Comparing Pain Sensitivity and the Nociceptive Flexion Reflex Threshold Across the Mid-follicular and Late-luteal Menstrual Phases in Healthy Women

Emily J. Bartley, MS and Jamie L. Rhudy, PhD

Objective: Understanding the relationship between the menstrual cycle and pain can contribute significantly to our knowledge of pain processing in women. Many early studies suggested that pain sensitivity was enhanced during the luteal phase of the menstrual cycle relative to the follicular phase; however, these studies were often limited by small sample sizes, lack of ovulation verification, focus on a single pain modality, inadequate assessment of menstrual cycle regularity, and low-powered statistical methods. The current study was designed to address these limitations and examine the difference in pain processing between the mid-follicular (days 5 to 8) and late-luteal (days 1 to 6 preceding menses) phases.

Methods: Forty-one healthy, regularly cycling women attended testing sessions that measured pain sensitivity from mechanical pain threshold, electrocutaneous pain threshold/tolerance, and ischemia pain threshold/tolerance, as well as McGill Pain Questionnaire sensory and affective ratings of electric and ischemic stimuli. Electrocutaneous stimulation was also used to assess nociceptive flexion reflex threshold, a physiological measure of spinal nociception.

Results: When analyses were limited to data collected only in the targeted menstrual phases (N = 30), results indicated no menstrual phase effect on any pain outcome (all P’s > 0.05), with the exception of lower electrocutaneous pain thresholds during the late-luteal phase. No outcomes differed by menstrual phase in the full sample (N = 41). This indicates nociceptive responding varies little between the mid-follicular and late-luteal phases.

Discussion: The present study suggests that experimental pain processing does not significantly differ between the mid-follicular and late-luteal phases of the menstrual cycle in healthy women. This implies hormonal variation across these 2 phases (ie, progesterone) has a minimal effect on subjective and physiological responses to pain.

Key Words: menstrual cycle, pain sensitivity, nociception, nociceptive flexion reflex


The relationship between the menstrual cycle and experimental pain has been a topic of much attention, in part fueled by interest in the influence of sex hormones on pain and sex differences in pain and by observations that clinical pain worsens during the late-luteal (premenstrual) phase in women with and without clinical pain disorders. Indeed, animal literature suggests that sex hormones alter nociceptive reactivity and response to analgesics. This given, the clinical importance of investigating menstrual cycle effects on nociceptive processing are likely to be manifold (eg, characterizing pain in women, informing therapeutic interventions for hormonally influenced pain conditions, identification of hormonal modulators of pain, and understanding sex differences in pain). A 1999 meta-analysis of experimental pain studies concluded that pain evoked by most stimuli was enhanced during the luteal phase, relative to the follicular phase. More recently, however, Sherman and LeResche have questioned whether clear conclusions can be drawn from these studies, noting several methodological limitations in the procedures used. For example, several studies failed to have women monitor multiple menstrual cycles to establish cycle regularity. Many studies also did not verify ovulation. Given that anovulation is common and changes the hormonal milieu, this could ultimately alter the association between menstrual phase and pain. Moreover, without clear identification of the time of ovulation, it is difficult to ensure that all participants are being tested at similar times during the menstrual cycle (eg, early-follicular, mid-follicular, ovulation, mid-luteal, and late-luteal). This can be critical given that sex hormones vary considerably both between and within follicular and luteal phases.

Furthermore, most studies have used small samples. Although recruiting large samples in menstrual cycle research is notably difficult, small samples may limit the generalizability of findings and cause low power and spurious results. Another issue that may contribute to heterogeneity in study findings is that many previous studies have assessed pain sensitivity from a single stimulus modality. Different stimulus modalities activate different receptor types and result in varying pain experiences; thus, responses to some stimuli may be more susceptible to menstrual effects than others. Of the studies published since Sherman and LeResche’s critical review, only 1 addressed the methodological limitations of previous studies. That study by Klatzkin et al found that experimental heat pain, cold pain, and ischemic pain did not differ across menstrual phases (early-follicular, late-follicular, and luteal) and that sex hormones (estradiol and progesterone) did not correlate with measures of pain sensitivity in either menstrual phase. Moreover, results from other human studies assessing the relationship between sex hormones and pain have been contradictory, most likely due to limitations in study methodologies.
The present study was designed to overcome many of the limitations noted by Sherman and LeResche through: (1) recruitment of a relatively large sample size; (2) verification of ovulation and timing of phases by luteinizing hormone (LH) surge assessment; (3) confirmation of menstrual phase regularity; and (4) assessment of pain sensitivity from multiple stimulus modalities. Given that clinical pain is often exacerbated during the late-luteal phase, we compared pain responsibility during this phase with a phase associated with low levels of female sex hormones (mid-follicular phase). Nociceptive responding was assessed from mechanical pain threshold, ischemia pain threshold/tolerance, electrocutaneous pain threshold/tolerance, and nociceptive flexion reflex threshold (NFR; a physiological correlate of spinal nociception). In addition, sensory and affective pain ratings of suprathreshold electric and ischemic stimuli were assessed.

To our knowledge, there have only been 5 studies that have assessed experimental pain sensitivity during the mid-follicular and late-luteal phases of the menstrual cycle, with results being mixed. Two studies found enhanced ischemic pain sensitivity during the late-luteal phase, whereas some found no phase differences in ischemia pain, thermal pain, cold pressor pain, or mechanical pressure pain. Unfortunately, none of these studies met all of the methodological recommendations of Sherman and LeResche. Therefore, it is unclear what differences in pain sensitivity would be noted between the mid-follicular and late-luteal phases.

MATERIALS AND METHODS

Participants

Participants were recruited from the surrounding community by means of radio/newspaper advertisement, flyers, and email distribution. In addition, a few participants were recruited from the University of Tulsa psychology subject pool. Participants were excluded for: <18 years of age; menopausal or postmenopausal; use of hormone preparations in the last 6 months; failure to regularly cycle; hysterectomy; pregnant or trying to get pregnant; pregnant or breastfeeding in the previous 6 months; body mass index > 35 (due to potential difficulties obtaining an NFR in individuals with high adiposity); history of cardiovascular, neuroendocrine, or neurological disorders; Raynaud’s disease; hypertension; history of chronic pain; current opioid, antidepressant, or anxiolytic medication use; or recent psychological trauma as defined by DSM-IV-TR. Fifty-three participants met initial inclusion criteria and agreed to participate; however, 10 women were later determined to not meet inclusion criteria (7 anovulatory, 1 irregular cycle, 1 using analgesic medication, and 1 using hormone preparations). Two women withdrew reporting the procedures were too painful. Hence, 41 women were included in the final analyses. Most were white non-Hispanic (71%), married (73%), and employed full-time (56%), with an average age of 31 years (SD = 8.86) and an average education of 15 years (SD = 1.17). All participants had regular menstrual cycles ranging from 21.67 to 37.77 days (M = 28.98, SD = 3.28). Average luteal phase length was 14.74 days (SD = 3.48) as calculated from the date of positive LH surge until 1 day preceding menses onset. Thirty-four women completed both experimental testing sessions, whereas 7 participants only completed 1 testing session (reported reasons: scheduling, health problems unrelated to menstrual cycle, procedures too painful). Of the 7 women who failed to complete both testing sessions, 3 completed the mid-follicular phase, whereas 4 completed the late-luteal phase. All participants provided full informed consent to participate and were provided an honorarium up to $185 for participation (or course credit if recruited from the University of Tulsa subject pool).

Menstrual Cycle Monitoring and Phase Determination

Participants completed a modified version of the Prospective Record of the Impact and Severity of Menstrual Symptoms (PRISM) for daily report of emotional and physical symptoms, basal body temperature (BBT), and LH test results. The PRISM calendar contains affective (eg, depressed), behavioral (eg, insomnia), and physical (eg, breast tenderness) symptoms that are rated daily for severity (0 = absent, 1 = mild, 2 = moderate, 3 = severe). Participants completed calendars daily for 3 consecutive menstrual cycles. To discourage retrospective reporting, participants were asked to mail in calendars on a weekly basis. Experimental pain assessments were scheduled within the mid-follicular and late-luteal phases of the participant’s menstrual cycle during cycles 2 and 3. The mid-follicular phase was defined as days 5 to 8 after menses onset. Of the 37 women who completed the mid-follicular testing session, 33 females (89%) were tested during days 5 to 8, with an average of 7.54 days after menses onset (SD = 1.17). The average testing day for the other 4 women was day 9.5 (range, 9 to 10), because their menses lasted longer than 8 days. The late-luteal phase was defined as days 1 to 6 preceding menses (or approximately 9 to 11 d after ovulation if luteal phase length was unable to be estimated from cycle 1 due to anovulation). The 9- to 11-d timeframe was based on evidence suggesting the mean luteal phase length for normal, menstruating women to be approximately 12.4 days (range, 9 to 15 d). Therefore, 9 to 11 days after ovulation should generally fall within days 1 to 6 preceding menses onset. Of the 38 participants who completed their late-luteal phase experimental session, 30 females (79%) were seen 1 to 6 days preceding the commencement of their subsequent cycle, with average timing occurring 4.84 days before menses (SD = 3.24). The average testing day for the other 8 women was 9.25 days preceding menses (range, 7 to 15), which was due to difficulties predicting the onset of menses from prior cycles and LH surges.

Verification of ovulation was conducted by BBT and LH surge (assessed from self-administered home urine QT tests), and this information was also used for scheduling of the late-luteal phase assessment. Participants were asked to date and retain each positive QT for confirmation of results by an experimenter.

Apparatus

A computer running LabVIEW software (National Instruments, Austin, TX) equipped with dual monitors and A/D board (National Instruments, PCI-6036E) controlled all stimuli, questionnaire presentation, and data acquisition and was used for offline data reduction. Physiological signals and experimental timing were monitored by an experimenter in an adjacent room by use of a 17” flat panel monitor. Questionnaires were presented by an LCD projector onto a large screen positioned approximately 2 m in front of the participant. Sound attenuating headphones and a video camera allowed the experimenter to communicate with and monitor the participant from an adjoining room. Noxious electrocutaneous stimulations were delivered to
the left ankle over the retromalleolar pathway of the sural nerve by use of a Grass Instruments stimulator (Model S88; West Warwick, RI), stimulus isolation unit (Model SIU8T), constant current unit (Model CCU1), and bipolar stimulating electrode (019-401400; Nicolet, Madison, WI). The onset/offset of the stimulator was controlled by computer, and a computer-controlled voltage regulator varied the current to the participant (maximum current = 40 mA). Mechanical pressure pain was measured with a Wagner Instruments Force Ten FDX Digital Force Gage with a 1.1-cm diameter tip (Wagner Instruments, Greenwich, CT). A Lafayette Instrument Hand Dynamometer (Models 78010 and 78011; Lafayette, IN) and Omron Tru-Gage blood pressure cuff were used during the ischemic pain procedures.

**Electrode Application and NFR Signal Acquisition**

Biceps femoris electromyography (EMG) for NFR recording was sampled at 1000 Hz and collected/filtered using a Grass Instruments Model 15LT Bipolar Amplifier with Quad AC (15A54) module. Recording electrodes were Ag-AgCl. To apply recording and stimulating electrodes, the skin was cleaned with alcohol, slightly abraded using NuPrep gel to attain impedances below 5 kΩ, and then conductive gel (EC60, Grass Instruments) was applied. NFR was recorded from 2 electrodes over the biceps femoris muscle of the left leg 10 cm superior to the popliteal fossa, and a common ground electrode was placed over the lateral epicondyle of the left femur. The raw biceps femoris EMG was amplified, bandpass filtered (10 to 300 Hz), and rectified.

**Assessment of Pain and Nociception**

**NFR Threshold Assessment**

The NFR is a spinally mediated withdrawal reflex elicited by activation of Aδ fibers after noxious stimulation.38,39 NFR threshold was determined by delivering trains of five 1-ms rectangular wave pulses at 250 Hz to the sural nerve with a varying intertrain interval of 8 to 12 seconds to reduce stimulus predictability. The first train began at 0 mA (current) and was increased in 1.5 mA steps until an NFR was detected. The mean biceps femoris EMG activity 90- to 150-ms poststimulation that exceeded mean EMG activity during the 60-ms prestimulus baseline interval by 1.4 SD was used to define the presence of a reflex.40 Prior research has shown that using the 90- to 150-ms timeframe avoids potential contamination by the nonnociceptive RII reflex, startle responses, and voluntary movements.41-42 The stimulus intensity was decreased in 0.75 mA steps until an NFR was no longer observed. Then, this up-down staircase procedure was repeated twice but by using 0.5 mA steps. NFR threshold was defined as the average stimulation intensity (in mA) of the last 2 peaks and troughs of this up-down staircase procedure.38,43

**Mechanical Pressure Pain**

Pressure pain threshold was assessed bilaterally by applying mechanical pressure on 3 body sites (occiput, lateral epicondyle, and fatty knee pad). These sites were chosen from tender points used to assess fibromyalgia criteria44 and include an assessment of all 4 body quadrants. Pain threshold (in kg) was assessed from each site by increasing the pressure at 1 kg/s until the participant reported pain. Pain threshold was defined as the average of each bilateral body site.

**Electrocutaneous Threshold and Tolerance**

Electrocutaneous pain threshold and tolerance were assessed by a single-ascending staircase of electric stimuli over the sural nerve. After each electric stimulus, participants rated their sensation using a computer-presented numerical rating scale oriented vertically.45,46 Arranged from bottom to top, the scale was labeled: 0 (no sensation), 1 (just noticeable), 25 (uncomfortable), 50 (painful), 75 (very painful), and 100 (maximum tolerable). Participants responded by moving an indicator along the scale and submitted their answers by computer mouse. Electric stimulations started at 0 mA and increased until the participant rated a stimulus as 100 or until the maximum of 40 mA was achieved. Electrocutaneous pain threshold was defined as the first stimulus (in mA) rated ≥ 50 on the rating scale, whereas electrocutaneous pain tolerance was defined as the stimulus (in mA) rated 100 (or 40 mA if the maximum current was reached).

**Ischemic Threshold and Tolerance**

To assess ischemia pain sensitivity, hand exercises were first conducted at 50% maximal effort with the left hand for 60 seconds with a dynamometer, followed by 15 seconds of arm elevation for exsanguination. Then, a blood pressure cuff was affixed to the left arm and inflated to 220 mm/Hg. After inflation, participants conducted another 20 hand exercises at 1-second intervals. Participants were then asked to rate the sensation evoked by the blood pressure cuff on the numerical rating scale, and the time until they reached pain threshold (rating of 50 on the numerical rating scale) and tolerance (rating of 100 on the numerical rating scale) was assessed. To ensure participant safety, a maximum of 25 minutes was used.19

**McGill Pain Questionnaire-Short Form (MPQ-SF)**

The MPQ-SF47 is a reliable and valid pain rating scale commonly used in pain research that allows quantitative, multidimensional pain ratings to be obtained in a brief period. Participants were asked to rate 11 sensory (eg, throbbing, shooting) and 4 affective (eg, sickening, fearful) pain descriptors on a scale ranging from 0 (none) to 3 (severe). The MPQ-SF was administered twice, once immediately after electrocutaneous pain tolerance and once immediately after ischemia pain tolerance. Sums of sensory words and affective words were used to compute sensory and affective pain rating scores, respectively, for electrocutaneous and ischemia stimuli.

**Menstrual Cycle-related Symptoms**

The modified version of the PRISM36 Calendar was used to assess daily behavioral, affective, and physical symptomatology. Participants were required to rate items for severity on a 4-point Likert scale ranging from 0 (absent) to 3 (severe). Menstrual cycle-related symptoms from the PRISM symptom severity ratings were averaged across 4 days (3 d before testing + day of testing) for each of the menstrual phases in which participants were tested.

**Procedure**

All procedures were fully approved by the University of Tulsa Institutional Review Board. A brief phone health screening was initially conducted to evaluate inclusion/exclusion criteria; however, a more comprehensive assessment was conducted during an initial laboratory session with those individuals not excluded by the phone screen.
During the initial laboratory session, participants were given a complete overview of the study, and informed consent was obtained. Then, a brief demographics and health status form was used to assess inclusion/exclusion criteria and attain relevant background information. If deemed eligible, the participant was instructed on how to monitor their menstrual cycle and then randomly assigned to a testing order (ie, mid-follicular/late-luteal vs. late-luteal/mid-follicular).

Participants were scheduled for 2 experimental testing sessions, once in the mid-follicular phase (days 5 to 8) and once during the late-luteal phase (1 to 6 d before menses onset) of their menstrual cycles. Each experimental testing session was scheduled at approximately the same time of the day to control for potential diurnal fluctuations in pain processing. At home, participants monitored 3 complete cycles. Cycle 1 was used to establish cycle length and ovulation timing. Experimental testing sessions occurred during cycles 2 and 3. Upon arrival to each experimental testing session, a complete overview of the procedures was provided, followed by review of informed consent and health status. Afterwards, participants were provided instruction for using the numerical pain rating scale. Mechanical pain threshold was then assessed, followed by application of electrodes. Next, participants completed questionnaires and then sat quietly for 5 minutes to help habituate to the testing environment. The rest of the session included pain testing in the following order: NFR threshold, emotional controls of nociception, diffuse noxious inhibitory controls (DNIC), electrocutaneous pain threshold and tolerance, MPQ-SF rating of electrocutaneous tolerance, ischemic pain threshold and tolerance assessment, and MPQ-SF rating of ischemia tolerance. Emotional controls of nociception and DNIC results have been reported elsewhere.48,49 At the culmination of the session, each participant was informed to continue menstrual phase monitoring until 3 cycles were complete. Participants were provided their honorarium after all study procedures were completed.

Data Analysis

All analyses were conducted using the MIXED procedure in SPSS 14.02 (IBM Corporation, Somers, NY).50 Menstrual phase (mid-follicular vs. late-luteal) was entered as a nominal within-subjects variable. No random effects were specified; therefore, this approach is similar to conducting 1-way within-subjects analysis of variances except that maximum likelihood (ML) estimation is used instead of general linear model (GLM). Although ML generally provides similar results as GLM, there are 3 major advantages to the MIXED procedure and ML: (1) cases with missing data on the within-subject variable are not excluded; and (3) the variance-covariance structure can be fit to the data rather than being fixed to compound symmetry as is true for GLM. The MIXED procedure uses Satterthwaite estimation for the denominator degrees of freedom that produces noninteger values that vary from analysis to analysis. These degrees of freedom were rounded to the nearest integer for ease of reporting. Because some women were tested outside of the targeted range of days for the mid-follicular (days 5 to 8) and late-luteal (days 1 to 6 preceding menses) phases, the pain data were analyzed in 2 ways: (1) with only data from women tested in the targeted phase windows and (2) with all data, even if testing occurred slightly outside of the targeted window. Only results from the first set of analyses are reported, although both produced similar outcomes. The data from the second set of analyses are presented as supplementary material for the interested reader (Supplemental Digital Content 1, http://links.lww.com/CJP/A40). To correct for positive skew, all ischemic pain variables were log-transformed. Cohen’s d was reported as the effect size for mean comparisons. Significance was set at \( P < 0.05 \) (2 tailed).

RESULTS

Menstrual Cycle-related Symptoms

Table 1 reports means, SDs, and effect sizes for menstrual cycle-related symptoms for the PRISM calendar for data collected during the targeted phase windows. Results revealed fatigue \((F_{1,35} = 4.29, P = 0.046)\) and depression \((F_{1,33} = 5.66, P = 0.023)\) were rated of higher severity during the mid-follicular phase, whereas breast tenderness was more severe during the late-luteal phase \((F_{1,30} = 4.39, P = 0.045)\). None of the other variables from the PRISM calendar varied by menstrual phase \((\text{all } F_s > 0.05)\).

Measures of Pain Sensitivity

Table 2 reports means, SDs, and effect sizes for measures of pain sensitivity for data collected inside the targeted phase windows. There were no significant differences found for any of the pain outcomes \((\text{all } P_s > 0.05)\), with the exception of lower electrocutaneous pain thresholds during the late-luteal phase relative to the mid-follicular phase \((F_{1,30} = 4.39, P = 0.049)\). When data from the full sample were considered \((\text{even if a woman was tested slightly outside of the targeted range})\,\text{results were identical, except that electro-cutaneous pain threshold was no longer significant (all } P_s > 0.05)\).

DISCUSSION

The present study assessed the relationship between nociceptive responding and menstrual phase in healthy, regularly cycling women and addressed the methodological limitations of prior research. We recruited a relatively large sample \((N = 41)\), verified menstrual timing through LH assessment, monitored for 3 consecutive cycles to confirm cycle regularity, assessed pain from multiple stimulus modalities, and used powerful statistical analyses. Although some studies have suggested enhanced pain during the late-luteal phase relative to the mid-follicular phase,2,19 we found no significant differences in any pain outcome between the mid-follicular and late-luteal phases, with the exception of lower electrocutaneous pain thresholds during the late-luteal phase. These findings are also similar to the rigorous study by Klatzkin et al13 who tested 49 women in the early-follicular, late-follicular, and luteal phases. So, when the 2 studies are taken together, this suggests that pain may vary little across the menstrual cycle in healthy women when rigorous methodology is used.

As a cautionary note, failure to reject the null hypothesis can never firmly establish that a relationship does not exist between menstrual phase and nociceptive responding. However, the statistical effect sizes for pain outcomes were small in both sets of analyses, ranging from \(d = 0.03\) (affective pain ratings of electric stimuli) to \(d = 0.29\) (electrocutaneous pain threshold). But what is more, the clinical significance of menstrual effects is likely...
to be minimal, given that menstrual phase only explained a maximum of 2% of the variance in pain sensitivity in the present study (electrocutaneous pain threshold). It is worth noting that electrocutaneous pain threshold achieved significance at \( P = 0.049 \) when the analysis was restricted to the 30 women tested only in the strict windows we defined as the mid-follicular and late-luteal phases. However, future research is needed to replicate this finding to determine whether this is a true difference that was observed after eliminating women outside of the testing windows (ie, removing error variance) or whether it is a spurious result of the smaller sample size given that only 1 out of 13 pain outcomes were significant.

**Relation to the Prior Literature**

A 1999 meta-analysis concluded that, relative to the follicular phase, the luteal phase is associated with hyperalgesia for mechanical pressure, ischemia, cold pressor, and thermal heat pain; but, electrocutaneous pain had the opposite pattern (hyperalgesia during follicular).\(^2\)\(^8\) However, in 2006, Sherman and LeResche\(^1\) conducted a critical review of the literature and noted that many of the studies examining the menstrual cycle and experimental pain suffered from numerous study design limitations and/or methodological inconsistencies that made it difficult to draw firm conclusions from the data. Of the 34 studies, we were able to identify on the topic,\(^2\)\(^3\)\(^5\)\(^7\)\(^-\)\(^9\),\(^13\)\(^-\)\(^15\),\(^17\)\(^-\)\(^19\),\(^32\)\(^-\)\(^34\),\(^51\)\(^-\)\(^69\)
only 16 studies verified ovulation through hormone assessment to exclude anovulatory cycles and accurately define menstrual phases.1,2,9,15,17,19,32–34,52–55 only 10 studies assessed pain from multiple stimulus modalities,14,18,19,32,33,52–54,56,57 and only 4 studies used sample sizes >33 (as recommended by Sherman and LeResche).1,32,58,59 Of the 9 studies we found that were published since Sherman and LeResche’s review,1–15,17,18,32–34,69 only Klatzkin et al22 adequately addressed the methodological concerns they noted and found no significant differences in heat pain, cold pain, and ischemia pain across the early-follicular, late-follicular, and luteal phases. Their study is in accordance with ours; however, our study supplements theirs by assessing nociceptive responding through mechanical pressure pain and NFR threshold, using powerful statistical models to test phase differences, and examining differences between the mid-follicular and late-luteal phases.

Of the 5 studies that specifically examined nociceptive responding during the mid-follicular and late-luteal phases of the menstrual cycle,2,9,15,19,34 4 failed to find phase differences in heat,19 ischemia,9 cold,15 and pressure pain34; whereas 2 found that ischemia pain sensitivity was enhanced during the late-luteal phase compared with the mid-follicular phase.2,19 However, these studies had the methodological limitations noted by Sherman and LeResche including small sample size,2,9,15,19,34 and failure to verify cycle regularity through multiple cycle monitoring.2,15,34 Moreover, most failed to assess multiple stimulus modalities to determine whether this contributed to the differences in results.2,9,15,34 Therefore, it is unclear whether our results can be directly compared with them. Nonetheless, they are generally consistent with our findings.

Menstrual Cycle and Spinal Nociceptive Processing

We found that NFR threshold did not differ across mid-follicular and late-luteal phases of the menstrual cycle (phase explained 0.4% variance in NFR threshold). Because NFR is a measure of spinal nociceptive processes that is under tonic modulation from supraspinal centers,39 this implies that descending modulatory processes are not affected by physiological changes associated with these menstrual phases. In contrast, Tassorelli et al38 found that NFR thresholds were lower (enhanced nociceptive responding) during the early-to-mid-luteal phase (days 6 to 8 after ovulation) relative to the late-luteal phase (days 8 to 10 from menses onset). Because their testing sessions were closer to ovulation, it is possible that descending modulation is influenced by the physiological changes that occur near ovulation. This notion is supported by a recent study18 that found descending inhibition of heat pain by DNIC was enhanced during ovulation (days 12 to 14) relative to the early-follicular (days 1 to 3) and mid-luteal (days 19 to 23) phases. However, it is important to note the Tassorelli and colleagues study was based on a small sample of 14 women and they used BBT to verify ovulation, which is prone to errors. Therefore, it is important for their results to be replicated before firm conclusions are drawn.

Implications and Future Directions

The current study corroborates findings from a previous methodologically rigorous study32 and other studies comparing the mid-follicular and late-luteal phases9,15,34 that suggest that the menstrual cycle may exert little influence on pain sensitivity in healthy women. However, menstrual cycle influences may be more pronounced in clinical populations. For example, Aberger et al36 found that women diagnosed with dysmenorrhea exhibit higher ischemic pain thresholds and tolerances during the premenstrual phase, relative to the menstrual and postmenstrual phases. Using rectal balloon distension, Houghton et al70 found that pain was greater during the menstrual phase (days 1 to 4) compared with the follicular phase (days 8 to 10) in women with irritable bowel syndrome. Further, Sherman et al35 found lower palpation pain thresholds during the ovulatory and late-luteal phases relative to the menstrual and mid-luteal phases in women with temporomandibular disorder. Women with premenstrual dysphoric disorder have also been found to exhibit greater ischemic pain sensitivity relative to healthy women, an effect that was independent of menstrual phase.71 Taken together, this suggests individuals with clinical pain may be more prone to menstrual phase-related changes in pain sensitivity or exhibit a generalized hyperalgesia relative to healthy populations.

The current study also provides further insight into the potential role of hormones on pain processing. Progesterone levels are relatively low during the mid-follicular phase and higher during the late-luteal phase.20 Given that progesterone levels should vary between these 2 phases, it seems that this variation in progesterone may be unrelated to pain sensitivity. Although there is some variation in estradiol between the mid-follicular and late-luteal phases, this variation is much smaller than progesterone; thus, we are not able to make a clear statement about the role of estradiol. However, it is important to note that there is considerable within-phase variability in sex hormone levels in addition to between-phase variability. Thus, future studies should measure intraindividual and interindividual variability in sex hormones to determine the relationships between hormone levels and pain processes.

Limitations

As previously noted, the present study had a number of strengths such as use of LH tests to verify ovulation, multiple phase monitoring for verification of cycle regularity, use of powerful statistical models, recruitment of a relatively large sample size, and assessment of pain sensitivity from multiple stimulus modalities. Further, the current study is the first to assess pain sensitivity from mechanical pressure and the physiologically measured NFR having addressed methodological limitations as suggested by Sherman and LeResche.1 Nonetheless, some limitations must be acknowledged. First, we did not directly measure sex hormones; thus, statements about the role of hormones are speculative. Second, pain sensitivity was assessed only during the mid-follicular and late-luteal phases; so, it is possible that variability in sex hormones associated with other phases (e.g., ovulation) or other within-phase periods (e.g., mid-luteal) may also influence pain sensitivity. Third, because of intraindividual and interindividual variability in menstrual cycles, some women were not tested within the targeted windows that we defined as the mid-follicular phase (N = 4) and the late-luteal phase (N = 8). Thus, our final sample was slightly restricted in size by this problem, although results were nearly identical when compared with the total sample of 41 women. Indeed, results suggested that pain sensitivity varies little between the mid-follicular and late-luteal phases of the menstrual cycle in healthy women. Fourth, our sample may not represent women more generally. We found few phase-related changes in menstrual symptoms, with the exception of increased severity of fatigue and depressed mood during the
mid-follicular phase and increased breast tenderness during the late-luteal phase. Therefore, the possibility exists that we recruited participants with less menstrual symptoms than the general population. And finally, our results may not generalize to clinical populations. For instance, menstrual phase has been found to influence disease-related symptomatology and experimental pain responsivity in individuals with temporomandibular disorder, dysmenorrhea, and irritable bowel syndrome.

CONCLUSIONS

In sum, the present study indicates that pain sensitivity (e.g., mechanical pain threshold, electrocutaneous pain threshold, ischemia pain threshold/tolerance, sensory/affective ratings of electrocutaneous and ischemic stimuli) and spinal nociceptive processing (NFR threshold) varies minimally between the mid-follicular and late-luteal (premenstrual) phases of the menstrual cycle. Future studies are needed to assess the specific association between sex hormones and nociceptive processing using rigorous methodologies and to determine whether our results extend to clinical populations (e.g., premenstrual dysphoric disorder, chronic pain).

ACKNOWLEDGMENTS

The authors thank Mary C. Chandler, Kara L. Kerr, and Ashley Vincent for their valuable assistance in data collection and data processing for this study.

REFERENCES