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## SCIENTIFIC ARTICLE

# The influence of the menstrual cycle on acute and persistent pain after laparoscopic cholecystectomy

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### KEYWORDS

Menstrual cycle;  
Acute pain;  
Chronic pain;  
Cholecystectomy;  
Laparoscopy;  
Postoperative pain

### Abstract

**Background and objectives:** Fluctuations of female sex hormones during menstrual cycle influence pain perception. Endogenous pain inhibition is impaired in follicular phase of menstrual cycle. We tested the primary hypothesis that the women having surgery during their follicular phase have more acute pain and require higher opioids than those in the luteal phase, and secondarily we tested that women who have surgery during their follicular phase have more incisional pain at 3 month postoperatively.

**Methods:** 127 adult females having laparoscopic cholecystectomy were randomized to have surgery during the luteal or follicular phase of their menstrual cycle. Standardized anesthesia and pain management regimen was given to all patients. Pain and analgesic consumption were evaluated in post-anesthesia care unit and every 4 h in the first 24 h. Adverse effects were questioned every 4 h. Time to oral intake and ambulation were recorded. Post-surgical pain, hospital anxiety, depression scale, SF-12 questionnaire were evaluated at 1 and 3 month visits. **Results:** There was no difference in acute pain scores and analgesic consumption through the 24 h period, Visual Analog Scale at 24 h was  $1.5 \pm 1.5$  cm for follicular group  $1.4 \pm 1.7$  cm for luteal group ( $p=0.57$ ). Persistent postoperative pain was significantly more common one and at three month, with an incidence was 33% and 32% in the patients at follicular phase versus 16% and 12% at luteal phase, respectively. The Visual Analog Scale at one and at three month

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was  $1.6 \pm 0.7$  cm and  $1.8 \pm 0.8$  cm for follicular group and  $2.7 \pm 1.3$  cm and  $2.9 \pm 1.7$  cm in the luteal group ( $p=0.02$ ), respectively. There were no significant differences between the groups with respect to anxiety and depression, SF-12 scores at either time. Nausea was more common in follicular-phase group ( $p=0.01$ ) and oral feeding time was shorter in follicular phase ( $5.9 \pm 0.9$  h) than in luteal phase ( $6.8 \pm 1.9$  h,  $p=0.02$ ).

**Conclusions:** Although persistent postoperative pain was significantly more common one and three months after surgery the magnitude of the pain was low. Our results do not support scheduling operations to target particular phases of the menstrual cycle.

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## PALAVRAS-CHAVE

Ciclo menstrual;  
Dor aguda;  
Dor crônica;  
Colecistectomia;  
Laparoscopia;  
Dor pós-operatória

## A influência do ciclo menstrual na dor aguda e persistente após colecistectomia laparoscópica

### Resumo

**Justificativa e objetivos:** As flutuações dos hormônios sexuais femininos durante o ciclo menstrual influenciam a percepção da dor. A inibição endógena da dor é prejudicada na fase folicular do ciclo menstrual. Testamos a hipótese primária de que cirurgias em mulheres durante a fase folicular têm mais dor aguda e precisam de mais opioide que aquelas na fase lútea e a hipótese secundária testada foi que as cirurgias em mulheres durante a fase folicular têm mais dor incisional aos três meses de pós-operatório.

**Métodos:** No total, 127 mulheres adultas submetidas à colecistectomia laparoscópica foram randomizadas para serem operadas durante a fase lútea ou folicular de seus ciclos menstruais. Um regime padronizado para anestesia e tratamento da dor foi administrado a todas as pacientes. A dor e o consumo de analgésico foram avaliados na sala de recuperação pós-anestésica e a cada quatro horas nas primeiras 24 horas. Efeitos adversos foram avaliados a cada quatro horas. Os tempo para ingestão oral e deambulação foram registrados. Dor pós-cirúrgica, ansiedade hospitalar, escala de depressão e questionário SF-12 foram avaliados em visitas feitas no primeiro e terceiro meses.

**Resultados:** Não houve diferença nos escores de dor aguda e no consumo de analgésicos durante o período de 24 horas, Escala Visual Analógica em 24 horas foi de  $1,5 \pm 1,5$  cm para o grupo folicular e  $1,4 \pm 1,7$  cm para o grupo lúteo ( $p=0,57$ ). A dor persistente no pós-operatório foi significativamente mais prevalente no primeiro e terceiro mês, com incidência de 33% e 32% nas pacientes em fase folicular versus 16% e 12% na fase lútea, respectivamente. A Escala Visual Analógica no primeiro e terceiro mês foram  $1,6 \pm 0,7$  cm e  $1,8 \pm 0,8$  cm no grupo folicular e  $2,7 \pm 1,3$  cm e  $2,9 \pm 1,7$  cm no grupo lúteo ( $p=0,02$ ), respectivamente. Não houve diferença significativa entre os grupos em relação à ansiedade e à depressão, escore SF-12 em ambos os tempos. Náusea foi mais comum no grupo na fase folicular ( $p=0,01$ ) e o tempo para alimentação oral foi menor na fase folicular ( $5,9 \pm 0,9$  horas) que na fase lútea ( $6,8 \pm 1,9$  horas,  $p=0,02$ ).

**Conclusões:** Embora a dor persistente no pós-operatório tenha sido significativamente mais prevalente no primeiro e no terceiro mês após a cirurgia, a magnitude da dor foi baixa. Nossos resultados não apoiam o agendamento de cirurgias tendo como alvo fases específicas do ciclo menstrual.

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## Introduction

Acute postoperative pain is complex and affected by multiple factors including sex. Sex seems to play an important role in the perception and interpretation of pain.<sup>1,2</sup> With comparable stimuli, for example, women report more pain than men. Women also have lower pain thresholds. Fluctuations of female sex hormones during the menstrual cycle also influence pain sensitivity, possibly via interaction with serotonergic and noradrenergic neurons, which

effect inhibitory pain pathways and sensory neurons.<sup>3-5</sup> Furthermore, there appear to be increases in opioid receptor expression prompted by higher circulating concentrations of estrogen and progesterone.<sup>5,6</sup> Another potential mechanism is that estrogen enhances activity of N-methyl-D-aspartate receptors, which are important modulators of both acute and chronic pain.<sup>6</sup>

Sex differences also play important roles in chronic pain; women are more likely than men to report chronic pain syndromes.<sup>7,8</sup> Animal models have also demonstrated

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