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# Impact of the Menstrual Cycle Phase on Postoperative Pain in Reproductive-Age Women Undergoing Laparoscopic Surgery

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**Research Article**

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**Title: Impact of the Menstrual Cycle Phase on Postoperative Pain in Reproductive-Age Women Undergoing Laparoscopic Surgery**

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**Abstract**

**Objective** To investigate the association between menstrual cycle phase and postoperative pain in reproductive-age women undergoing laparoscopic surgery, and to explore potential hormonal mechanisms.

**Methods** This retrospective cohort study enrolled 232 reproductive-age women who underwent elective laparoscopic surgery. Patients were classified into follicular (D1–D13, n = 81), periovulatory (D14–D16, n = 52), and luteal (D17–D28, n = 99) phases according to the last menstrual period, assuming a standard 28-day cycle. The primary outcome was the 24-hour movement visual analogue scale (VAS) score. Secondary outcomes included resting and movement VAS at 24 and 48 hours, moderate-to-severe pain (VAS ≥ 4) incidence, rescue analgesic use, postoperative nausea and vomiting (PONV), and a composite endpoint. Hierarchical multivariable linear and logistic regression models were constructed. Restricted cubic splines (RCS), linear mixed-effects models, and hormone–pain correlation analyses were performed.

**Results** Baseline characteristics were balanced across groups (all $P > 0.05$) except for surgical department distribution ($P = 0.005$), which was adjusted for in multivariable models. In the fully adjusted model, the primary outcome did not reach statistical significance for the luteal versus follicular comparison (β = 0.218, $P = 0.156$). However, 48-h movement VAS (β = 0.244, $P = 0.020$) and 48-h resting VAS (β = 0.264, $P = 0.011$) remained significantly higher in the luteal phase. The adjusted odds ratio for moderate-to-severe pain was 2.27 ($P = 0.016$). Luteal-phase PONV risk (OR = 3.15, $P = 0.002$) and composite endpoint risk (OR = 3.51, $P = 0.001$) were also significantly elevated. RCS analysis revealed a near-linear ascending trend of VAS with advancing cycle day (nonlinearity P > 0.4). Progesterone correlated positively with movement VAS (Spearman rho = 0.240, $P < 0.001$), while the estradiol-to-progesterone ratio correlated inversely (rho = −0.223, $P = 0.001$). Subgroup and sensitivity analyses confirmed the robustness of findings.

**Conclusions** The luteal phase was associated with significantly higher 48-h postoperative pain and a two- to threefold increased risk of moderate-to-severe pain and PONV compared with the follicular phase. The primary 24-h outcome did not reach significance after full adjustment. These findings indicate that menstrual cycle phase may inform perioperative pain management, warranting prospective confirmation.

**Keywords:** menstrual cycle; follicular phase and luteal phase; postoperative pain; laparoscopic surgery; visual analogue scale

## 1 Introduction

Postoperative pain remains highly prevalent and is often undertreated. A nationwide survey in the United States showed that approximately 86% of surgical patients experience pain in the early postoperative period, and 75% rate their pain as moderate to severe [1]. Although laparoscopic surgery reduces tissue trauma compared to open surgery, 25% to 50% of patients undergoing gynecological or abdominal laparoscopic procedures still require analgesic medication postoperatively. Among modifiable factors, sex has emerged as an important but not yet fully elucidated factor, with women exhibiting a higher clinical pain burden and greater pain sensitivity in most experimental pain models compared with men [2, 3].

In reproductive-age women, cyclical fluctuations in estrogen and progesterone provide a biologically plausible explanation for intragender differences in pain perception [4, 5]. Gonadal steroids modulate pain through opioid, serotonergic, and GABAergic pathways and influence peripheral and central sensitization processes [6]. Experimental human studies further indicate that pain thresholds undergo systematic changes across the menstrual cycle; the follicular phase is typically associated with the lowest sensitivity, whereas the luteal and premenstrual phases are associated with the highest sensitivity [7]. However, it remains unclear whether these laboratory observations apply to clinical surgical settings: previous perioperative studies have yielded conflicting results regarding pain intensity and analgesic requirements, and although the preovulatory phase has distinct hormonal characteristics, it has rarely been studied as a separate category [8, 9].

Several methodological limitations have contributed to this inconsistency. Most prior studies have employed a binary follicular-versus-luteal classification, thereby failing to independently assess the periovulatory window. Preoperative hormone levels were rarely reported, limiting the biological validation of calendar-phase-based categorization. Sample sizes were generally small (40–80 patients per group), limiting the adjustment for confounding factors and the detection of small effects. Furthermore, only a few studies to date have simultaneously assessed pain, analgesic use, postoperative nausea and vomiting (PONV), and composite recovery endpoints at multiple postoperative time points within a single analytical framework; consequently, the temporal dynamics of menstrual cycle effects and their specific impact on outcomes have not been fully explored.

To address these limitations, we conducted a single-center retrospective cohort study of reproductive-age women with regular menstrual cycles undergoing elective laparoscopic surgery. This study aimed to: (1) assess the association between menstrual cycle phase and

postoperative pain; (2) examine the associations of cycle phase, cycle day, and preoperative hormone levels with pain outcomes using multivariable regression, restricted cubic splines, and linear mixed-effects models; and (3) compare PONV, supplemental analgesic use, and composite recovery outcomes across menstrual cycle phases.

## 2 Methods

### 2.1 Study Design and Ethical Approval

This single-center retrospective cohort study included reproductive-age women who underwent laparoscopic surgery. The study was conducted from December 2025 to July 2026 at the Gansu Province Maternity and Child Care Hospital (Gansu Province Central Hospital). The study protocol was approved by the Institutional Review Board of Gansu Province Maternity and Child Care Hospital (Gansu Province Central Hospital) (approval No. [2025] GSFY Ethics Review NO.159).

### 2.2 Study Population

#### 2.2.1 Inclusion Criteria

Patients were eligible if they met all of the following criteria: (1) female, aged 18–50 years; (2) undergoing elective laparoscopic surgery (gynecological or urological); (3) American Society of Anesthesiologists (ASA) physical status I–II; (4) known last menstrual period (LMP) date with regular menstrual cycles (21–35 days); and (5) available preoperative serum estradiol (E2) and progesterone (P4) measurements.

#### 2.2.2 Exclusion Criteria

Patients were excluded for any of the following criteria: (1) age under 18 years; (2) an unknown LMP date; (3) missing visual analog scale (VAS) pain scores at either 24 or 48 hours postoperatively; (4) chronic pain history or long-term opioid use; (5) severe cardiac, pulmonary, hepatic, or renal dysfunction; or (6) psychiatric disorders or cognitive impairment precluding VAS assessment.

### 2.3 Menstrual Cycle Phase Classification

Cycle day was calculated as the interval from the LMP to the surgery date plus one (cycle day = surgery date − LMP date + 1). Because the retrospective design precluded ascertainment of individual cycle length, a standard 28-day cycle was assumed [10]. Raw cycle day was converted to the current cycle position using a modular operation (cycle day = MOD [raw days − 1, 28] + 1; range 1–28). Patients were then classified into three phases: follicular (D1–D13), periovulatory (D14–D16), and luteal (D17–D28), following previously described classification schemes [11].

### 2.4 Anesthesia and Perioperative Management

All patients underwent laparoscopic surgery under general anesthesia. Anesthesia was induced with intravenous propofol and sufentanil, and rocuronium was administered for neuromuscular blockade. Maintenance was achieved with continuous remifentanil infusion combined with propofol, titrated to hemodynamic response. Intraoperative flurbiprofen axetil (50 mg intravenously) and/or oxycodone (5–10 mg) were administered at the discretion of the attending surgeon and anesthesiologist.

Postoperative analgesia comprised two approaches: (1) patient-controlled intravenous analgesia (PCIA) with hydromorphone 6~10 mg plus ondansetron 8 mg; or (2) oral analgesics on demand for patients without PCIA. All patients received intraoperative ondansetron 4 mg for PONV prophylaxis. Rescue analgesia consisted of oral ibuprofen and/or acetaminophen, administered by ward nurses as requested.

**2.5 Data Collection**

The following data were retrospectively extracted from medical records: (1) demographics: age, height, weight, body mass index (BMI); (2) perioperative variables: ASA class, surgical department, operative duration, anesthesia duration, estimated blood loss, crystalloid infusion volume, and urine output; (3) medication data: sufentanil, remifentanil, propofol, oxycodone, and flurbiprofen axetil dosages, and PCIA configuration; (4) preoperative hormone levels: estradiol (E2, pg/mL) and progesterone (P4, ng/mL); and (5) postoperative outcome measures.

**2.6 Outcome Measures**

2.6.1 Primary Outcome

The primary outcome was the 24-hour movement VAS (M-VAS) score (0–10 scale), assessed by ward nurses during patient turning or coughing.

2.6.2 Secondary Outcomes

Secondary outcomes included: (1) 24-h resting VAS (R-VAS); (2) 48-h resting and movement VAS; (3) incidence of moderate-to-severe pain (movement VAS $\geq 4$); (4) rescue analgesic use at 12, 24, and 48 hours; (5) PONV incidence; (6) patient satisfaction with analgesia (neutral/satisfied/very satisfied); and (7) length of hospital stay.

2.6.3 Composite Endpoint

A composite endpoint was defined as the occurrence of any of the following: 24-h movement VAS $\geq 4$, use of rescue analgesics within 24 hours, or PONV.

**2.7 Statistical Analysis**

Continuous variables with normal distribution were expressed as mean ± standard deviation; skewed variables were reported as median (interquartile range). Between-group comparisons

used one-way analysis of variance or Kruskal–Wallis tests. Categorical variables were presented as counts (percentages) and compared using chi-squared or Fisher exact tests.

Hierarchical multivariable linear regression models were constructed to assess the independent association between menstrual cycle phase and postoperative VAS, with the follicular phase as reference. Model 1 adjusted for age and BMI; Model 2 additionally adjusted for surgical department, operative duration, and estimated blood loss; Model 3 (fully adjusted) further included PCIA use. For continuous VAS outcomes, beta coefficients with 95% confidence intervals (CIs) were reported; for moderate-to-severe pain (movement VAS $\geq$ 4), logistic regression was used to estimate odds ratios (ORs) with 95% CIs. Confounding effects were evaluated by observing changes in effect estimates across model tiers. Multicollinearity was assessed using variance inflation factors (VIF < 5), and heteroscedasticity-consistent standard errors (HC3) were computed to verify the robustness of inferences.

To explore nonlinear dose–response relationships between cycle day and VAS, restricted cubic splines (RCS) with four knots were fitted to the fully adjusted models. Overall and nonlinearity effects were evaluated using Wald tests. Given that 24-h and 48-h VAS measurements represented repeated observations within patients, linear mixed-effects models (LMMs) were constructed with a random intercept per patient and fixed effects for menstrual phase, time point (24 h vs 48 h), and their interaction, adjusted for the aforementioned confounders.

Hormone–pain associations were evaluated using Spearman rank correlation for unadjusted analyses and multivariable linear regression for adjusted associations, with preoperative E2, progesterone, and the E2-to-progesterone (E2:P4) ratio as independent variables.

Subgroup analyses were performed by age (< 35 vs $\geq$ 35 years), BMI (< 24 vs $\geq$ 24 kg/m$^2$), PCIA use (yes vs no), flurbiprofen axetil use (yes vs no), and operative duration ($\leq$ median vs > median). Adjusted models were fitted within each stratum, and interaction terms were tested for effect modification. When the subgroup variable overlapped with a model covariate (e.g., PCIA use), the corresponding covariate was removed from the interaction and within-stratum models to avoid collinearity. Only subgroups with $\geq$ 20 patients in each level were included. Adjusted logistic regression models were fitted for PONV, composite endpoint, and 24-h rescue analgesic use.

Five sensitivity analyses were conducted: (1) binary classification at D14 (D1–14 vs D15–28); (2) exclusion of periovulatory patients, comparing follicular with luteal phases only; (3) additional adjustment for postoperative day-1 C-reactive protein (CRP); (4) expanded periovulatory definition to D14–D17; and (5) HC3 robust standard errors. As a retrospective study, the sample size was determined by the number of eligible cases during the study period.

All analyses were performed in R version 4.4.2. Two-sided $P < 0.05$ was considered statistically significant.

## 3 Results

### 3.1 Study Population and Baseline Characteristics

A total of 232 patients were included and classified into follicular (n = 81, 34.9%), periovulatory (n = 52, 22.4%), and luteal (n = 99, 42.7%) groups. There were no significant differences in age, BMI, ASA classification, operative duration, estimated blood loss, intraoperative opioid morphine equivalent (OME), flurbiprofen axetil use, or PCIA use across the three groups (all $P > 0.05$; Table 1). Surgical department distribution differed significantly among groups ($P = 0.005$). Hormone levels conformed to expected physiological patterns: median follicular progesterone was 0.20 ng/mL, periovulatory estradiol peaked at 207.2 pg/mL, and luteal progesterone reached 9.62 ng/mL (all $P < 0.001$) (Table 1).

**Table 1. Baseline characteristics stratified by menstrual cycle phase**

| Variable | Overall (N=232) | Follicular (n=81) | Periovulatory (n=52) | Luteal (n=99) | p-value |
|---|---|---|---|---|---|
| Age (years) | 34.0 ± 6.0 | 34.2 ± 5.6 | 33.6 ± 6.0 | 34.1 ± 6.4 | 0.844 |
| BMI (kg/m$^2$) | 23.6 ± 3.9 | 24.2 ± 3.8 | 23.3 ± 4.1 | 23.3 ± 3.7 | 0.173 |
| ASA class | | | | | 0.393 |
| I | 9 (3.9%) | 5 (6.2%) | 1 (1.9%) | 3 (3.0%) | |
| II | 223 (96%) | 76 (94%) | 51 (98%) | 96 (97%) | |
| Estradiol (pg/mL) | 108.4 (71.9-152.8) | 56.2 (42.6-91.3) | 207.2 (154.8-279.9) | 110.9 (86.3-132.4) | <0.001 |
| Progesterone (ng/mL) | 1.92 (0.26-7.77) | 0.20 (0.16-0.30) | 1.48 (0.92-2.46) | 9.62 (6.04-12.98) | <0.001 |
| Surgery duration (min) | 120.7 ± 32.8 | 120.7 ± 33.4 | 119.0 ± 29.3 | 121.6 ± 34.4 | 0.876 |
| Blood loss (mL) | 10.0 (5.0-20.0) | 10.0 (5.0-10.0) | 5.0 (5.0-10.0) | 10.0 (5.0-20.0) | 0.054 |
| Department | | | | | 0.005 |
| Endocrine | 111 (48%) | 47 (58%) | 29 (56%) | 35 (35%) | |
| GynOnc | 45 (19%) | 10 (12%) | 7 (13%) | 28 (28%) | |
| TCM | 28 (12%) | 13 (16%) | 7 (13%) | 8 (8.1%) | |
| GenGyn | 39 (17%) | 10 (12%) | 6 (12%) | 23 (23%) | |

| Variable | Overall (N=232) | Follicular (n=81) | Periovulatory (n=52) | Luteal (n=99) | p-value |
|---|---|---|---|---|---|
| Urology | 9 (3.9%) | 1 (1.2%) | 3 (5.8%) | 5 (5.1%) | |
| Flurbiprofen axetil use | 192 (83%) | 68 (84%) | 42 (81%) | 82 (83%) | 0.893 |
| PCIA use | 108 (47%) | 31 (38%) | 28 (54%) | 49 (49%) | 0.158 |
| Intraop oxycodone use | 24 (10%) | 6 (7.4%) | 5 (9.6%) | 13 (13%) | 0.447 |
| Intraop opioid OME (mg) | 104.9 ± 31.7 | 105.9 ± 34.9 | 99.7 ± 28.4 | 107.0 ± 30.6 | 0.201 |

### 3.2 Descriptive Comparison of Postoperative Pain Outcomes across Menstrual Cycle Phases

All pain-related outcomes differed significantly among the three groups (Table 2, Fig. 1). The 24-h movement VAS scores were 3.4 ± 1.0, 3.6 ± 1.0, and 3.7 ± 1.0 for the follicular, periovulatory, and luteal groups, respectively ($P = 0.014$). The 48-h movement VAS showed a similar ascending pattern (2.3 ± 0.7 vs 2.5 ± 0.7 vs 2.7 ± 0.7; $P < 0.001$), as did both resting VAS measures at 24 and 48 hours ($P = 0.008$ and $P < 0.001$, respectively).

The incidence of moderate-to-severe pain (movement VAS ≥ 4) in the luteal group was 60%, compared with 35% in the follicular and 44% in the periovulatory groups ($P = 0.003$). Rescue analgesic use at 24 hours was 49% in the luteal versus 27% in the follicular group ($P = 0.010$). PONV incidence was 52% in the luteal versus 26% in the follicular group ($P = 0.002$). The composite endpoint rate was 81% in the luteal versus 52% in the follicular group ($P < 0.001$).

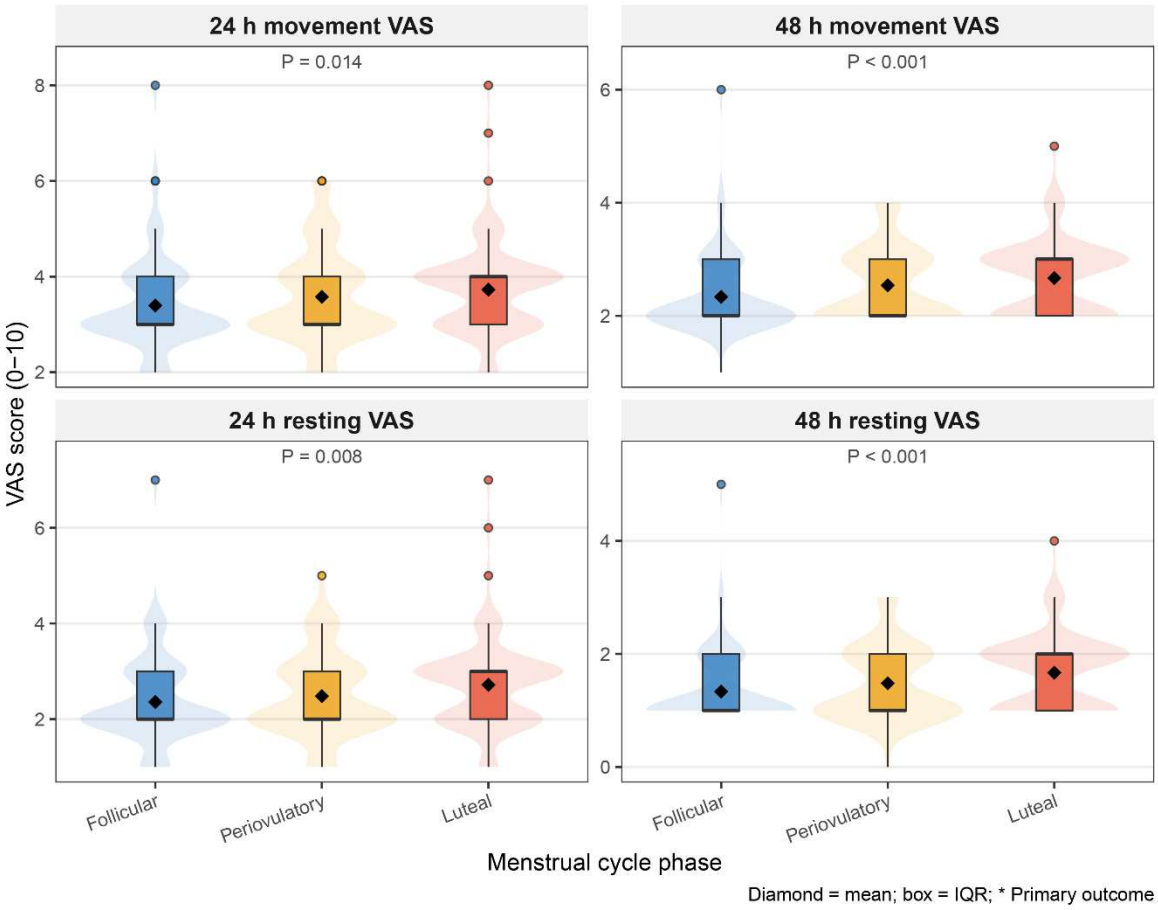



**Figure 1. Box plots of movement and resting VAS pain scores at 24 hours and 48 hours postoperatively during the follicular, periovulatory, and luteal phases.**

**Table 2. Primary and secondary outcomes stratified by menstrual cycle phase**

| Outcome | Overall (N=232) | Follicular (n=81) | Periovulatory (n=52) | Luteal (n=99) | p-value |
|---|---|---|---|---|---|
| **24 h resting VAS** | 2.5 ± 0.9 | 2.4 ± 0.9 | 2.5 ± 0.9 | 2.7 ± 0.9 | 0.008 |
| **24 h movement VAS** | 3.6 ± 1.0 | 3.4 ± 1.0 | 3.6 ± 1.0 | 3.7 ± 1.0 | 0.014 |
| **48 h resting VAS** | 1.5 ± 0.7 | 1.3 ± 0.7 | 1.5 ± 0.7 | 1.7 ± 0.7 | <0.001 |
| **48 h movement VAS** | 2.5 ± 0.7 | 2.3 ± 0.7 | 2.5 ± 0.7 | 2.7 ± 0.7 | <0.001 |
| **Moderate-severe pain (VAS ≥ 4)** | 110 (47%) | 28 (35%) | 23 (44%) | 59 (60%) | 0.003 |
| **Rescue analgesic 12 h** | 48 (21%) | 11 (14%) | 18 (35%) | 19 (19%) | 0.012 |
| **Rescue analgesic 24 h** | 92 (40%) | 22 (27%) | 21 (40%) | 49 (49%) | 0.010 |
| **Rescue analgesic 48 h** | 61 (26%) | 14 (17%) | 13 (25%) | 34 (34%) | 0.034 |

| Outcome | Overall (N=232) | Follicular (n=81) | Periovulatory (n=52) | Luteal (n=99) | p-value |
|---|---|---|---|---|---|
| **PONV** | 90 (39%) | 21 (26%) | 18 (35%) | 51 (52%) | 0.002 |
| **Composite endpoint** | 161 (69%) | 42 (52%) | 39 (75%) | 80 (81%) | <0.001 |
| **Satisfaction** | | | | | 0.008 |
| **Neutral** | 16 (6.9%) | 2 (2.5%) | 4 (7.7%) | 10 (10%) | |
| **Satisfied** | 178 (77%) | 57 (70%) | 44 (85%) | 77 (78%) | |
| **Very satisfied** | 38 (16%) | 22 (27%) | 4 (7.7%) | 12 (12%) | |
| **First flatus on surgery day** | 4 (1.7%) | 2 (2.5%) | 2 (3.8%) | 0 (0%) | 0.119 |
| **Length of stay (days)** | 6.0 (5.0-7.0) | 6.0 (5.0-7.0) | 5.5 (4.0-7.0) | 6.0 (5.0-7.0) | 0.117 |
| **CRP day 1 (mg/L)** | 2.8 (1.2-5.8) | 2.5 (1.2-4.7) | 3.2 (1.5-5.3) | 3.0 (1.3-7.6) | 0.773 |

Abbreviations: VAS,visual analogue scale; PONV, postoperative nausea and vomiting; CRP, C-reactive protein.

### 3.3 Multivariable Regression Analysis

In Model 1 (adjusted for age and BMI), all VAS outcomes were significantly higher in the luteal compared with the follicular phase (24-h movement VAS: β = 0.313, *P* = 0.036; 48-h movement VAS: β = 0.323, *P* = 0.002; 24-h resting VAS: β = 0.343, *P* = 0.016; 48-h resting VAS: β = 0.322, *P* = 0.001). After additional adjustment for surgical department, operative duration, and estimated blood loss (Model 2) and PCIA use (Model 3, fully adjusted), the 24-h movement VAS effect attenuated to β = 0.218 (95% CI: −0.084 to 0.520) and did not reach statistical significance (*P* = 0.156). However, the 48-h movement VAS remained significant after full adjustment (β = 0.244, 95% CI: 0.039–0.448, *P* = 0.020), as did the 48-h resting VAS (β = 0.264, 95% CI: 0.062–0.466, *P* = 0.011). The adjusted OR for moderate-to-severe pain was 2.27 (95% CI: 1.17–4.47, *P* = 0.016), indicating that luteal-phase patients had approximately 2.3-fold higher odds of experiencing moderate-to-severe pain compared with follicular-phase patients (Table 3).

Restricted cubic spline (RCS) analysis demonstrated a near-linear relationship between cycle day and VAS, with no significant nonlinearity (P-nonlinear > 0.4), suggesting a gradual rather than threshold-like effect. The overall effect reached significance for 48-h resting VAS (P-overall = 0.022), with the most pronounced increase occurring between D18 and D25, corresponding to the mid-luteal phase (Fig. 2).

**Table 3. Hierarchical multivariable regression: menstrual phase and postoperative pain**

| Characteristic | Model 1 | | Model 2 | | Model 3 | |
|---|---|---|---|---|---|---|
| | Beta (95% CI) | p-value | Beta (95% CI) | p-value | Beta (95% CI) | p-value |
| **24 h movement VAS** | | | | | | |
| Follicular | ref | | ref | | ref | |
| Periovulatory | 0.160 (-0.185, 0.506) | 0.362 | 0.156 (-0.187, 0.499) | 0.372 | 0.141 (-0.205, 0.486) | 0.423 |
| Luteal | 0.313 (0.021, 0.605) | **0.036** | 0.227 (-0.074, 0.528) | 0.139 | 0.218 (-0.084, 0.520) | 0.156 |
| **48 h movement VAS** | | | | | | |
| Follicular | ref | | ref | | ref | |
| Periovulatory | 0.194 (-0.043, 0.430) | 0.108 | 0.201 (-0.031, 0.433) | 0.090 | 0.195 (-0.038, 0.429) | 0.101 |
| Luteal | 0.323 (0.123, 0.522) | **0.002** | 0.247 (0.043, 0.450) | **0.018** | 0.244 (0.039, 0.448) | **0.020** |
| **24 h resting VAS** | | | | | | |
| Follicular | ref | | ref | | ref | |
| Periovulatory | 0.104 (-0.224, 0.433) | 0.532 | 0.114 (-0.214, 0.442) | 0.494 | 0.107 (-0.223, 0.437) | 0.523 |
| Luteal | 0.343 (0.066, 0.621) | **0.016** | 0.291 (0.004, 0.578) | **0.047** | 0.287 (-0.001, 0.576) | 0.051 |
| **48 h resting VAS** | | | | | | |
| Follicular | ref | | ref | | ref | |
| Periovulatory | 0.136 (-0.096, 0.367) | 0.249 | 0.144(-0.085, 0.374) | 0.216 | 0.145 (-0.087, 0.376) | 0.219 |
| Luteal | 0.322 (0.126, 0.517) | **0.001** | 0.264 (0.063, 0.466) | **0.010** | 0.264 (0.062, 0.466) | **0.011** |
| **Moderate-severe pain (OR)** | | | | | | |
| Follicular | ref | | ref | | ref | |

| Characteristic | Model 1 | | Model 2 | | Model 3 | |
|---|---|---|---|---|---|---|
| | Beta (95% CI) | p-value | Beta (95% CI) | p-value | Beta (95% CI) | p-value |
| Periovulatory | 1.41 (0.68, 2.91) | 0.356 | 1.46 (0.68, 3.14) | 0.332 | 1.45 (0.67, 3.14) | 0.338 |
| Luteal | 2.64 (1.44, 4.94) | **0.002** | 2.28 (1.17, 4.49) | **0.026** | 2.27 (1.17, 4.47) | **0.016** |

Abbreviations: CI, confidence interval; OR, odds ratio; VAS,visual analogue scale.

Model 1: adjusted for age and BMI. Model 2: additionally adjusted for department, surgery duration, and blood loss. Model 3: fully adjusted (+ PCIA use). * Primary outcome. VAS outcomes: linear regression (beta, 95% CI). Moderate-severe pain: logistic regression (OR, 95% CI).

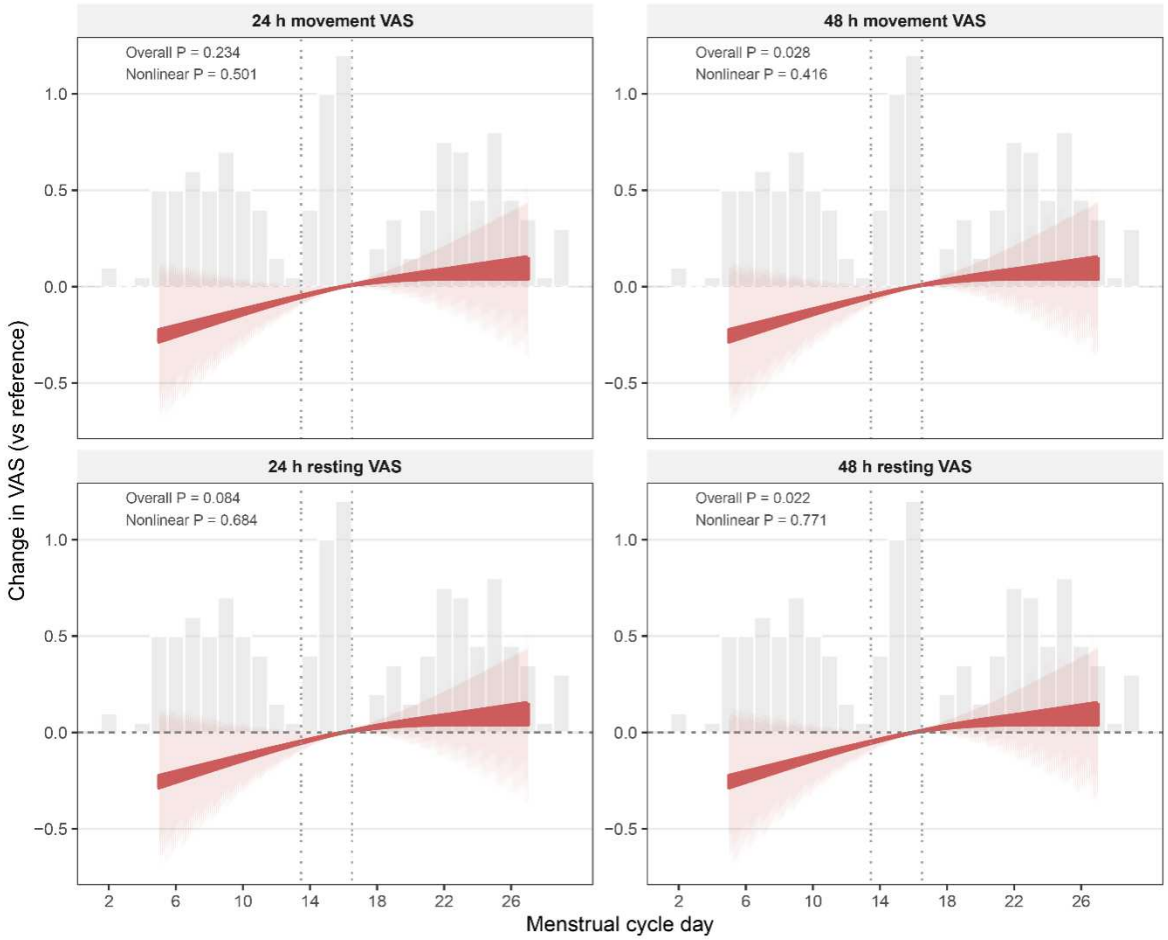



**Figure 2. Restricted cubic spline fitting graph of menstrual cycle days and postoperative 24-hour and 48-hour movement and resting VAS pain scores.**

### 3.4 Pain Trajectory and Associations between Hormone and Pain

Linear mixed-effects modeling showed significant decreases in both movement and resting VAS from 24 to 48 hours (movement: $\beta = -1.062$, $P < 0.001$; resting: $\beta = -1.025$, $P < 0.001$). For movement VAS, the main effect of the luteal phase was $\beta = 0.230$ ($P = 0.078$), and the phase × time interaction was not significant ($P = 0.965$), indicating that the menstrual cycle

effect on movement pain was consistent between 24 and 48 hours. For resting VAS, the luteal-phase main effect reached significance (β = 0.289, *P* = 0.022), with no significant interaction (*P* = 0.843) (Table 4).

Hormone–pain correlation analyses revealed that progesterone was positively correlated with 24-h movement VAS (Spearman rho = 0.179, *P* = 0.006) and more strongly with 48-h movement VAS (rho = 0.240, *P* < 0.001). The E2:P4 ratio was inversely correlated with VAS (24-h: rho = −0.165, *P* = 0.012; 48-h: rho = −0.223, *P* = 0.001), suggesting that relative estrogenic dominance was associated with lower pain scores. After adjustment for confounders, the association between E2:P4 ratio and 48-h movement VAS remained significant (β = −0.005 per unit, *P* = 0.039); other hormone–pain associations were attenuated, suggesting partial mediation or confounding by clinical factors (Table S1, Fig. 3).

**Table 4. Linear mixed-effects model for VAS (repeated measures)**

| Outcome | Term | Beta (95% CI) | P |
|---|---|---|---|
| Movement VAS | Periovulatory vs Follicular | 0.156 (-0.137, 0.449) | 0.296 |
| | Luteal vs Follicular | 0.230 (-0.025, 0.485) | 0.078 |
| | 48 h vs 24 h | -1.062 (-1.179, -0.945) | <0.001 |
| | Periovulatory x 48 h | 0.023 (-0.164, 0.211) | 0.808 |
| | Luteal x 48 h | 0.001 (-0.157, 0.159) | 0.989 |
| Resting VAS | Periovulatory vs Follicular | 0.114 (-0.169, 0.396) | 0.432 |
| | Luteal vs Follicular | 0.289 (0.043, 0.535) | 0.022 |
| | 48 h vs 24 h | -1.025 (-1.137, -0.913) | <0.001 |
| | Periovulatory x 48 h | 0.025 (-0.155, 0.204) | 0.787 |
| | Luteal x 48 h | -0.026 (-0.177, 0.125) | 0.738 |

Random intercept per patient. Adjusted for age, BMI, dept, surgery duration, blood loss, PCIA use. Phase x time interaction: movement P=0.965, resting P=0.843. Ref: Follicular, 24 h.

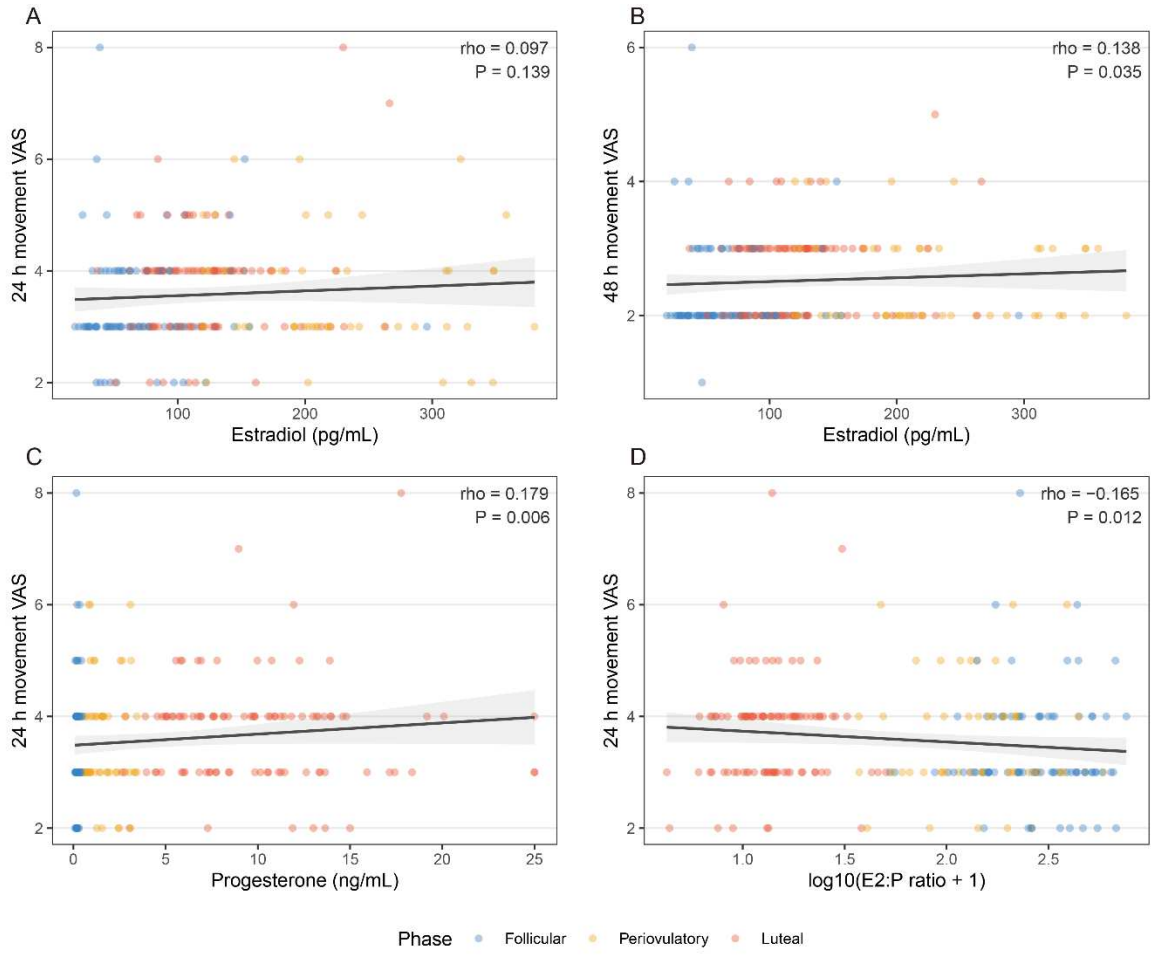



**Figure 3. Correlation scatter plot grouped by menstrual cycle stages.** (A) Spearman correlation analysis of estradiol and postoperative 24-hour movement VAS score; (B) Spearman correlation analysis of estradiol and postoperative 48-hour movement VAS score; (C) Spearman correlation analysis of progesterone and postoperative 24-hour movement VAS score; (D) Spearman correlation analysis of $\log_{10}$(estradiol/progesterone ratio + 1) and postoperative 24-hour movement VAS score.

### 3.5 Subgroup Analyses

In subgroup analyses for both 24-h and 48-h movement VAS, the direction of the luteal-phase effect was consistent across all subgroups (age, BMI, PCIA use, flurbiprofen axetil use, and operative duration), with no significant effect modification detected (all P-interaction > 0.1). For 48-h movement VAS, the effect was most pronounced among PCIA users ($\beta = 0.353$, $P = 0.029$), flurbiprofen axetil recipients ($\beta = 0.307$, $P = 0.005$), and patients with operative duration above the median (> 111 min; $\beta = 0.321$, $P = 0.027$) (Fig. 4).

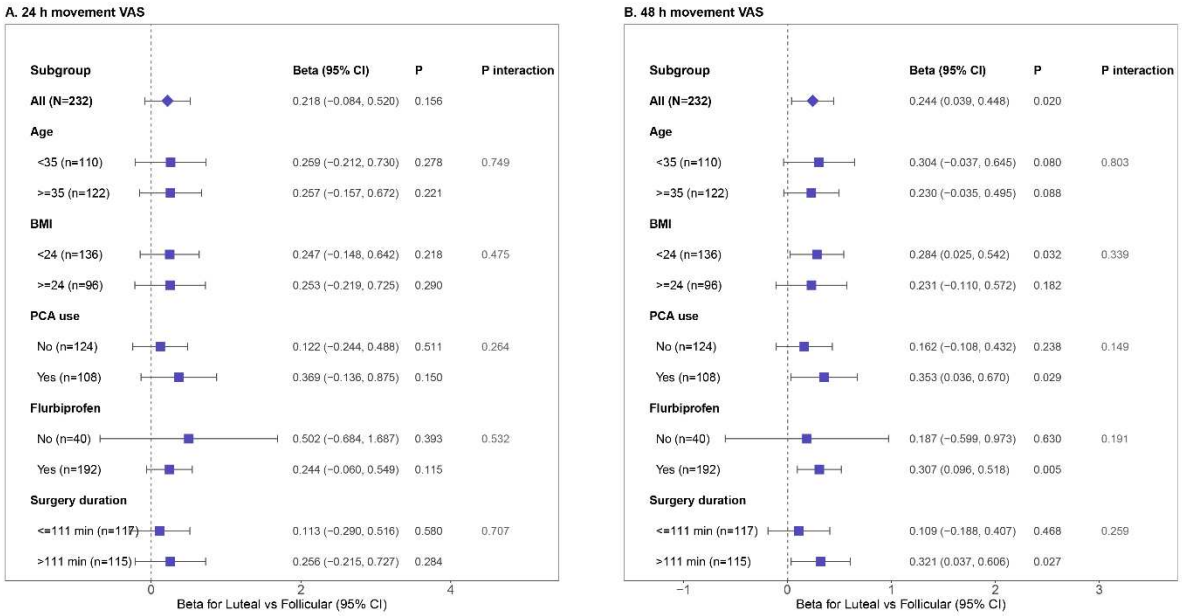



**Figure 4. Forest plot of subgroup analysis of postoperative VAS pain scores at 24 hours (A) and 48 hours (B) compared between luteal phase and follicular phase.**

## 3.6 Secondary Outcomes and Sensitivity Analyses

Adjusted logistic regression demonstrated significantly elevated PONV risk in the luteal phase (OR = 3.15, 95% CI: 1.53–6.71, $P = 0.002$), along with higher composite endpoint risk (OR = 3.51, 95% CI: 1.68–7.55, $P = 0.001$) and 24-h rescue analgesic use (OR = 2.48, 95% CI: 1.21–5.17, $P = 0.014$). Periovulatory PONV risk did not differ from the follicular phase (OR = 1.09, $P = 0.843$), although composite endpoint (OR = 2.81, $P = 0.015$) and rescue analgesic use (OR = 2.37, $P = 0.040$) were significantly higher than in the follicular group (Table 5).

Sensitivity analyses confirmed the robustness of the 48-h movement VAS finding across all five alternative strategies: binary classification (D1–14 vs D15–28: β = 0.191, $P = 0.040$), exclusion of the periovulatory group (β = 0.279, $P = 0.009$), additional CRP adjustment (β = 0.262, $P = 0.040$), expanded periovulatory definition to D14–D17 (β = 0.244, $P = 0.020$), and HC3 robust standard errors (β = 0.244, $P = 0.020$). The 24-h movement VAS did not reach significance in any sensitivity analysis (P range: 0.060–0.282), although the effect direction was consistently positive (Table S2).

**Table 5. Adjusted logistic regression for secondary outcomes**

| | PONV (OR) | | Composite (OR) | | Rescue 24 h (OR) | |
|---|---|---|---|---|---|---|
| **Characteristic** | **OR (95% CI)** | **p-value** | **OR (95% CI)** | **p-value** | **OR (95% CI)** | **p-value** |

| | PONV (OR) | | Composite (OR) | | Rescue 24 h (OR) | |
|---|---|---|---|---|---|---|
| **Characteristic** | **OR (95% CI)** | **p-value** | **OR (95% CI)** | **p-value** | **OR (95% CI)** | **p-value** |
| **Menstrual phase** | | | | | | |
| Follicular | ref | | ref | | ref | |
| Periovulatory | 1.09 (0.46, 2.57) | 0.843 | 2.81(1.24, 6.62) | **0.015** | 2.37 (1.04, 5.46) | **0.040** |
| Luteal | 3.15 (1.53, 6.71) | **0.002** | 3.51 (1.68, 7.55) | **0.001** | 2.48 (1.21, 5.17) | **0.014** |
| **Age (years)** | 0.99 (0.94, 1.05) | 0.738 | 0.99 (0.93, 1.05) | 0.706 | 0.97 (0.92, 1.02) | 0.298 |
| **BMI** | 0.96 (0.88, 1.04) | 0.325 | 0.91 (0.84, 1.00) | **0.039** | 0.93 (0.85, 1.00) | 0.063 |
| **Department** | | | | | | |
| Endocrine | ref | | ref | | ref | |
| GynOnc | 0.90 (0.38, 2.12) | 0.808 | 3.07 (1.20, 8.71) | **0.025** | 6.37 (2.73, 15.6) | **<0.001** |
| TCM | 0.61 (0.21, 1.64) | 0.337 | 3.25 (1.14, 10.5) | **0.035** | 4.18 (1.61, 11.2) | **0.004** |
| GenGyn | 0.53 (0.20, 1.33) | 0.185 | 3.86 (1.40, 12.1) | **0.013** | 3.89 (1.65, 9.48) | **0.002** |
| Urology | 0.76 (0.14, 3.84) | 0.742 | 0.63 (0.13, 3.21) | 0.568 | 0.48 (0.02, 3.11) | 0.513 |
| **Surgery duration (min)** | 0.98 (0.97, 1.0) | **0.005** | 0.99 (0.98, 1.00) | **0.014** | 1.00 (0.99, 1.01) | 0.944 |
| **Blood loss (mL)** | 1.01 (1.00, 1.03) | 0.051 | 1.00 (0.99, 1.02) | 0.637 | 1.00 (0.98, 1.00) | 0.327 |
| **PCIA use** | 5.92 (3.14, 11.5) | **<0.001** | 1.48 (0.77, 2.89) | 0.241 | 0.26 (0.13, 0.50) | **<0.001** |
| **Flurbiprofen axetil** | | | | | | |

| | PONV (OR) | | Composite (OR) | | Rescue 24 h (OR) | |
|---|---|---|---|---|---|---|
| **Characteristic** | **OR (95% CI)** | **p-value** | **OR (95% CI)** | **p-value** | **OR (95% CI)** | **p-value** |
| No | ref | | ref | | ref | |
| Yes | 0.65 (0.28, 1.48) | 0.304 | 0.49 (0.18, 1.21) | 0.137 | 1.05 (0.46, 2.46) | 0.915 |

Abbreviations: CI = Confidence Interval, OR = Odds Ratio

Composite = VAS≥4 OR rescue OR PONV. Ref: Follicular.

## 4 Discussion

This study explored the association between menstrual cycle phase and postoperative pain in 232 reproductive-age women who underwent elective laparoscopic surgery. The results showed that the M-VAS score at 24 hours did not differ between the luteal and follicular phases. Meanwhile, the direction of effect remained consistent across all secondary outcomes, with higher scores for activity- and rest-related pain at 48 hours, a higher proportion of moderate-to-severe pain, a higher rate of rescue analgesia use, and a higher incidence of PONV during the luteal phase. Therefore, while the data from this study do not yet prove that the menstrual cycle phase is a determining factor for early postoperative pain, they suggest that physiological changes associated with the menstrual cycle may help identify subgroups with a heavier burden of postoperative symptoms.

Several studies have shown that gonadal hormone fluctuations specific to the menstrual cycle may have significant effects on the central nervous system and pain perception [2, 12]. Estradiol and progesterone can influence descending inhibition at the spinal cord and brainstem levels through opioid, GABAergic, and monoaminergic pathways; both the absolute concentrations and rates of change of these hormones may play a role [13-16]. The effects of progesterone are bidirectional: its metabolite, allopregnanolone, exerts analgesic and sedative effects through positive modulation of GABA_A receptors, whereas progesterone itself can enhance neuronal excitability under specific conditions [16]; gonadal hormones can also directly alter the analgesic efficacy mediated by μ-opioid receptors (MOR) [13]. Studies have shown a significant correlation between increased pain perception and elevated serum progesterone levels and reduced estrogen levels [17]. However, evidence from experimental pain studies is inconsistent. One meta-analysis reported higher pain thresholds during the follicular phase in several non-electrical pain models [7]. Subsequent

reviews, however, emphasized that the magnitude and direction of the menstrual cycle's influence depend on the pain model, the definition of the menstrual cycle phase, and the method used to confirm ovulation [14]. This study employed a three-phase classification system designed to distinguish between a follicular phase characterized by low estradiol and low progesterone, a periovulatory phase characterized by higher estradiol, and a luteal phase characterized by higher progesterone. The expected distributions of estradiol and progesterone across the groups supported the biological plausibility of this classification at the group level. It is important to emphasize that this does not prove that the menstrual phase was accurately determined for every patient, nor does it confirm that the measured hormones caused the observed differences in pain.

The findings of this study are consistent with those of Piroli et al. [18]. That study included 60 young women who underwent gynecological laparoscopic surgery and reported that patients in the luteal phase experienced more severe pain than those in the follicular phase, with the difference being most pronounced 30 and 45 minutes postoperatively in the post-anesthesia care unit [18]. The earliest pain assessment point in that study was 24 hours, whereas the 48-hour time point at which differences emerged in the present study fell outside the observation window of that study. Therefore, while the two studies agree on the general trend of a heavier symptom burden during the luteal phase, they do not corroborate each other at any common time point. Additionally, differences in analgesic intensity may also play a role. In this study, nearly half of the patients used hydromorphone for patient-controlled analgesia (PCIA), which may have more effectively masked intergroup differences in the early postoperative period; in contrast, the other study employed continuous buprenorphine infusion combined with titrated tramadol, representing a different approach to early analgesia.

In a prospective observational study involving 80 women who underwent laparoscopic gynecological surgery, Miniksar et al. found no clear differences in postoperative pain scores across groups; however, patients in the luteal phase used more tramadol and pressed the patient-controlled analgesia (PCA) pump more frequently. Additionally, serum MOR concentrations were lower in the luteal phase group [19]. Sener et al. also reported that patients in the luteal phase following gynecological laparoscopic surgery had a higher demand for non-opioid analgesics and antiemetics, but the demand for opioids was similar across different phases of the menstrual cycle [20]. These studies collectively suggest that symptom scores do not necessarily correlate with analgesic usage, particularly when analgesic regimens are standardized or titrated based on patient-reported symptoms.

Therefore, it is reasonable to use multiple outcome measures rather than relying solely on a single VAS assessment. In this study, the adjusted odds ratio for moderate-to-severe pain complemented the finding of a small difference in mean VAS scores, suggesting that more patients in the luteal phase reached a clinically meaningful pain threshold.

Our study indicates that, after full adjustment, the effect of the luteal phase on M-VAS was positive at both 24 and 48 hours, but reached statistical significance only at 48 hours. The interaction between menstrual phase and time in the mixed-effects model was not statistically significant. Therefore, the available data do not support the conclusion that the menstrual phase influences pain exclusively at 48 hours postoperatively, nor do they support the notion that this effect increases over time. Differences in analgesic exposure, clinical pain assessment, and relatively small intergroup differences may all have contributed to these findings. After adjusting for PCIA use, the estimated effect at 24 hours was somewhat attenuated, suggesting that postoperative analgesic practices are closely related to the observed pain scores. Future prospective studies should predefine analgesic regimens, collect analgesic dosage as a time-resolved outcome, and employ repeated, standardized pain measurements to determine whether an interaction effect between menstrual phase and time truly exists.

The association between menstrual cycle phase and PONV is clinically significant, but uncertainty remains. In this cohort study, the luteal phase was independently associated with PONV and the composite endpoint. This finding is consistent with the study by Sener et al. [20], which observed higher rates of ondansetron use among patients in the luteal phase; however, they contradict the findings of a pilot study by Simurina et al. [21], which found a lower incidence of early PONV in patients in the luteal phase following elective gynecological laparoscopic surgery. This may be related to the fact that PONV is influenced by patient-specific factors, anesthetic techniques, opioid exposure, surgical approach, and prophylactic antiemetics. Subtle differences in the definition of menstrual cycle phases, the time window for PONV assessment, baseline risk criteria, and prophylactic regimens may all alter the observed associations. Further studies should be conducted to develop antiemetic recommendations tailored to specific phases of the menstrual cycle.

This study offers clinical insights and provides a useful reference for stratifying postoperative follow-up. For women of childbearing age undergoing gynecological laparoscopic surgery, the menstrual cycle can serve as a practical supplement to preoperative risk assessment, to be considered alongside established predictive factors such as surgical type, preoperative pain, dysmenorrhea, anxiety, and analgesic regimens [22, 23]. This may help identify patients who

require closer monitoring for pain and nausea after leaving the post-anesthesia care unit.

This study has several limitations. First, cycle staging was based on forward counting from the date of the last menstrual period and a uniform assumption of a 28-day cycle; however, empirical studies have shown that the consistency between the counting method and single hormone measurements in determining cycle phase is limited, and misclassification is difficult to avoid [24, 25]. A single preoperative blood draw cannot confirm whether ovulation has occurred, nor can it adequately characterize the rapid changes during the peri-ovulatory period and late luteal regression. At the group level, the distribution of estradiol and progesterone was consistent with physiological expectations for each phase, which supports the biological validity of the phase classification method at the population level but does not validate its accuracy at the individual level. Second, retrospective data cannot rule out residual confounders, including preoperative anxiety, pain catastrophizing, severity of dysmenorrhea, chronic pain, sleep quality, and unrecorded differences in surgical procedure type or postoperative care. Third, the use of rescue analgesia carries different implications for patients with and without PCIA, leading to information bias. Furthermore, since PCIA may influence both recorded pain scores and postoperative clinical decision-making, including it as a covariate in the model would complicate the causal interpretation of the effect estimates.

**Conclusion**

Among reproductive-age women undergoing elective gynecological laparoscopic surgery, after thorough adjustment, menstrual phase was not independently associated with the M-VAS score at 24 hours postoperatively. Patients in the luteal phase had slightly higher pain scores at 48 hours postoperatively, and moderate-to-severe pain, the use of rescue analgesia, and PONV were more common; however, the differences in pain intensity were below the minimum clinically important difference. These findings support further prospective studies to evaluate whether the menstrual cycle phase can serve as a reference factor for individualized perioperative risk assessment.

**Abbreviations:** ASA, American Society of Anesthesiologists; BMI, body mass index; CI, confidence interval; CRP, C-reactive protein; E2, estradiol; E2:P4, estradiol-to-progesterone ratio; LMP, last menstrual period; LMM, linear mixed-effects model; MME, morphine milligram equivalents; MOR, μ-opioid receptor; M-VAS, movement visual analog scale; OR, odds ratio; P4, progesterone; PACU, post-anesthesia care unit; PCIA, patient-controlled intravenous analgesia; PONV, postoperative nausea and vomiting; RCS, restricted cubic

spline; R-VAS, resting visual analog scale; VAS, visual analog scale.

## Ethics approval and consent to participate

This study was approved by the Institutional Review Board of Gansu Province Maternity and Child Care Hospital (Gansu Province Central Hospital) (approval No. 2025GSFY Ethics Review NO.159). The requirement for informed consent was waived by the same Institutional Review Board because of the retrospective nature of the study. The study was conducted in accordance with the Declaration of Helsinki and relevant guidelines and regulations.

## Consent for publication

Not applicable.

## Data availability

The datasets used and analyzed during the current study are available from the corresponding author on reasonable request.

## Conflicts of Interest

The authors declare no conflicts of interest related to this study.

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## Author Contributions

YC contributed to the conceptualization and design of the study. Y acquired and curated the clinical data. SS and FJ performed the formal analysis and visualization. XD developed the methodology and conducted statistical modeling. SS wrote the original draft of the manuscript. All authors contributed to the review and editing of the manuscript. All authors have read and approved the final manuscript.

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