Published in final edited form as:

J Pain. 2013 November ; 14(11): . doi:10.1016/j.jpain.2013.07.008.

Mechanical pain sensitivity and the severity of chronic neck pain and disability are not modulated across the menstrual cycle

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Abstract

Despite the high prevalence of neck pain among women, menstrual effects on regional pain outcomes have not been investigated in this clinical population. This study evaluated menstrual effects on mechanical pain sensitivity (Pressure Pain Threshold; PPT), neck pain intensity (Numeric Pain Rating Scale; NPRS) and neck-related disability (Neck Disability Index; NDI) in 22 normally menstruating (NM) and 17 hormonal contraceptive (HC) users with chronic neck pain. Sex hormones, PPT, and NDI were measured during the early follicular (F1), late follicular (F2), and luteal (L) menstrual phases. Daily NPRS scores were recorded in an online symptom diary and averaged within each phase. Estradiol and progesterone increased only for NM women in F2 and L, respectively. Phase effects on PPT ($\eta^2=0.003$), NDI ($\eta^2=0.003$), and NPRS ($\eta^2=0.016$) for NM women were small, and did not differ from the HC group ($p = 0.386$). Averaged across the menstrual cycle, PPT scores explained 29% of the variance in NPRS scores for NM women, but were not associated with NDI scores in either group. Results indicate that that magnitude of menstrual effects on mechanical pain sensitivity, and the severity of neck pain and disability do not exceed thresholds of clinically detectable change in women with chronic neck pain.

PERSPECTIVE—Fluctuations in evoked and clinical pain outcomes across the menstrual cycle do not appear to be of sufficient magnitude to impact clinical decision-making for women with chronic neck pain.

Keywords

disability; trapezius muscle; sex hormones; pressure pain threshold; contraceptive

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Disclosures

The authors have no conflicts of interest to disclose.

INTRODUCTION

Annual prevalence estimates for neck pain range from 30–50%, with a consistently higher prevalence in women than men¹⁷. This disparity is consistent with other pain syndromes for which women report pain of greater magnitude, frequency, and duration compared with men⁴⁵. The prevalence of musculoskeletal pain syndromes, including neck pain, reaches a plateau after increasing during the peak reproductive years (18–45 years)³⁷, suggesting that fluctuations in ovarian hormones may be associated with altered pain sensitivity in premenopausal women.

Multiple reviews^{4, 13, 30, 35, 39} have examined sex differences and menstrual cycle effects on pain in both healthy and clinical populations with mixed results. Most research has been conducted in healthy individuals, with the majority of studies reporting mild to moderate increases in pain sensitivity in the early follicular and late luteal phases of the menstrual cycle³⁰. Fewer studies have examined whether women with existing pain syndromes exhibit similar changes in pain sensitivity across the menstrual cycle as observed for healthy women. Although increases in pain severity have been reported across various phases of the menstrual cycle among patients with migraine headache, temporomandibular joint disorder, irritable bowel syndrome, rheumatoid arthritis, and widespread musculoskeletal pain, findings from these clinical investigations are largely inconclusive due large variations in the study populations, methodologies, and results across studies³⁰.

Several methodological issues limit the interpretation of previous findings on menstrual effects among clinical populations^{30, 39}. The most commonly cited methodological limitations include inaccuracies in determining menstrual phase based only on self-reported menses onset, inadequate documentation of sex hormone levels, large variation in pain stimuli and outcome measures across studies, an inability to generalize findings from healthy participants to patients with a wide variety of clinical pain syndromes, and small study samples that lack power to detect the presence of subtle phase effects.

Similar to studies of naturally occurring changes in endogenous hormones, many studies have examined the effect of exogenous ovarian hormone use on pain sensitivity among healthy individuals^{11–12, 18, 21, 23–25, 33–34, 44}, whereas few studies have examined their effect among clinical populations with existing pain^{10, 31, 43}. Some studies have reported that exogenous hormones can increase the risk of certain pain syndromes²⁷, increase the severity of self-reported pain^{18, 41, 43}, and increase experimentally evoked pain sensitivity^{3, 11–12, 24, 34}. However, other studies have failed to demonstrate differences in pain severity, frequency, and phase modulation between women taking exogenous hormones and those without^{10, 21, 23, 31}. Thus, the role of sex hormone use among women with existing pain remains unclear.

Inconsistent findings regarding pain modulation across the menstrual cycle indicate a need for well-controlled studies to better elucidate the role of ovarian hormones on clinical and experimentally evoked pain sensitivity, especially among individuals with persistent pain. Despite the high prevalence of chronic neck pain among women, changes in regional pain sensitivity across the menstrual cycle have not yet been investigated in this population. The primary purpose of this study was to assess whether mechanical pain sensitivity (Pressure Pain Threshold; PPT) and the severity of self-reported clinical pain (Numeric Pain Rating Scale; NPRS) and neck-related disability (Neck Disability Index; NDI) are modulated with changes in sex hormones across the menstrual cycle in normally menstruating (NM) women and hormonal contraceptive (HC) users with chronic neck pain. We hypothesized that only NM women would exhibit changes in clinical and mechanical pain sensitivity, with reduced pain during the peak estrogen phase of the menstrual cycle. A second aim was to examine

the association between experimentally evoked and self-reported clinical pain outcomes in individuals with chronic neck pain.

MATERIALS AND METHODS

Subjects

Fifty-five women were recruited through advertisements in the local community. All women worked >20 hours per week in an office setting and reported persistent (duration >3 months) neck pain of non-specific origin, with localized tender points in the upper trapezius muscle confirmed by physical examination performed by a trained research assistant during enrollment screening at the time of consent. To ensure a significant restriction of functional activities due to neck pain at enrollment, only those individuals who met the Neck Pain Task Force¹⁶ definition of grade II interfering neck pain were included. Neck pain was defined as unilateral or bilateral pain located between the superior nuchal line and the superior spine of the scapula.

Exclusion criteria included any reported history of central nervous system impairment, signs or symptoms consistent with cervical nerve root compression or other non-musculoskeletal source of pain, and prior surgery involving the cervical or thoracic spine. Any participant undergoing professional treatment for neck pain was excluded due to the confounding effects of concurrent treatment on symptom severity. At enrollment, all women reported having regular menstrual cycles, with cycles every 26 to 31 days during the previous 6 months. Women using HC (oral HC, n=16; vaginal HC, n=2) reported >6 months of continuous monophasic HC use prior to enrollment, whereas NM women (n=37) reported no HC or other sex hormone use in the previous 6 months. All participants provided written informed consent according to study procedures approved by the Colorado Multiple Institutional Review Board. Subjects remained naïve to the study hypotheses throughout their participation in the study.

Determination of menstrual phase and assessment time points

All women participated in three experimental sessions scheduled to occur in the early follicular phase (F1; low estradiol, low progesterone), the late follicular phase (F2; high estradiol, low progesterone), and the middle luteal phase (L; intermediate estradiol; high progesterone) of the menstrual cycle. To minimize any effects of test order, the phase corresponding to the initial test session was randomly assigned and counterbalanced between groups. For the NM group, experimental sessions for F1 were scheduled 2–6 days after the onset of menses. In the month prior to testing, NM women used an ovulation kit (Accu-Clear Early Ovulation Predictor, Inverness Medical, MA) to estimate the date of ovulation for the subsequent month. Experimental sessions for F2 were then scheduled 1–3 days prior to the estimated luteinizing hormone (LH) surge, which was confirmed using a second ovulation kit during the month of testing. Experimental sessions for the L phase were scheduled 6–12 days after a confirmed LH surge. For the HC group, time-matched experimental sessions were scheduled 2–6 days (F1), 9–12 days (F2), and 18–23 days (L) after the onset of menses. Menstrual cycle length was calculated for all participants as the number of days between the onset of menses in two consecutive cycles. Average (SD) cycle length and the timing of each experimental session with respect to the onset of menses are provided for both groups in Table 1.

All experimental sessions were scheduled at approximately the same time of day in the afternoon ($\pm$ 30 minutes) to control for diurnal fluctuations in hormone levels. Participants were asked to refrain from: 1) consuming a major meal, caffeine, or dairy products within 1 hour of testing; 2) chewing gum or brushing their teeth within 2 hours of testing; 3) use of

non-prescription analgesic medications within 24 hours of testing; 4) use of alcohol or excessive intake of acidic and high sugar foods within 24 hours of testing; and 5) participating in heavy exercise within 48 hours of testing. Prescription medications were not discontinued, but were documented at each experimental session for all participants. Subjects were otherwise advised to adhere to their normal daily routines for physical activity, dietary intake, and medications.

Salivary hormone assays

Whole saliva samples were collected at the beginning of each experimental session by asking participants to drool into a collection vial through a straw. Samples were promptly stored at -80°C until later analyzed in duplicate for estradiol (lower detection limit = 0.1 pg/mL, intra-assay CV = 7.9%) and progesterone (lower detection limit = 5.0 pg/mL; intra-assay CV = 4.9%) concentrations using a commercially available kinetic reaction assay (Salimetrics LLC, State College, PA). The salivary estradiol assay has a small cross-reactivity with both estrone (1.3%) and estriol (0.2%), and unknown reactivity with ethinyl estrogen.

Mechanical pain sensitivity

Mechanical pain sensitivity was assessed using a digital algometer (FPIX 50, Wagner Instruments, Greenwich, CT, USA) with a 1 cm² tip to measure pressure pain thresholds (PPT) in the dominant upper trapezius muscle as described by Fischer¹⁴. This test was selected because mechanical hyperalgesia of the neck musculature has previously been reported among individuals with chronic neck pain³⁸, and upper trapezius PPT values are known to be highly reliable with a minimum detectable change of 0.48 kg/cm².⁴⁸ During testing, subjects were positioned prone with their arms resting at their sides and their face turned away from the side of testing. Pressure from the algometer was applied 2 cm lateral to the midpoint of the line between the spinous process of the seventh cervical vertebrae and the acromion at a target rate of 0.1 kgF/s. Subjects were instructed to indicate the moment at which the sensation of pressure turned to pain, and the pressure reading on the algometer at this moment was recorded. This procedure was repeated 3 times with 60 seconds rest between trials, and PPT was defined as the mean value of the three recordings. The same examiner performed all PPT assessments for each participant, and remained blinded to group status and menstrual phase throughout the experiment. A standardized test site on the dominant limb was used for all PPT assessments based on our experience with this clinical population in which the location of tender points vary widely both between individuals and across time within the same individual.

Severity of clinical pain and neck-related disability

The severity of self-reported clinical pain was assessed using a secure, web-based symptom diary administered through Research Electronic Data Capture (REDCap)¹⁹. During the same cycle in which experimental sessions occurred, participants were sent a link to the online symptom diary at the end of each work day for thirty-one consecutive days, excluding weekends. Participants recorded the average intensity of their neck pain for the current work day in the daily symptom diary using an 11-point Numeric Pain Rating Scale (NPRS), where a score of 0 indicated no pain and a score of 10 indicated the worst pain imaginable. NPRS scores were aligned with respect to the onset of menses for each participant, and all scores reported within the time period defined above for F1, F2, and L phases of the menstrual cycle were averaged to determine the overall intensity of clinical pain within each phase. For phases with missing data, a fewer number of daily pain ratings contributed to the individual phase average. Eight women (4 NM, 4 HC) completed the symptom diary for 2 consecutive months to assess the reliability of clinical pain scores calculated by this method.

Neck-related disability was assessed at each experimental session using the Neck Disability Index (NDI), a 10-item questionnaire designed to evaluate limitations in daily activities and participation among patients with disabling neck pain⁴⁶. Each survey item was scored on a 0–5 point scale, with the sum of all items expressed as a percentage of the total possible score, which ranged from 0% (no disability) to 100% (severe disability).

The NPRS and NDI have previously been shown to have acceptable test-retest reliability among patients with non-specific mechanical neck pain, with a minimum detectable change of 2.1 points for the NPRS and 19.6% for the NDI⁷.

Statistical analyses

Independent t-tests and Chi-square tests were used to compare demographic characteristics and assessment time points between the NM and HC groups. Changes in estradiol and progesterone across time were analyzed separately for each group with one-way analysis of variance (ANOVA) for repeated measures. Primary pain outcomes (PPT, NPRS, and NDI) were compared between groups (NM vs. HC) and across time (F1 vs. F2 vs. L) using separate two-factor, mixed model ANOVAs with group as the between-subjects factor and time as the within-subjects factor. When significant interaction or main effects were identified, a priori post-hoc comparisons of pain outcomes across time were performed separately for each group using paired t-tests with Bonferroni correction. Effect sizes for menstrual phase effects on pain outcomes were computed separately for each group, and were qualitatively interpreted as small ($\eta^2=0.0099$), moderate ($\eta^2=0.059$), or large ($\eta^2=0.138$) effects based on standard conventions⁸. Pearson correlations were used to test for significant associations between experimentally evoked and self-reported clinical pain outcomes averaged across the three phases of the menstrual cycle for each individual. A similar analysis was used to examine associations between salivary hormone concentrations and pain outcomes separately for each phase. Mixed model intra-class correlation coefficients (ICC) for absolute agreement were used to determine the reliability of NPRS scores assessed separately for each time point (F1, F2, and L) using a daily symptom diary across two consecutive menstrual cycles. All analyses were performed using SPSS software (version 16.0.1, Chicago, IL, USA). Unless otherwise noted, data are presented as mean (SD) in the text and tables, and as mean (SEM) in the figures.

RESULTS

Subjects

Of the 55 women initially recruited for the study, 22 women from the NM group and 17 women from the HC group were included in the final analyses. One woman in the HC group was withdrawn from the study due to an abnormally long cycle length (>31 days). Four women in the NM group elected to not complete the study due to their work schedule. Three NM women were withdrawn from the study due to pregnancy (n=1) or abnormal cycle length (<26 or >31 days; n=2). An additional 8 NM women were excluded from analysis after completing the study due to atypical hormone profiles (i.e., lower estradiol levels in F2 compared to F1), indicative of irregular fluctuations in sex hormones or inaccurate determination of the menstrual phase in these women. The remaining participants in each group did not differ in body mass index, menstrual cycle length, or age of menarche; however, women in the NM group were 5 years older than those in the HC group on average ($p < 0.05$, Table 1). Sixteen women in the NM group and 11 women in the HC group reported bilateral neck pain. Six women in both groups reported unilateral neck pain, with symptoms located on the dominant side for 3 NM women and 5 HC women.

Medication use did not differ between groups or across sessions ($p > 0.05$). Self-reported medications included daily vitamins (NM=23%; HC=29%), thyroid medication (NM=9%; HC=12%), prescription pain medications, excluding opioids (NM=0%, HC=12%), non-prescription pain medications (NM=18%; HC=18%), anti-depressant medications (NM=14%; HC=30%), and muscle relaxants (NM=0%; HC=12%). Eighty-six percent of NM women and 82% of women in the HC group completed an optional survey in which 23% of NM respondents reported previous use of HC that were discontinued 10.0 (6.1) (range: 3–16) years prior to testing. Women in the HC group reported taking their current contraceptive medication for 5.4 (3.1) (range: 1–10) years at the time of enrollment. Seventy-nine percent of HC respondents reported using HC for birth control purposes, 14% for regulation of menstrual symptoms, and 7% for the treatment of acne.

Changes in sex hormone levels across the menstrual cycle

Salivary estradiol and progesterone concentrations at the three assessment time points for F1, F2, and L are illustrated for the NM and HC groups in Figure 1. As expected, the HC group showed no significant change in estradiol ($F=0.59$; $p=0.562$) or progesterone ($F=0.28$; $p=0.760$) across time. A significant main effect of time was observed for estradiol ($F=9.17$; $p<0.001$) and progesterone ($F=14.07$; $p<0.001$) in the NM group. Post-hoc comparisons confirmed the expected increase in estradiol levels during F2 compared to both F1 ($p<0.001$) and L ($p=0.010$) phases of the menstrual cycle. Progesterone levels were significantly higher during the L phase compared to both F1 ($p<0.001$) and F2 ($p=0.003$) phases of the menstrual cycle. When these analyses were repeated including the 8 NM women who showed atypical hormone profiles, there was no longer a significant main effect of time for estradiol ($F=0.42$; $p=0.661$); however, progesterone levels remained significantly higher during the L phase compared to both F1 and F2 ($F=22.31$, $p<0.001$).

Changes in mechanical pain sensitivity across the menstrual cycle

PPT values assessed in the upper trapezius muscle of women with chronic neck pain and trapezius myalgia are shown for the NM and HC groups in Figure 2a. Pressure from the algometer was applied at a rate of 0.11 (0.01) kgF/s, with no significant difference in the rate of application across sessions or between groups ($F_{\text{Group} \times \text{Time}} = 2.11$, $p=0.131$). There were no significant changes in pain sensitivity across the menstrual cycle for either group. No significant interaction ($F = 0.79$; $p=0.456$) or main effects ($F_{\text{Group}}=0.17$; $p=0.681$; $F_{\text{Time}}=0.07$; $p=0.935$) were found for PPT, indicating that mechanical pain sensitivity remained relatively constant across the menstrual cycle for both groups. The same result was obtained when this analysis was repeated including the full sample of 30 NM women who completed the study, regardless of hormone profiles ($F_{\text{Group} \times \text{Time}}=0.49$; $p=0.615$; $F_{\text{Group}}=0.01$; $p=0.944$; $F_{\text{Time}}=0.02$; $p=0.985$). Effect sizes for changes in PPT across the menstrual cycle were $\eta^2=0.003$ for the NM group ($n=22$), and $\eta^2=0.001$ for the HC group.

Changes in the severity of clinical pain and disability across the menstrual cycle

Mean compliance rates with the daily symptom diary used to assess fluctuations in the intensity of neck pain were 84(11)% (range: 64–100%) for the NM group, and 89(12)% (range: 50–100%) for the HC group. NPRS scores averaged within F1 (ICC; 95% CI = 0.87(0.33–0.98)), F2 (ICC; 95% CI = 0.96(0.79–0.99) and L (ICC; 95% CI = 0.92(0.56–0.98)) phases of the menstrual cycle were highly reliable across two consecutive months of symptom reporting. For descriptive purposes only, Figure 3 shows group averages for neck pain intensity across each day of one complete menstrual cycle, as well as the average (range) timing of each experimental session with respect to the confirmed LH surge. The range of daily fluctuations in neck pain intensity was approximately 2 NPRS points for the HC group and 1 NPRS point for the NM group, with no obvious cyclic variations corresponding to any phase of the menstrual cycle. Figure 2b illustrates findings from the

statistical comparison of neck pain intensity across groups and time. No significant interaction ($F=0.45$; $p=0.638$) or main effects ($F_{\text{Group}}=0.36$; $p=0.552$; $F_{\text{Time}}=1.13$; $p=0.328$) were found for NPRS scores, indicating that neck pain intensity remained relatively constant across the menstrual cycle for both groups. The same result was obtained when this analysis was repeated including the full sample of 30 NM women who completed the study, regardless of hormone profiles ($F_{\text{Group} \times \text{Time}}=0.22$; $p=0.803$; $F_{\text{Group}}=0.88$; $p=0.354$; $F_{\text{Time}}=1.29$; $p=0.28$). Effect sizes for changes in NPRS across the menstrual cycle were $\eta^2=0.016$ for the NM group ($n=22$) and $\eta^2=0.002$ for the HC group.

Changes in neck-related disability across the menstrual cycle are illustrated for both groups in Figure 2c. There was no significant group $\times$ time interaction ($F=0.96$; $p=0.386$) or main effect of group ($F_{\text{Group}}=0.18$; $p=0.675$). However, a significant main effect of time ($F_{\text{Time}}=3.51$; $p=0.035$) revealed that neck-related disability was lowest in the F2 phase across both groups. The same result was obtained when this analysis was repeated including the full sample of 30 NM women who completed the study, regardless of hormone profiles ($F_{\text{Group} \times \text{Time}}=1.67$; $p=0.193$; $F_{\text{Group}}=0.73$; $p=0.397$; $F_{\text{Time}}=3.81$; $p=0.026$). Effect sizes for changes in NDI across the menstrual cycle were $\eta^2=0.003$ for the NM group ($n=22$) and $\eta^2=0.050$ for the HC group.

Association between mechanical pain sensitivity and clinical pain outcomes

Associations between mechanical pain sensitivity and the severity of clinical pain and disability averaged across the menstrual cycle are shown separately for each group in Figure 4. PPT scores were inversely correlated with NPRS scores in NM women ($r=-0.46$, $r^2=0.29$; $p=0.01$), indicating that lower sensitivity to mechanical pressure (higher PPT) was associated with a reduced intensity of clinical pain. PPT scores were not significantly correlated with NPRS scores for women in the HC group ($r=-0.14$, $r^2=0.02$; $p=0.57$). Furthermore, no associations were found between PPT and NDI scores for women in either the NM ($r=-0.25$, $r^2=0.08$; $p=0.21$) or HC ($r=-0.03$, $r^2=0.00$; $p=0.98$) groups.

Association between sex hormones and pain outcomes

Salivary sex hormone concentrations explained less than 6% of the variance in mechanical pain sensitivity (PPT) and clinical pain outcomes (NPRS, NDI) across the menstrual cycle. Correlation coefficients ranged from -0.01 to 0.13 ($r^2=0.00$ to 0.02) for estradiol, and from 0.02 to 0.19 ($r^2=0.00$ to 0.04) for progesterone in the NM group. Correlation coefficients ranged from 0.02 to 0.22 ($r^2=0.00$ to 0.05) for estradiol, and from -0.04 to 0.24 ($r^2=0.00$ to 0.06) for progesterone in the HC group.

DISCUSSION

Verification of sex hormone fluctuations across the menstrual cycle

A major strength of this study was the use of ovulation kits during two consecutive menstrual cycles to first predict, and then to verify the time of ovulation relative to experimental sessions for the late follicular and luteal phases of the menstrual cycle in NM women. Further verification of accurate phasing was obtained from salivary assays of estradiol and progesterone at each session. Although salivary sex hormone concentrations are only 2–3% of serum levels, salivary assays are cost-effective, non-invasive, and valid for the assessment of ovarian hormone levels in pre-menopausal women^{40,28}.

Rigorous exclusion criteria helped ensure that experimental sessions were appropriately timed with respect to expected fluctuations in sex hormone levels across the menstrual cycle. However, this approach also resulted in the exclusion of a large number of NM women who were initially deemed eligible based on self-reported menstrual cycle length.

Reasons for exclusion included pregnancy (3%), atypical cycle length verified by menses onset for two consecutive cycles (5%), and hormone profiles showing evidence of higher estradiol levels in F1 compared to F2 (22%). The latter may be attributed either to atypical hormone fluctuations in 'normally' menstruating women¹, or to individual variation in timing of the LH surge between menstrual cycles resulting in inaccurate estimation of the estrogen peak for F2. In either case, these observations strongly support the assertion that 'typical' fluctuations in sex hormone levels cannot be assumed based solely on self-reported cycle length and number of days since menses onset^{30, 39}. To better isolate the effects of sex hormone fluctuations on pain outcomes, we chose a conservative analytic approach that excluded women for whom accurate phasing could not be verified. However, secondary analyses including the larger sample of all NM women who completed the study regardless of hormone status did not change the primary conclusion that menstrual phase has no measurable effect on the sensitivity of a painful muscle to noxious mechanical stimuli, or the clinical severity of neck pain and disability.

Menstrual cycle effects on clinical and mechanical pain sensitivity

Both pro- and anti-nociceptive effects of estrogens and progesterone have been documented^{9, 26}. Although the mechanisms underlying these effects are not completely understood, they likely involve hormone-mediated changes in nociceptive processing within the central and peripheral nervous system^{13, 42}. It is currently unclear to what extent such changes manifest as hormonal alterations in experimentally evoked pain and, perhaps more importantly, reports of clinical pain and disability among individuals with chronic neck pain.

A meta-analysis of early studies examining menstrual effects on sensitivity to evoked noxious stimuli in healthy women concluded that pain thresholds are generally highest during the follicular phase with small to moderate effect sizes³⁵. Although our results appear to show a similar trend for reduced pain sensitivity (higher PPT), with corresponding reductions in the severity of neck pain and disability, during the late follicular phase in NM women with chronic neck pain, these effects were small in magnitude ($\eta^2=0.003-0.016$) and did not differ significantly across phases or between groups. On average, PPT scores for NM women during F2 were 0.08 and 0.12 kg/cm² higher than PPT scores during F1 and L phases, respectively. These differences were substantially lower than the minimum detectable change of 0.48 kg/cm² previously documented for patients with neck pain⁴⁸. This observation suggests a negligible effect of the menstrual cycle on sensitivity of a chronically painful muscle to mechanical stimuli. This finding is consistent with the lack of phase effects on evoked pain in healthy women reported by more recent studies that used appropriate controls to verify accurate phasing^{2, 22}.

In contrast to experimentally evoked pain, few studies have examined changes in clinical pain and disability across the menstrual cycle among patients with persistent pain. Using a reliable method of online symptom reporting, we found that day-to-day fluctuations in the intensity of neck pain varied within a range of approximately 2-points on the NPRS, with no significant phase effects for either group. The range of daily fluctuations in NPRS scores is consistent with previous reports that a change of greater than 2-points is necessary to detect a clinically significant change in neck pain that exceeds the inherent variability of the measure⁷. As a consequence of this variability, the NPRS does not appear to be sensitive to subtle changes in the intensity of neck pain across the menstrual cycle. However, others have demonstrated a significant 1-point decrease in chronic pain intensity during the ovulatory (F2) compared to the menstrual (F1) phase when averaging daily pain scores across three consecutive cycles²⁰.

Curiously, the NDI showed a similar pattern of change across the menstrual cycle in NM and HC groups, with significantly reduced disability in F2. However, the magnitude of this

change was well below the 20% threshold required to detect a clinically significant change in the NDI⁷. Thus, the clinical relevance of subtle changes in neck disability across the menstrual cycle is questionable. Given that NDI scores changed similarly in the two groups of women despite their differing hormone profiles, it seems unlikely that these changes were mediated by sex hormones. The mechanisms responsible for small, yet systematic, changes in neck disability across the menstrual cycle remain to be determined.

Association between mechanical pain sensitivity and clinical pain outcomes

Trapezius PPT scores have been proposed as an objective clinical tool for the assessment of treatment effects among patients with neck pain^{15, 48}. Therefore, we examined the construct validity of PPT scores as an index of the severity of clinical pain and disability by examining their association with NPRS and NDI scores averaged across the menstrual cycle. Results indicated that mechanical pain sensitivity was not associated with neck disability for either group, and explained only 29% of the variance in self-reported pain intensity for NM women. These findings for NM women with chronic neck pain contrast with previous reports of an inverse association between PPT and NDI in patients with acute whiplash³⁶, and a lack of association between PPT and neck pain intensity in individuals with non-specific neck pain³². Given that PPT assesses the sensory-discriminative dimension of pain, it is not surprising that PPT explains little to none of the variance in the severity of clinical pain and disability, which are strongly influenced by a variety of psychosocial and environmental factors²⁹. This observation suggests that PPT scores provide unique information on evoked pain sensitivity that can supplement, but not replace, more global measures of clinical neck pain and disability.

Study Limitations

This investigation was designed to address several recognized limitations of existing studies on changes in pain sensitivity across the menstrual cycle. To our knowledge, this was the first study to document concurrent changes in experimentally evoked and clinical pain outcomes in a chronic pain population with verified fluctuations in sex hormone levels across the menstrual cycle. Although we excluded individuals currently undergoing treatment for their symptoms, the study sample included individuals with a wide range of neck pain severity (NPRS scores ranging from 1–7 points; NDI scores ranging from 5–70%; Figure 4) representative of the broader clinical population^{5–6}. The use of salivary assays to verify phasing is more accurate than methods that rely on self-report, yet is not without limitations. Salivary concentrations of sex hormones were low, and these assays may have lacked sensitivity to detect the full range of hormone changes between phases. This may explain why we observed only weak correlations between salivary hormone concentrations and pain outcomes. We were also unable to collect daily hormone samples, making it difficult to ensure that the experimental session for F2 occurred during the peak in estradiol for each individual. Therefore, the magnitude of estradiol-mediated effects during F2 may be underestimated. Although daily neck pain scores did not change significantly across the menstrual cycle, we did not monitor symptoms during PPT assessments so any testing effects or change in chronic pain intensity on evoked pain responses are unknown. Finally, we did not examine interactions between sex hormones other than estradiol and progesterone that potentially mediate changes in pain processing across the menstrual cycle (e.g., testosterone⁴⁷), nor did we examine non-hormonal mechanisms that may explain differences in pain sensitivity such as coping strategies, anxiety levels, resting blood pressure, and genetic influences (reviewed by Fillingim and Ness¹³).

Conclusions

Although group means for normally menstruating women showed a consistent trend for lower mechanical pain sensitivity (higher PPT) and reduced severity of neck pain and

disability in the late follicular (peak estrogen) phase consistent with the anti-nociceptive effects of estrogen, the size of these effects were small and did not meet established criteria for clinically detectable change. Additionally, mechanical pain sensitivity explained only a small proportion of the variance in self-reported pain intensity for normally menstruating women, and was not related to neck disability in either group of women. We conclude that fluctuations in mechanical pain sensitivity and the clinical severity of neck pain and disability across the menstrual cycle are not of sufficient magnitude to significantly impact clinical decision-making.

Acknowledgments

The authors would like to thank Courtney Wiseman and Crystal Langer for assistance with data collection, and members of the Investigations in Metabolism, Aging, Gender, and Exercise (IMAGE) group for helpful comments on an initial draft of the manuscript.

This research was supported by NIH award R01 AR056704, and career development awards from the Colorado Clinical and Translational Science Institute (NIH Award TL1 RR025778) and the Center for Women's Health to KSM.

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A) NM Group

B) HC Group

Figure 1. Sex Hormone Fluctuations across the Menstrual Cycle

Concentrations of salivary estradiol (left axis; black) and progesterone (right axis; gray) in the early follicular (F1), late follicular (F2), and luteal (L) menstrual phases for normally menstruating (panel A) and hormonal contraceptive (panel B) groups. A significant main effect of time was observed for estradiol and progesterone in the NM group, with no significant time effect in the HC group. *p 0.01 for pair wise comparisons

Figure 2. Changes in Mechanical Pain Sensitivity and the Severity of Clinical Pain and Disability across the Menstrual Cycle

Pressure Pain Threshold (PPT, panel A), Numerical Pain Rating Scale (NPRS, panel B), and Neck Disability Index (NDI, panel C) scores are shown for the early follicular (F1), late follicular (F2), and luteal (L) phases in normally menstruating (NM; black) and hormonal contraceptive (HC; gray) groups. * p=0.035 for main effect of time in F2

Figure 3. Daily Fluctuations in Neck Pain Intensity across the Menstrual Cycle

Mean Numerical Pain Rating Scale (NPRS) scores for neck pain intensity reported at the end of each workday in an online symptom diary are plotted for one complete menstrual cycle in the normally menstruating (NM; black) and hormonal contraceptive (HC; gray) groups. Corresponding assessment time points for the early follicular (F1), late follicular (F2), and luteal (L) phases of the menstrual cycle are indicated as solid circles (group mean) and dashed lines (range). Timing of the luteinizing hormone (LH) surge relative to the onset of menses is similarly depicted for the NM group. Statistical comparison of daily pain scores was not performed due to variations in the sample size across days.

Figure 4. Associations between Mechanical Pain Sensitivity and the Severity of Clinical Pain and Disability

Panel A illustrates the association between PPT and NPRS scores averaged across three phases of the menstrual cycle in normally menstruating women (NM; left) and hormonal contraceptive users (HC; right). Panel B illustrates the association between PPT and NDI scores as depicted in panel A. The solid line represents a significant association between mechanical pain sensitivity and self-reported intensity of neck pain ($r^2=0.29$, $p=0.01$) only for the NM group.

Table 1

Demographic Characteristics and Assessment Time Points for Study Participants

Group	N	Age (yrs)	BMI (kg/m ²)	Age of Menarche (yrs)	Cycle Length (days)	Assessment Time Points (days post-menses)		
						Early Follic. (F1)	Late Follic. (F2)	Mid-Luteal (L)
NM	22	32.5 (7.8)*	27.1 (6.8)	12.7 (1.4)	28.2 (1.7)	3.9 (1.4)	11.2 (1.9)	23.0 (2.4)
HC	17	27.4 (5.3)	23.7 (4.7)	12.6 (1.0)	27.9 (0.5)	4.1 (1.5)	10.8 (1.9)	20.9 (1.6)

Abbreviations: NM=normally menstruating; HC=homonal contraceptive user; BMI=body mass index.

* p<0.05