Assessment of Experimental Pain Sensitivity Across the Menstrual Cycle

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Introduction
Pain sensitivity varies across the menstrual cycle, with the mid-follicular phase generally associated with enhanced pain and non-nociceptive sensitivity. However, research is conflicting and methodological limitations such as small sample size, lack of verification of ovulation, and inadequate assessment of menstrual cycle regularity may explain these inconsistencies. The current study was designed to address some of these limitations by (i) assessing several pain outcomes from multiple stimulus modalities, (ii) recruiting a relatively large sample size, (iii) verifying menstrual phase timing by using hormone levels and daily menstrual calendars, (iv) having women monitor their menstrual phases over three menstrual cycles to verify cycle regularity, and (v) using powerful mixed model statistical analyses.

Objective
Examine whether changes exist across the mid-follicular and late-luteal phases of the menstrual cycle in measures of experimental pain sensitivity (electrocutaneous pain threshold/tolerance, physiological pain responses (e.g., NFR), ischemic pain threshold/tolerance, mechanical pain-behavior, and subjective sensory and affective pain) in healthy women.

Participants
Healthy female participants: R = 41
- Participant Characteristics: White, non-Hispanic (71%), married (73%), employed full-time (96%), BMI of education = 15 (SD = 3.28), average menstrual cycle length = 28 (SD = 3.28), average length of cycle phase = 15 days (SD = 3.46).
- Exclusion Criteria:
  - > 16 yrs of age
  - Failure to regularly cycle within 2 months of study inclusion
  - Use of hormone preparations within past 6 months
  - Menopause or died premature
  - Cardiovascular, metabolic, or circulatory problems
  - History of chronic pain
  - History of resistance to anesthesia
  - History of allergy to local anesthetics
  - History of alcohol or substance abuse
  - History of medication use
  - Current use of anxiolytics, antidepressant, and/or antipsychotic medication

Experimental Procedure
- Procedure:
  - Ischemic Pain Threshold: Time when participant rated ischemia as maximum tolerable (=100) on the NRS
  - Ischemic Pain Tolerance: Time when participant rated ischemia as maximum tolerable (=100) on the NRS
  - Electrocutaneous Pain Threshold: Time when participant rated electrocutaneous pain as first stimulus (in mA) rated > 100 on the NRS
  - Electrocutaneous Pain Tolerance: Time when participant rated electrocutaneous pain as first stimulus (in mA) rated > 100 on the NRS

Data Analysis
- Overall, results indicate ischemic pain sensitivity (ischemia threshold, ischemia tolerance, ischemic pain threshold/tolerance, and MPQ sensory and affective ratings) across the mid-follicular and late-luteal phases of the menstrual cycle.
- This suggests the menstrual cycle may exert little influence on pain sensitivity in healthy women; however, future studies are warranted to assess pain sensitivity across other phases of the menstrual cycle (e.g., ovulation).
- Given research indicating women experience more pain-related symptomatology during the late-luteal phase of their menstrual cycle, and have more chronic pain conditions than men (e.g., fibromyalgia, migraine headaches), this research is important in further elucidating the pain hormone relationship and its impact on pain sensitivity in women.
- Future research is needed to assess endogenous hormones across the menstrual cycle and extend these findings in females who experience menstrual cycle-related changes in pain (e.g., dysmenorrhea, PMDD).

Conclusions
- Results indicated there were no phase-dependent changes in any of the outcome variables (i.e., mechanical-pain pressure-threshold, NFR threshold, electrocutaneous pain threshold/tolerance, ischemic pain threshold/tolerance, and MPQ sensory and affective ratings) across the mid-follicular and late-luteal phases of the menstrual cycle. (p > .07)
- Overall, results indicate electrocutaneous pain sensitivity (electrocutaneous pain threshold, electrocutaneous pain threshold/tolerance, MPQ sensory ratings, and MPQ affective ratings) does not significantly differ across the mid-follicular and late-luteal phases of the menstrual cycle (p > .16).

Participants
Convenience sample of 41 healthy females (71% White, 73% married, 96% employed full-time; BMI = 15, SD = 3.28; average menstrual cycle length = 28, SD = 3.28; average length of cycle phase = 15 days, SD = 3.46). Exclusion criteria included age > 16 yrs, regular cycling within 2 months of study inclusion, use of hormone preparations within past 6 months, menopause or died premature, cardiovascular, metabolic, or circulatory problems, history of chronic pain, history of resistance to anesthesia, history of allergy to local anesthetics, history of alcohol or substance abuse, history of medication use, current use of anxiolytics, antidepressant, and/or antipsychotic medication.

Procedure
- Ischemic Pain Threshold: Time when participant rated ischemia as maximum tolerable (=100) on the NRS
- Ischemic Pain Tolerance: Time when participant rated ischemia as maximum tolerable (=100) on the NRS
- Electrocutaneous Pain Threshold: Time when participant rated electrocutaneous pain as first stimulus (in mA) rated > 100 on the NRS
- Electrocutaneous Pain Tolerance: Time when participant rated electrocutaneous pain as first stimulus (in mA) rated > 100 on the NRS

Statistical Analysis
- Mixed model statistical analyses were conducted to assess phase-dependent changes in pain sensitivity. The statistical model included fixed factors of phase (mid-follicular vs. late-luteal) and cycle phase (mid-follicular vs. late-luteal), as well as an interaction term. The random effect was nested within participant. The statistical model was adjusted for baseline pain sensitivity, as determined by a pilot study.

Results
- Ischemic Pain Threshold: Results indicated there were no phase-dependent changes in ischemic pain sensitivity across the mid-follicular and late-luteal phases of the menstrual cycle (p > .07).
- Electrocutaneous Pain Threshold: Results indicated there were no phase-dependent changes in electrocutaneous pain sensitivity across the mid-follicular and late-luteal phases of the menstrual cycle (p > .16).
- Electrocutaneous Pain Tolerance: Results indicated there were no phase-dependent changes in electrocutaneous pain sensitivity across the mid-follicular and late-luteal phases of the menstrual cycle (p > .16).
- Ischemic Pain Tolerance: Results indicated there were no phase-dependent changes in ischemic pain sensitivity across the mid-follicular and late-luteal phases of the menstrual cycle (p > .16).

Discussion
- Overall, results indicate ischemic pain sensitivity (ischemia threshold, ischemia tolerance, ischemic pain threshold/tolerance, and MPQ sensory and affective ratings) across the mid-follicular and late-luteal phases of the menstrual cycle.
- This suggests the menstrual cycle may exert little influence on pain sensitivity in healthy women; however, future studies are warranted to assess pain sensitivity across other phases of the menstrual cycle (e.g., ovulation).
- Given research indicating women experience more pain-related symptomatology during the late-luteal phase of their menstrual cycle, and have more chronic pain conditions than men (e.g., fibromyalgia, migraine headaches), this research is important in further elucidating the pain hormone relationship and its impact on pain sensitivity in women.
- Future research is needed to assess endogenous hormones across the menstrual cycle and extend these findings in females who experience menstrual cycle-related changes in pain (e.g., dysmenorrhea, PMDD).