Endogenous modulation of pain and spinal nociception across the menstrual cycle
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Introduction
Recent evidence suggests that endogenous pain inhibition is greater during ovulation compared to follicular and luteal phases of the menstrual cycle. Ovulation may be associated with increased levels of oxytocin, which has been shown to decrease pain. Pain perception is modulated by neural mechanisms that act to suppress pain sensation. The conditioned pain modulation (CPM) paradigm, which involves afferent input from a peripheral stimulus being conditioned to a nociceptive input, is a useful method to assess pain modulation. In this study, CPM was assessed across three phases of the menstrual cycle: mid-follicular, ovulatory, and late-luteal.

Objective
To examine endogenous inhibition of pain and spinal nociception across the menstrual cycle via conditioned pain modulation of pain perception and the nociceptive flexion reflex (NFR).

Participants
Healthy Female Participants: N = 54
- Participant Characteristics: White, non-Hispanic (85%), single (48%), employed (86%), average age = 29.06 years (SD = 8.21), average years of education = 16.54 (SD = 2.51), average menstrual cycle length = 30 days (SD = 4.05), average length of luteal phase = 15 days (SD = 3.11)

Exclusion Criteria:
- <18 yrs of age
- Failure to regularly cycle within 2 months of study inclusion
- Use of hormone preparations within past 6 months
- Menopausal or post-menopausal
- Cardiovascular, neurological, circulatory problems
- Chronic pain condition (e.g., back pain)
- History of migraine headaches
- Use of current analgesics, antidepressants, and/or antihypertensive medication

Procedure
- Tested during three phases: mid-follicular, ovulatory, and late-luteal
- Testing order was counterbalanced
- Menstrual phase and ovulation were verified via daily symptoms, lanitizing hormone tests, and salivary estradiol and progesterone
- During each testing session:
  - Informed consent obtained. Sensors and stimulating electrode applied
  - NFR threshold and pain threshold assessed by sending electrical stimulations to the left ankle over the sural nerve
  - CPM of pain perception and NFR administered

Methods: Nocticeptive Flexion Reflex
- Nociceptive Flexion Reflex (NFR) Threshold: tibialis anterior EMG activity in the 50-150 ms post-stimulation window
- NFR strength: mean of tibialis anterior EMG in the 50-150 ms post-stimulation window minus mean of 50 ms prestimulation window
- NFR magnitude: NFR threshold correlated with pain ratings

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Methods: CPM Phases
- Pre-Ischemia
  - 4 electroucrocaneous stimulations delivered to sural nerve (120% pain or NFR threshold, whichever was greater): 15-25 s interval between stimulations
  - Pain ratings and NFR recorded after each stimulation

- Ischemia
  - 2 minutes of hand exercises (50% maximum grip strength) followed by 15 s of arm elevation then blood pressure cuff inflated to 220 mmHg
  - After cuff inflated, 4 electroucrocaneous stimulations delivered to sural nerve (intensity=120% pain or NFR threshold): 15-25 s interval between stimulations. Pain ratings and NFR recorded after each stimulation

- Post-Ischemia
  - Blood pressure cuff deflated
  - After 2 minutes, 4 electroucrocaneous stimulations delivered to sural nerve (120% pain or NFR threshold): 15-25 s interval between stimulations
  - Pain ratings and NFR recorded after each stimulation

Results: CPM of Pain Perception
- Linear mixed model analyses were used to assess conditioned modulation of pain perception & NFR magnitude across phases.
- Correlational analyses were used to investigate individual differences in CPM of pain and NFR magnitudes.

Results: Individual Differences in CPM of Pain Perception & NFR
- To quantify degree of CPM, change scores were created by taking the difference between ischemia and baseline for pain ratings and NFR magnitudes.

Conclusions
- These results indicate that endogenous modulation of pain is similar across these 3 menstrual phases in healthy women.
- Pain ratings were lowest during the late-luteal phase, as indicated by a main effect of menstrual cycle phase (p < .001).
- Pain modulation was not as stable due to changes during the ovulation phase.

Funding Source:
- This work was funded by a grant (HR09-086) from the Oklahoma Center for the Advancement of Science and Technology (OCAST)