (actual range = −4 to −11) and the midfollicular phase defined as all days between the perimenstrual and next periovulatory phase (actual range = 3–10).

Analytic Steps

Diagnostic Analyses—First, we utilized the Carolina Premenstrual Assessment Scoring System (C-PASS; Eisenlohr-Moul, Girdler, et al., 2016) to determine whether any item in any cycle met criteria for the DSM-5 PMDD symptom pattern (luteal phase confinement of symptoms). Next, we used a modified perimenstrual exacerbation version of the C-PASS that we have employed in prior work (Eisenlohr-Moul et al., 2018). This perimenstrual exacerbation version eliminates the requirement of absolute follicular symptom clearance (the requirement that symptoms in the postmenstrual week are low or absent, with maximum rating of 3 = *mild*) and uses the cycle phases used in the present article (as in Eisenlohr-Moul et al., 2018). to determine whether any of the core emotional symptoms (DRSP1–8) in any cycle met criteria for perimenstrual exacerbation. In this adapted use of the C-PASS, to meet criteria for perimenstrual exacerbation, symptoms must be elevated by at least 30% in the premenstrual week relative to the postmenstrual week, as in PMDD, but do not need to demonstrate “absolute clearance,” that is, they do not need to decline to a “mild” level in the week following menses. As a result, an individual may meet criteria for perimenstrual exacerbation if they experience high levels of symptoms throughout their cycle without full relief in the follicular phase, as long as these symptoms worsen by at least 30% in the premenstrual phase.

Testing Hypotheses 1–2—Multilevel regression models (daily observations nested within participants) were used to examine pairwise within-person phase contrasts comparing daily outcomes (untransformed) across menstrual cycle phases. Three different models for each outcome with rotating reference phase allowed for all six pairwise cycle phase contrasts, as follows, with the six unique contrasts indicated by superscript: in Model 1, perimenstrual (reference) versus midfollicular[1], perimenstrual versus midluteal[2], and perimenstrual versus periovulatory[3]; in Model 2, midluteal (reference) versus perimenstrual, midluteal versus midfollicular[4], and midluteal versus periovulatory[5]; in

Model 3, midfollicular (reference) versus perimenstrual, midfollicular versus midluteal, and midfollicular versus periovulatory[6]. In SAS PROC MIXED, a random intercept was specified to account for between-person differences in overall symptom levels. An autoregressive (day −1) error term was included to account for the autocorrelation of outcomes day-to-day within a given participant. Random effects of cycle phase were examined but not included as they did not improve model fit (and did not alter the significance of contrasts when included); therefore, the impact of the menstrual cycle on symptoms could be described as roughly uniform across participants in this sample. For each model reported in this manuscript, normality of Level-1 residuals was confirmed. Additional robustness-check models also controlled for person-centered physical symptoms; we observed no substantive model changes when including this covariate, suggesting cyclical exacerbation in the perimenstrual phase was not an epiphenomenon of perimenstrual physical pain (e.g., dysmenorrhea). Participants were instructed to hold medication use stable during the study, resulting in few within-person changes in medication use; therefore, medication use was not covaried. In sum, no covariates were included in the final models; each model included three cycle phase contrasts as predictors of a single symptom. For graphical depictions only, we utilized 5-day rolling averages of person-standardized outcomes (Schmalenberger et al., 2021). All available data were used in the multilevel models, and no data were imputed. All complete daily observations (i.e., observations with a nonmissing value on each variable in the model) were included.

Each participant provided up to 73 daily surveys (average lower-level *N* was 42; min = 28; max = 152). Participants began providing daily ratings immediately following the enrollment visit, and provided daily ratings until they had completed one full C-PASS cycle (including Day −7 to +10). Due to the fact that participants started the study at varying times in their cycles, the length of time it took for participants to complete a full consecutive cycle of daily ratings varied, and the total number of daily surveys per participant varied accordingly. To estimate power for phase contrasts, we consulted simulation output provided in Arend and Schäfer (2019; *Table 5: Minimum Detectible Effect Sizes for L1 Direct Effects*). Given a Level-2 sample size of roughly 40, a Level-1 sample size of roughly 30, and the conventionally small-to-medium intraclass correlations (ICCs) observed for our outcomes (see Table 2), we determined that the minimum detectible L1 direct effect size was around $r = .16$, a conventionally small effect size.

Transparency and Openness

Poweranalyses for determining sample size, the handling of missing data, all data exclusions, and all manipulations are reported. Materials and analysis code for this study are available by emailing the corresponding author. Data were analyzed using SAS OnDemand for Academics and R. The design and analyses of this secondary data analysis were not preregistered.

[1]Given the focus of this work on ovarian function and mental health, we use the term *female* to refer to chromosomal sex, and more specifically, individuals with normally functioning ovaries. Of note, we are also referring to those cycling individuals who do not identify as “female” with respect to gender.

Results

Descriptive Analyses

Descriptives for between-person variables are outlined in Table 1. Thirty-eight participants completed daily ratings in the baseline phase. The sample was relatively diverse concerning income, age, and psychiatric diagnoses. All participants met current criteria for a mood, anxiety, or stress-related disorder. A large proportion of the sample reported a history of abuse, which has been associated with hormone-dependent affective fluctuations in prior studies (Eisenlohr-Moul, Girdler, et al., 2016). Nearly all participants reported a lifetime history of suicidal planning or behavior, and the majority reported a history of nonsuicidal self-injury. All participants were receiving either pharmacologic therapy or talk therapy during the study.

Descriptives for within-person variables are presented in Table 2, and within-person correlations among daily measures are reported in Figure S1 in the online supplemental materials. In total, 89% of possible daily surveys were completed, for a total of 1,524 daily surveys. ICCs ranged from .29 (suicidal ideation severity) to .46 (hopelessness). Intraclass correlations reflect the percentage of variance in a repeated outcome that is attributable to trait-like (between-person) stable individual differences. Higher intraclass correlations indicate more stability in a repeated measure within an individual, while lower intraclass correlations reflect greater within-person variability. Thus, our outcomes contained both between- and within-person variance, with the majority of the variance at the within-person level.

Plotting Symptoms Across the Cycle

First, we plotted mean person-standardized variables for daily ASIQ suicidal ideation across menstrual cycle phase (Figure 1) and across menstrual cycle day (Figure 2). Person-standardized DRSP affective variables across cycle day are presented in Figure 3. (*Note*: Worthlessness/Guilt and Interpersonal Conflict are not pictured but show highly similar patterns to Depressed Mood and Anger/Irritability, respectively.) In all figures, lines connecting two phases indicate a significant phase difference in that outcome.

Using the C-PASS to Diagnose PMDD and Perimenstrual Exacerbation

We used the C-PASS to determine whether any of our participants met criteria for PMDD on any core emotional (DRSP1–8) symptom in any cycle. No participant met C-PASS PMDD pattern criteria for any core emotional symptom (DRSP1–8; Eisenlohr-Moul et al., 2018). When the C-PASS perimenstrual exacerbation criteria were applied—that is, when *absolute clearance* was no longer required, six participants (15.7%) met C-PASS criteria on at least one core emotional symptom in one cycle.

Since studies show considerable interindividual differences in the timing of premenstrual emotional symptoms (Eisenlohr-Moul et al., 2019), we further examined whether a higher number might meet C-PASS perimenstrual exacerbation criteria when more flexible definitions of high- and low-risk cycle phases were utilized. When the typical C-PASS premenstrual (−7 to −1) symptom mean was replaced with the maximum mean of the

high-risk (midluteal, premenstrual, and perimenstrual) phases, and the typical C-PASS postmenstrual (4–10) symptom mean was replaced with the minimum mean of the low-risk (postmenstrual, midfollicular, and periovulatory) phases, 23 participants (60.53%) met criteria for perimenstrual exacerbation on at least one symptom in one cycle. Therefore, there was evidence at the individual level for cyclicity in the sample, although the timing of these symptoms did not always fit neatly into typical DSM-5 PMDD diagnostic windows (i.e., week before menses and week after menses). These percentages can be compared with the ~5.5% prevalence of PMDD in the general population (Gehlert et al., 2009) and the ~60% prevalence of perimenstrual exacerbation in females with depressive disorders (Hartlage et al., 2004).

Testing Hypothesis 1: Perimenstrual Exacerbation of SI and Affective Symptoms (vs. All Other Phases)

Results of phase contrast models were generally consistent with predictions that the perimenstrual phase would be associated with higher SI than all other cycle phases (see Table 3). Severity of SI was greater in the perimenstrual phase relative to the midluteal and periovulatory phases, although there was no significant difference between the perimenstrual and follicular phases. None of the other phases significantly differed from one another, suggesting an acute exacerbation in the perimenstrual phase only. All other symptoms were greater in the perimenstrual phase than in the *periovulatory* phase, and these contrasts were consistently the largest. Most symptoms were also significantly greater in the perimenstrual phase than the *midluteal* phase, although feelings of worthlessness/guilt did not significantly differ from midluteal to perimenstrual phase, due to rising levels of symptoms through the midluteal phase. Although symptoms of anxiety, mood swings, rejection sensitivity, anger/irritability, and interpersonal conflict were greater in the perimenstrual phase than the *midfollicular* phase, this was not the case for SI severity nor any depressive symptom (depressed mood, hopelessness, and worthlessness/guilt) since these symptoms remained somewhat elevated in the midfollicular phase. Finally, anger/irritability was higher in the midluteal phase than in the midfollicular phase. In Table 2, we present Level-1 pseudo-R^2 for each outcome (Raudenbush & Bryk, 2002), representing the proportion of within-person variance accounted for by the inclusion of cycle predictors. Of note, the cycle accounted for 25% (pseudo-R^2 = .25) of the within-person variance in SI.

Testing Hypothesis 2: Midluteal and Midfollicular Elevation of SI and Affective Symptoms (vs. Periovulatory Phase)

We predicted that daily SI severity, as well as severity of each affective symptom, would be higher in the midluteal and midfollicular phase than in the periovulatory phase. This hypothesis was not fully supported; none of the symptoms were significantly different between the periovulatory and midluteal phases, and most symptoms did not differ significantly between the periovulatory and midfollicular phases, with the exception of depressive symptoms (depression, hopelessness, and worthlessness/guilt) which were significantly higher in the midfollicular phase than in the periovulatory phase, partially supporting the hypothesis that symptom exacerbation would continue into the midfollicular phase (see Table 3).

Discussion

This study is the first to describe cyclical exacerbation of SI and related affective symptoms in naturally cycling participants with ongoing SI using prospective daily ratings. These findings build on a substantial cross-sectional body of research indicating a correlation between increases in hospitalization for SI and suicide attempts in the weeks before and after menstrual onset (Owens & Eisenlohr-Moul, 2018). Daily ratings indicated perimenstrual exacerbation of SI, and various related hormone-sensitive symptoms (depressed affect, hopelessness, anxiety, mood swings, rejection sensitivity, anger/irritability, feelings of worthlessness/guilt, and interpersonal conflict). All symptoms peaked in the perimenstrual phase and reached a nadir in the periovulatory phase, which indicates these results may also partially reflect a periovulatory improvement (as opposed to or in addition to a perimenstrual worsening). Symptoms of anger/irritability rose in the midluteal phase, peaked in the perimenstrual phase, and declined across the midfollicular phase. Depressive symptoms were exacerbated perimenstrually and in the midfollicular phase, before showing improvements in the periovulatory and midluteal phases. These patterns of change in affective and behavioral symptoms may play a role in the increased SI severity—and ultimately risk of attempt—in the weeks before and after menses onset (Owens & Eisenlohr-Moul, 2018).

Our observation that the majority of the variance in SI (71%) lies at the within-person level is particularly noteworthy, given the recent call to identify within-person predictors of SI, which may be mediators of acute suicide risk with clinical utility. Further, the ability of the cycle to account for 25% of this within-person variance underscores that the menstrual cycle is an important potential risk factor deserving of additional study in the detection and prevention of acute suicide risk. Although replication in larger studies will be required to build a clearer picture of these risk pathways, we believe that such studies should be prioritized, particularly given the historical lack of progress in the identification of imminent risk factors. Currently, the menstrual cycle may represent the only candidate recurrent risk factor under study that follows a predictable temporal course.

Overlap With Patterns of Cyclical Symptom Change in Other Disorders

Although none of the patients in this study met prospective criteria for PMDD (due to elevated baseline symptom levels that did not entirely remit in the midfollicular and periovulatory phases), the cyclical patterns of affective symptom fluctuation in this sample can also be linked to patterns of symptom expression in PMDD, which is characterized by the occurrence of clinically significant affective symptoms occurring only in the luteal phase (Pearlstein et al., 2005). These shared patterns of symptom change (though at different mean levels) may indicate possible shared etiology with PMDD.

Of note, the observed pattern of cyclical exacerbation in the present sample is also consistent with a large longitudinal epidemiological study finding that 60% of female with a depressive disorder show a cyclical exacerbation in the perimenstrual phase of at least one depressive symptom (Hartlage et al., 2004). In fact, in this transdiagnostic sample of naturally cycling patients, 61% of participants were classified as experiencing cyclical exacerbation of a chronic affective disorder using daily ratings. In previous studies,

we demonstrated individuals with BPD are at elevated risk of cyclical exacerbation of their symptoms (Eisenlohr-Moul et al., 2015, 2018). In that sample, symptoms such as anxiety, anger/irritability, and interpersonal conflict were exacerbated in the midluteal phase, peaked in the perimenstrual phase, and improved around ovulation. In contrast, depressive symptoms (depression, hopelessness, and shame) exhibited a delayed/extended pattern of exacerbation that arose primarily in the premenstrual week and extended into the follicular phase (Eisenlohr-Moul et al., 2018). In the present study, we replicated the prolonged exacerbation of depressive symptoms, and we also observed increased anger/irritability in the midluteal phase relative to the midfollicular phase. However, we did not replicate the finding of increased interpersonal conflict or anxiety in the midluteal phase, suggesting that this pattern could be unique to samples with PMDD or perimenstrual exacerbation of borderline personality disorder, which may be characterized by more severe interpersonal or high-arousal symptoms than the current sample, which was recruited only for SI.

Although individuals with BPD experience high rates of SI and behavior, only one-third of our sample met BPD criteria, suggesting that the perimenstrual phase (and, to a lesser degree, the midluteal, and midfollicular) is a recurring *transdiagnostic* window of acute elevation in suicide risk. The shared patterns of cycle-linked symptom changes in recently suicidal females and females with BPD may be due in part to shared etiological factors. Suicidality, BPD, and hormone sensitivity share a set of common risk factors, including early life adversity, proximal experiences of stress, and impulsivity (Eisenlohr-Moul, Girdler, et al., 2016; Namavar Jahromi et al., 2011; Roberts et al., 2018). Further research should examine these potential shared risk mechanisms to elucidate whether long-term suicide risk factors such as early life adversity increase suicide risk in part via sensitivity to normal fluctuations in hormones.

Possible Underlying Physiological Mechanisms of Cyclical SI Changes

The present study relies on longitudinal correlations and does not allow for clear mechanistic inferences concerning etiology. However, research on the underlying pathophysiology of cyclical mood changes in other disorders provides clues concerning potential mechanisms of these cyclical changes in suicide risk.

Although the DSM-5 diagnosis of PMDD explicitly excludes those with premenstrual exacerbation of ongoing affective disorders, the similar patterns of cyclical symptom change observed in this sample of patients with ongoing affective disorders suggests that the pathophysiology of PMDD may indeed overlap with those of perimenstrual exacerbation in many cases. Studies indicate that those with PMDD do not have abnormal hormone levels or patterns across the cycle that differentiate them from healthy individuals; instead, they demonstrate an abnormal sensitivity to the normal hormone *changes* that occur across the cycle (as induced in experimental studies; e.g., Schmidt et al., 2017). PMDD symptoms can be eliminated by both (a) experimental induction of menopause (low, stable ovarian hormones) with gonadotropin-releasing hormone (GnRH) analogs and (b) GnRH analogs in combination with experimental stable add-back of E2 and P4 (high, stable ovarian hormones; Schmidt et al., 2017). These and other findings indicate that females with PMDD do not tolerate normal cyclical *changes* in E2 or P4, which may be mediated by a sensitivity

to the neurosteroid metabolites of progesterone (e.g., allopregnanolone; Martinez et al., 2016) and/or luteal changes in serotonergic function (Menkes et al., 1994; Rapkin et al., 1987; Roca et al., 2002). The present results suggest that similar mechanisms may be relevant in the cyclical exacerbation of SI. For example, as SI peaked in the perimenstrual phase, it is possible that the cyclical exacerbation of SI is similarly triggered by either a delayed effect of rising levels of E2 and P4 in the early luteal phase (Schmidt et al., 1991), or a proximal effect of E2 or P4 withdrawal in the perimenstrual phase. In sum, given the overlap in patterns of symptom expression between PMDD and some cyclically exacerbated symptoms, there may be a shared pathophysiology for cyclical exacerbation of these symptoms and PMDD.

However, there is reason for caution when attempting to extrapolate mechanisms from PMDD to cyclical exacerbation of other disorders. First, emerging research supports the possibility of diverse symptom trajectories across the cycle among those with PMDD, suggesting that the pathophysiology of PMDD itself may be heterogeneous across individuals and not yet fully understood (Eisenlohr-Moul et al., 2019). In addition, there appear to be some differences in the most commonly observed symptom patterns across disorders with documented cyclical exacerbation. For example, unlike most individuals with PMDD, some individuals with chronic affective disorders appear to display continued exacerbation of depressive symptoms into the early follicular phase, much like the current sample (Eisenlohr-Moul et al., 2018). It is possible that these individuals have a more prolonged sensitivity to periovulatory hormone flux (Schmidt et al., 1991), or an additional or alternative sensitivity to the falling (or low) levels of ovarian hormones that characterize the perimenstrual and follicular phases. The current data do not allow us to make this differentiation. In addition, in contrast to PMDD, research on the pathophysiology of cyclical worsening (e.g., of depressive disorders or BPD) is almost nonexistent, and most data come from subset analyses in PMDD clinical trials. Though this should be treated as preliminary, several trials have found that many effective ovulation–suppression treatments for PMDD fail to beat placebo among females with cyclical exacerbation of depression, suggesting a possible alternative or additional pathophysiology of cyclical changes in depression that has yet to be discovered (e.g., perimenstrual E2 or P4 withdrawal). This includes combined drospirenone-containing oral contraceptives (Peters et al., 2017), Sepranolone (a synthetic form of isoallopregnanolone, which antagonizes effects of allopregnanolone at the gamma-aminobutyric acid-A receptor; Bixo et al., 2017), and GnRH analogs (Freeman et al., 1993, 1997). More work is needed to determine whether there might be unique pathophysiology of cyclical exacerbation of chronic symptoms, particularly with respect to depressive or lower-arousal symptoms, and whether these symptoms may require alternative treatments.

Possible Underlying Psychological Mechanisms of Cyclical SI Changes

Almost no research to date has examined psychological and behavioral mechanisms of cyclical symptom exacerbation. Although this study is underpowered to explore mediation effects, coincident fluctuations in SI and affect suggest promising future directions for examining short-term psychological influences on the cyclical worsening in SI. Limited prior research suggests that divergent fluctuations in symptoms may be driven by cognitive

and behavioral responses to emotion. In particular, emotion-related impulsivity predicts greater severity of premenstrual interpersonal symptoms like anger, while rumination may delay the follicular remission of depressive symptoms (Dawson et al., 2018).

Limitations and Future Directions

The primary limitation of the present study was its observational design, which precludes causal interpretations with respect to specific hormonal antecedents of suicidality. Since the impact of hormones on psychological and behavioral processes can be rapid, delayed, or both, experimental methods will be necessary to clarify specific endocrinological antecedents of acute suicide risk across the cycle. From a behavioral standpoint, it is critical that the field also develop a clearer picture of the specific behavioral mechanisms that may sustain these hormonal effects on suicidality and examine fluctuations in symptoms that may facilitate the transition from suicidal thoughts to behaviors. For example, inhibitory control and impulsivity have been shown to fluctuate across the cycle in some samples (Owens & Eisenlohr-Moul, 2018) and higher trait-level impulsivity has been associated with greater changes in affective and behavioral symptoms across the cycle (Roberts et al., 2018). Future studies should examine how inhibitory control and impulsive behavior might fluctuate across the cycle for individuals with SI, and how this might translate to increased risk for suicidal behaviors. This information can then be used to develop or strategically apply evidence-based strategies for suicide prevention, such as dialectical behavioral therapy (Linehan, 1993).

In addition, while this study is novel in its description of an understudied predictor of suicidal thoughts and behaviors, the generalizability of these results is limited in several ways. First, individuals with recent suicide attempts were excluded from this study. As a result, the present data may not reflect the full range of severity of suicidal thoughts; with the inclusion of these individuals, these models may have had greater power to detect cyclical effects. In addition, approximately 45% of the samples were taking selective serotonin reuptake inhibitors (SSRIs) during data collection (see Table 1). As SSRIs have been shown to reduce symptoms for some hormone-sensitive individuals (Halbreich, 2008), this sample likely had reduced cyclical symptoms compared to what would be expected in an unmedicated sample. However, given that most outpatients with suicidality take psychotropic medications, stable medication use was not exclusionary to increase the generalizability of these findings. In addition, this sample was primarily composed of white participants with some level of college education. We are not aware of any prospective research exploring whether hormone sensitivity differs by race, ethnicity, or education; this remains an important area of exploration for future research. Future research would also benefit from longer follow-up periods (e.g., daily diary data across several months to years) to explore whether these effects might change within individuals over time (e.g., with development).

Finally, although this study advances the field by presenting the first prospective data evaluating SI changes across the menstrual cycle, the remaining exploratory descriptive analyses of the eight emotional symptoms should be interpreted with caution given the increased risk of Type I error in such analyses. In addition, given the moderate-to-strong

within-person correlations among daily symptoms, shared daily variance in negative affect may drive each of the effects presented in this article to some extent. This study was also limited by a small sample size, which prevented the use of more complex models (e.g., multilevel structural equation modeling, mediation analyses). As a result, the tests presented here do not allow us to draw conclusions about the unique effects of the cycle on specific outcomes, or whether changes in emotional symptoms might underlie changes in suicidality. These questions should be evaluated in a larger sample with the power to evaluate mediation in a multilevel context.

Conclusions

Despite decades of research, short-term fluctuations in SI and behavior remain poorly understood. This study is the first to demonstrate menstrual cycle fluctuations in SI and affective suicide risk factors in a clinical sample using prospective daily assessments. SI severity, along with related symptoms, peaked in the perimenstrual phase and showed a nadir in the periovulatory phase. These patterns suggest possible overlap in pathophysiology with PMDD or cyclical exacerbation of other disorders (e.g., depression or BPD), but experimental studies are essential to elucidate specific mechanisms.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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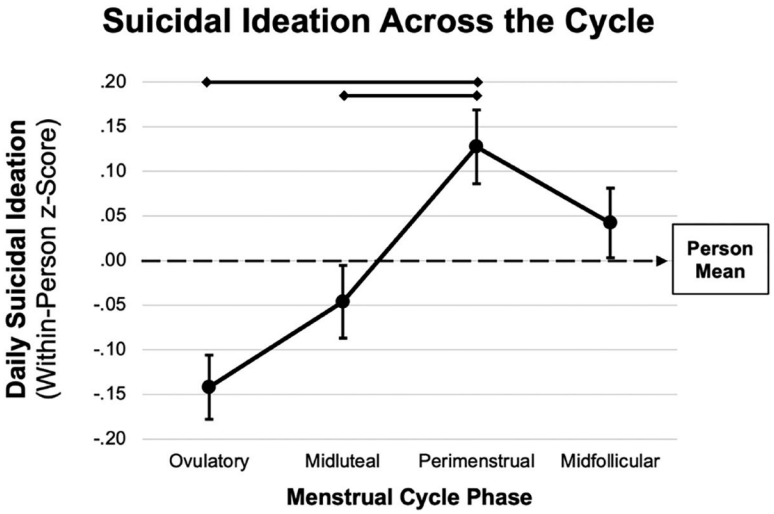

Figure 1.

Cyclical Fluctuations in Suicidal Ideation Severity Across Menstrual Cycle Phase Among 38 Female Recruited for Past-Month Suicidal Ideation

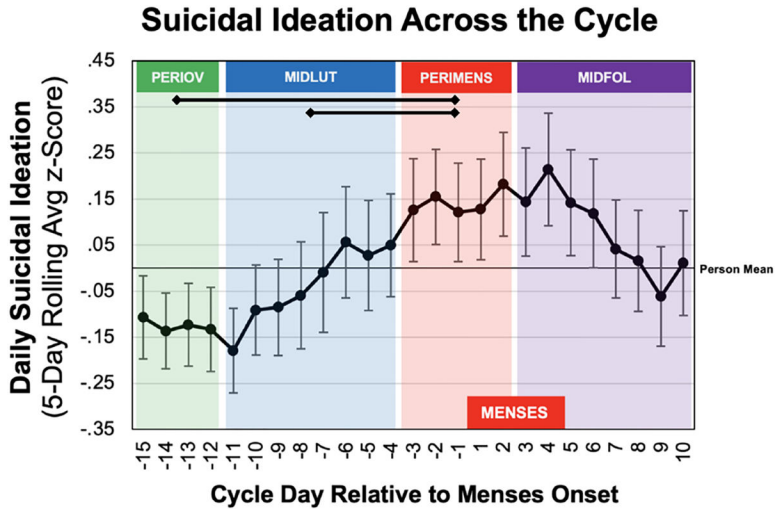

Figure 2.

Cyclical Fluctuations in Suicidal Ideation Severity Across Menstrual Cycle Day Among 38 Female Recruited for Past-Month Suicidal Ideation

Note. Day 1 represents the onset of menses. See the online article for the color version of the figure.

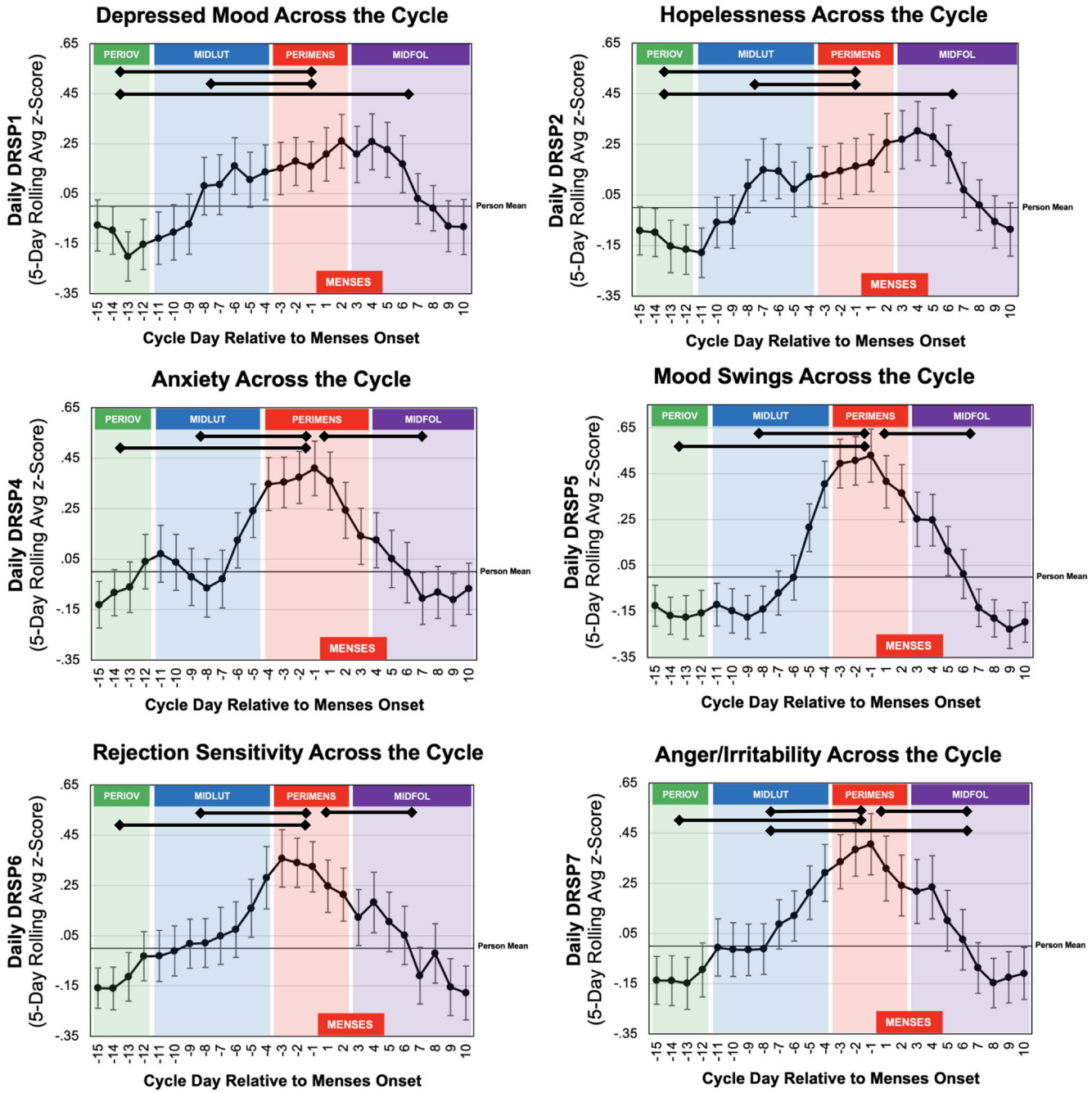

Figure 3.

Cyclical Fluctuations in DRSP Core Affective Symptoms Across the Menstrual Cycle Among 38 Female Recruited for Past-Month Suicidal Ideation

Note. DRSP = Daily Record of Severity of Problems. See the online article for the color version of the figure.

Table 1

*Demographics (*N = *38)*

Variable	Mean (*SD*) or *n* (%)	Range
Age	28.29 (6.92)	19–42
Gender		
Cisgender woman	35 (92.1%)	
Nonbinary or gender fluid	3 (7.9%)	
Race		
African American	1 (2.6%)	
Asian	1 (2.6%)	
More than one race	3 (7.9%)	
White	32 (84.2%)	
Ethnicity (Hispanic)	1 (2.6%)	
Education level		
Some high school	1 (2.6%)	
Graduated from high school	1 (2.6%)	
Some college	9 (23.7%)	
Graduated from 4-year college	17 (44.7%)	
Postgraduate work at a university	10 (26.3%)	
Yearly household income		
Less than $20,000	13 (34.2%)	
$20,000–$29,999	4 (10.5%)	
$30,000–$39,999	3 (7.9%)	
$40,000–$49,999	5 (13.2%)	
$50,000–$79,999	6 (15.8%)	
$80,000–$99,999	2 (5.3%)	
$100,000 or above	5 (13.2%)	
BMI at recruitment	25.96 (6.08)	
Partnership status		
Married	11 (29%)	
Divorced	2 (5.3%)	
Never married	25 (65.7%)	
Reproductive characteristics		
Length of baseline cycle (days)	28.75 (1.03)	
Age at menarche in years	12.59 (2.06)	8.5–18.0
History of known pregnancy	21 (31.6%)	
Parity	6 (16%)	0–3 children
Treatment characteristics		
Current psychotherapy	13 (34.2%)	
Cognitive or behavioral therapy	4 (10.5%)	
Current pharmacotherapy	25 (65.7%)	
Selective serotonin reuptake inhibitor	17 (44.7%)	

Variable	Mean (*SD*) or *n* (%)	Range
Bupropion	6 (15.8%)	
Benzodiazepine (as needed)	6 (15.8%)	
Serotonin and norepinephrine reuptake inhibitor	4 (10.5%)	
Methylphenidate	2 (5.2%)	
Aripiprazole	2 (5.2%)	
Buspirone	2 (5.2%)	
Lamotrigine	1 (2.6%	
Eszopiclone	1 (2.6%)	
Current diagnoses		
Borderline personality disorder	13 (34.2%)	
Avoidant personality disorder	7 (18.4%)	
Obsessive-compulsive personality disorder	3 (7.9%)	
Current depressive episode	29 (76.3%)	
Major depressive disorder	25 (65.8%)	
Persistent depressive disorder	25 (65.8%)	
Adult attention-deficit/hyperactivity disorder	7 (18.4%)	
Generalized anxiety disorder	21 (55.3%)	
Social anxiety disorder	19 (50%)	
Panic disorder	4 (10.5%)	
Agoraphobia	5 (13.2%)	
Specific phobia	11 (28.9%)	
Obsessive-compulsive disorder	5 (13.2%)	
Anorexia nervosa	1 (2.6%)	
Bulimia nervosa	2 (5.3%)	
Binge eating disorder	1 (2.6%)	
Posttraumatic stress disorder	12 (31.6%)	
Reproductive mood disorder screening		
History of postpartum depression (EPDS ≥ 13; first 4 weeks following birth)	4 of 6 parous (66%)	
C-PASS premenstrual dysphoric disorder pattern for any core emotional symptom (DRSP1–8)	0 (0%)	
Suicidal behavior history		
Number of individuals with past suicidal planning	36 (94.7%)	
Number of individuals with past suicide attempts	25 (65.8%)	
Number of individuals with past nonsuicidal self-injury	26 (68.4%)	
Average number of attempts	1.45 (1.65)	0–7
Average number of interrupted attempts	13 (0.34)	0–1
Average number of aborted attempts	66 (1.02)	0–4
Early adverse experiences		
Lifetime physical abuse	7 (18.4%)	
Lifetime sexual abuse	23 (60.5%)	

Note. BMI = body mass index; C-PASS = Carolina Premenstrual Assessment Scoring System; DRSP = Daily Record of Severity of Problems; EPDS = Edinburgh Postnatal Depression Scale.

Table 2

Descriptive Statistics for Within-Person Variables

Within-person variable	Null model intercept (*SE*)	% Variance between (ICC × 100)	% Variance within ([1 − ICC] × 100)	% Within-person variance explained by cycle (L1 pseudo-R^2)
ASIQ suicidal ideation	1.50 (0.06)	29	71	25
DRSP depressed, down, blue	2.80 (0.12)	37	63	27
DRSP hopelessness	2.61 (0.15)	46	54	22
DRSP worthless, guilty	2.63 (0.15)	45	55	29
DRSP anxiety	2.97 (0.14)	39	61	17
DRSP mood swings	1.90 (0.10)	34	66	25
DRSP rejection sensitivity	2.17 (0.12)	36	64	30
DRSP anger/irritability	2.22 (0.09)	23	77	10
DRSP interpersonal conflict	1.74 (0.09)	27	73	16

Note. The intercept and standard error in a multilevel model with no predictors (i.e., “null model”) are analogous to the mean and standard deviation, but are more appropriate due to correction for within-person clustering. The Level-1 pseudo-R^2 values reflect the percent of the total within-person variance in each daily variable accounted for by the menstrual cycle. ICC = intraclass correlation; ASIQ = Adult Suicidal Ideation Questionnaire (mean of seven selected items); DRSP = Daily Record of Severity of Problems.

Table 3

Results of Cycle Phase Contrasts for Suicidal Ideation and Affective Symptom Severity

	Within-person phase contrasts					
	Perimenstrual reference			Midluteal reference		Midfollicular reference
Outcome	vs. Midfollicular	vs. Midluteal	vs. Periovulatory	vs. Midfollicular	vs. Periovulatory	vs. Periovulatory
ASIQ suicidal ideation	−.04 (.03)[−.10 to .01]	−.07 * (.03)[−.12 to −.01]	−.07 * (.03)[−.12 to −.01]	.02 (.03)[−.03 to .07]	−.01 (.03)[−.06 to .04]	−.03 (.03)[−.08 to.02]
DRSP depressed, down, blue	−.10 (.06)[−.21 to .01]	−.14 ** (.06)[−.26 to −.04]	−.23 *** (.06)[−.35 to −.11]	.05 (.05)[−.06 to .15]	−.08 (.06)[−.19 to .03]	−.13 * (.05)[−.24 to −.01]
DRSP hopelessness	−.06 (.06)[−.17 to .05]	−.13 * (.06)[−.25 to −.02]	−.20 ** (.06)[−.32 to −.08]	.07 (.06)[−.03 to .18]	−.07 (.06)[−.19 to .05]	−.14 * (.06)[−.26 to −.02]
DRSP worthless, guilty	−.05 (.06)[−.17 to .06]	−.11 (.06)[−.23 to .01]	−.22 *** (.06)[−.34 to −.09]	.06 (.06)[−.06 to .17]	−.10 (.06)[−.23 to .02]	−.16 ** (.06)[−.28 to −.04]
DRSP anxiety	−.33 *** (.06)[−.46 to −.21]	−.26 ** (.06)[−.38 to −.13]	−.39 *** (.07)[−.52 to −.25]	−.07 (.06)[−.19 to .05]	−.12 (.06)[−.26 to .01]	−.05 (.07)[−.18 to .08]
DRSP mood swings	−.33 *** (.05)[−.44 to −.23]	−.32 *** (.05)[−.43 to −.23]	−.37 *** (.06)[−.48 to −.26]	−.01 (.05)[−.11 to .09]	−.04 (.05)[−.15 to .07]	−.03 (.05)[−.14 to .07]
DRSP rejection sensitivity	−.24 *** (.06)[−.36 to −.13]	.21 ** (.06)[−.33 to −.09]	−.31 *** (.07)[−.43 to −.18]	−.04 (.06)[−.15 to .08]	−.10 (.06)[−.23 to .02]	−.07 (.06)[−.19 to .06]
DRSP anger/irritability	−.32 *** (.06)[−.43 to −.20]	−.19 ** (.06)[−.32 to −.08]	−.32 *** (.07)[−.44 to −.19]	−.13 * (.06)[−.24 to −.01]	−.12 (.07)[−.25 to .01]	.003 (.06)[−.12 to .12]
DRSP interpersonal conflict	−.15 ** (.05)[−.25 to −.04]	−.16 ** (.05)[−.26 to −.04]	−.22 *** (.06)[−.34 to −.11]	.01 (.05)[−.09 to .11]	−.06 (.06)[−.18 to .05]	−.07 (.06)[−.18 to .04]

Note. "Reference" means that phase was set as the reference category in the category coding used in multilevel regression models. ASIQ = Adult Suicidal Ideation Questionnaire (mean of seven selected items); DRSP = Daily Record of Severity of Problems.

* $p < .05$.

** $p < .01$.

*** $p < .001$.