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Effect of the menstrual cycle phase on post-operative pain perception and analgesic requirements

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Background: Research has shown that menstrual cycle phase may affect pain sensitivity. There is a lack of studies evaluating this effect on post-operative pain and analgesic needs. Methods: In this prospective cohort study, we determined the effect of menstrual cycle phase on pain perception and analgesic requirements following total abdominal hysterectomy. Sixty women with regular menstrual cycles undergoing elective surgery were recruited and divided into ‘follicular’ and ‘luteal’ groups according to their menstrual history. Post-operative pain was managed with intravenous patient-controlled analgesia using tramadol. Intravenous morphine was used for rescue analgesia, and pain was assessed for 24 h.

Results: Pain scores in the recovery room and ward six and 24 h post-operatively were similar in the groups at rest and on coughing. Pain scores at rest 12 h post-operatively were significantly higher in the luteal group (P = 0.043), while they were similar on coughing. There was no significant difference in the total tramadol requirement. Number of patients requiring rescue analgesia and the amount of morphine used was also similar.

Conclusion: There was no difference in pain scores or analgesic requirements between the two groups except for rest pain at 12 h, which was significantly higher in the luteal group. As pain was assessed at 13 different time points, a significant difference seen only at one point could be due to random chance. We suggest that future research should concentrate on studying this issue in patients of relatively younger age groups with more pronounced hormonal variations during the cycle.

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Influence of gonadal hormones on pain perception is an interesting area of pain-related research. Research on rats has shown that the effects of gonadal hormones mediate the enhanced female tactile and thermal hypersensitivity following L5 nerve root injury.1 Studies on women have shown differences in pain sensitivity and analgesic requirements during different phases of menstrual cycle.2–5 Most of these animal and human studies have used experimental pain stimuli to assess pain perception.2–5 Riley and colleagues6 have reported, in a meta-analysis of pain perception across the menstrual cycle, that most researchers have found pain threshold to be lower during the luteal and pre-menstrual phases, with the exception of electrical pain, which shows the opposite results. However, more recent research has not shown a consistent evidence for the effect of menstrual cycle on experimental painful stimuli in humans.7

Research on the effect of menstrual cycle on real-life acute pain, including post-operative pain, is scarce.8,9 Further research is required to see if the reports obtained from experimental and non-surgical pain are reproduced for post-operative pain. We could find only one study on the effects of menstrual cycle phase on analgesic requirements following laparoscopic gynaecological surgery.8 Further research examining these effects on moderate to severe post-operative pain will help in enhancing the understanding of post-operative pain management of the female patients. If significant differences are identified, the selection criteria for female participants of pain-related research may need to include their menstrual cycle phase.

This prospective cohort study was performed to determine the effect of the menstrual cycle phase on pain perception and analgesic requirements following total abdominal hysterectomy. We chose follicular and luteal phases of the cycle so as to compare data during different hormonal profiles.
Methods

Approval was obtained from the Ethical Review Committee (ERC) of the Aga Khan University (610-Ane/ERC-06). Recruitment of patients was done by the consultant gynaecologist involved in the study, who, at the time of scheduling the surgery, obtained informed consent. The post-operative analgesia and method of pain assessment was explained during pre-operative assessment by one of the anaesthetist involved in the study.

The inclusion criteria for patient selection were pre-menopausal women aged 35–48 years, belonging to American Society of Anesthesiologists (ASA) physical status I–II, having regular menstrual cycles of 28 to 32 days, undergoing an elective total abdominal hysterectomy for uterine fibroids through a pfannensteil incision under general anaesthesia. The patients were divided into two groups, ‘follicular’ or F and ‘luteal’ or L. The phase of menstrual cycle was decided on the basis of days counted from the first day of the last menstrual period. Days 6–12 were considered as the follicular phase and days 20–24 as the luteal phase. No surgery was scheduled during the menstrual period, i.e., days 1–5. As luteinizing hormone peaks on day 18 of an average normal menstrual cycle, patients on days 13 and progesterone starts to rise on day 18 of an average normal menstrual cycle, patients on days 13–19 of the cycle were excluded to better delineate the two phases. Patients in their pre-menstrual phase (day 25 to the beginning of menstruation) were also excluded, as progesterone levels start declining at this time. Other patients excluded were those undergoing surgery through a midline incision, or undergoing bilateral salpingo-oophorectomy or cancer surgery, those allergic to the study drugs, or unable to understand instructions, or having severe cardiac, hepatic or renal dysfunction or a history of convulsions, or taking regular analgesics, oral contraceptive pills or hormone replacement therapy. The consultant gynaecologist involved in the study saw the patients in the clinic and scheduled the surgeries according to the available operation theatre slots. On patient’s admission, she took a detailed menstrual history. Patients who fell in the specified days of the cycle and fulfilled the other inclusion criteria were recruited and assigned to the appropriate groups; those who did not were excluded. The groups were entered in the study form by her after the completion of data collection.

During pre-operative evaluation, all patients were instructed on the use of an 11-point numeric rating scale (NRS) by one of the researchers, with 0 = no pain and 10 = worst pain imaginable. The use of patient-controlled intravenous (IV) analgesia (PCIA) was also explained to the patients. All patients received pre-medication with oral midazolam 7.5 mg 1h before the induction of anaesthesia. At the time of IV cannulation in the operating room, a 5 ml blood sample was drawn from each patient and sent to the laboratory of Aga Khan University Hospital for measurement of oestradiol and progesterone levels before starting IV infusion of Ringer’s lactate solution. Oestradiol assay was performed by a solid-phase competitive chemiluminescent enzyme immunoassay on Immulite 2000 (Siemens, Munich, Germany), while progesterone assay was performed by an electrochemiluminescence immunoassay ‘ECLIA’ 2010 analyzer (Roche Diagnostic, Pleasanton, CA, USA). The laboratory participates in external quality control programme from Bio-Rad, UK.

Patient’s demographic data were recorded. The anaesthetic technique was standardized, and all patients received general anaesthesia with tracheal intubation and controlled ventilation. Electrocardiogram (ECG), non-invasive blood pressure, oxygen saturation, end-tidal carbon dioxide level and temperature monitoring were employed using Datex-Ohmeda S5 (Planer Systems, Inc., Beaverton, OR, USA) monitors. After administration of 100% oxygen, induction of anaesthesia was done with propofol 2–3 mg/kg, atracurium 0.5 mg/kg and tramadol 2 mg/kg, and trachea was intubated after 3 min of mask ventilation. Anaesthesia was maintained with nitrous oxide and oxygen mixture in a ratio of 60:40 and isoflurane 1–1.5%. After bladder catheterization, a 100 mg suppository of diclofenac sodium was administered to all the patients. A further bolus of tramadol 20 mg was given if heart rate or blood pressure increased by more than 20% of baseline during surgery. All procedures were performed through the pfannenstiel incision by one of two identified consultant gynaecologists. Neostigmine 2.5 mg with glycopyrrolate 0.5 mg was used for reversal of residual neuromuscular blockade, and trachea was extubated on opening of eyes to command.

ECG, non-invasive blood pressure, respiratory rate and oxygen saturation were monitored in the recovery room. Once responsive, the patients were asked to rate their baseline pain on the NRS of 0 to 10. The anaesthetist involved in data collection was blinded to the menstrual cycle phase of the patient. Pain was assessed every 10 min in the recovery room and was managed by IV tramadol boluses, 10 mg for
pain score of 3–5 and 20 mg for pain score of more than 5. If NRS did not decrease to less than 3 after two additional boluses of tramadol, rescue analgesia was provided with IV morphine in 2 mg aliquots. The degree of pain improvement was assessed 10 min after each intervention by using the five-point Likert scale (none, minimal improvement, much improvement, very much or complete pain relief). Once initial pain control had been achieved (NRS less than 3) in the recovery room, the PCA pump (Graseby 3300; SIMS Graseby Ltd; Watford Herts, UK, WD2 4LG) containing tramadol was attached with a bolus dose set at 10 mg and a lock-out interval of 10 min and no background infusion. IV metoclopramide was prescribed 8 hourly for 24 h. The patients were discharged from the recovery room after 60 min, provided they were haemodynamically stable and their pain score was less than 3.

Patients were followed up in the ward, and observations were made at 6, 12 and 24 h. Patients were asked to rate their pain at rest and on coughing. Data on tramadol demands (number of times PCA button pressed), amount delivered to the patient and total tramadol used in 24 h were retrieved from the PCA pump memory. Pain management strategy and indication for rescue analgesia was same as that for recovery room. Diclofenac sodium 100 mg suppository was used 12 hourly. The study groups were entered in the form by the gynaecology consultant after the 24-h observation period had been completed. The levels of oestradiol and progesterone were also obtained after 24 h.

Statistical analysis
To achieve 80% power at 5% level of significance with an anticipated difference in the pain score of at least 2 and standard deviation (SD) of 2.75 in each group, a total of 60 female patients equally divided into two groups was included in the study. As a similar study involving post-operative pain could not be retrieved, a difference of two in the pain scores was used in sample size calculation to achieve clearer appreciation of the difference in pain perception.

Data were double entered using EpiData version 3.2 (EpiData Association, Odense, Denmark), and analysis was done using Statistical Analysis Systems version 9.1 (SAS Institute Inc., Cary, NC, USA 2002–2008). The difference in pain intensity between the two groups and in tramadol requirement for post-operative analgesia was measured by using repeated-measures analysis of variance (ANOVA) for ordinal measures. Comparison of the number of patients with NRS score more than 3 in the two groups was also done by using repeated-measures ANOVA. The total dose of tramadol required to decrease the pain intensity was assessed using independent samples t-test.

Results
Sixty ASA physical status I–II pre-menopausal females with regular menstrual cycles of 28–32 days, aged 35–48 years, undergoing elective total abdominal hysterectomy for uterine fibroids, through a Pfannenstiel incision under general anaesthesia were included. It took more than 2 years to collect data on 60 female patients satisfying all the inclusion criteria, and none of the patients were excluded after recruitment. There was no difference in the demographic characteristics between the two groups (Table 1).

Hormone levels
Mean oestradiol levels were 25 (SD = 7.1) picogram/ml in the follicular group and 107 (SD = 68.5) picogram/ml in the luteal group (P = 0.0001). Similarly, mean progesterone levels were 0.36 (SD = 0.29) nanogram/ml in the follicular group and 3.6 (SD = 4.7) nanogram/ml in the luteal group (P = 0.0001). Thus, levels of both hormones were significantly increased in the luteal phase, as expected.

Assessment of pain
Recovery room. The difference in the mean pain score was not statistically significant between the follicular and the luteal groups at any point of measurement (Table 2).

In the ward at 6 h:
The difference in the mean pain score at rest and on coughing was not statistically significant

Table 1
Demographics and baseline haemodynamic parameters of the patients: mean (standard deviation).

<table>
<thead>
<tr>
<th></th>
<th>Follicular group</th>
<th>Luteal group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>41.67 (4.24)</td>
<td>42.60 (3.72)</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>68.06 (9.94)</td>
<td>66.37 (11.76)</td>
</tr>
<tr>
<td>Duration of surgery (min)</td>
<td>99.43 (30.47)</td>
<td>115.63 (37.79)</td>
</tr>
<tr>
<td>Baseline SAP (mmHg)</td>
<td>124.90 (13.29)</td>
<td>129.07 (13.13)</td>
</tr>
<tr>
<td>Baseline DAP (mmHg)</td>
<td>77.33 (8.87)</td>
<td>79.37 (8.04)</td>
</tr>
<tr>
<td>Baseline HR (beats/min)</td>
<td>82.77 (11.47)</td>
<td>83.70 (12.64)</td>
</tr>
</tbody>
</table>

SAP, systolic arterial pressure; DAP, diastolic arterial pressure; HR, heart rate.
In the recovery room, the mean pain score at rest was significantly higher during the luteal phase ($P = 0.043$), whereas there was no difference in the pain on coughing (Table 2). At 12 h, two patients in the follicular group and five in the luteal group reported a pain score higher than 3 ($P = 0.235$).

In the ward at 12 h. The mean pain score at rest was similar in the two groups (Table 2). On coughing, one patient in each group had a score higher than 3 at 24 h.

**Tramadol requirement**

Tramadol requirement during the intraoperative period, in the recovery room and ward is shown in Table 3. No significant difference was seen between the two groups in the total tramadol administered and the number of patients who required additional tramadol boluses intraoperatively. The mean dose of tramadol required as boluses in the recovery room was also similar. There was no difference in the number of patients requiring rescue analgesia and the amount of morphine used. The difference was also not significant between the two groups in the number of demands on PCIA and the total tramadol consumed in 24 h (Table 3).

**Hormonal levels and pain**

Correlations were sought between oestradiol and progesterone levels and tramadol requirement and pain scores as additional data analysis, although the study was not powered for this analysis. Very weak negative correlation was found between oestradiol levels and tramadol requirement ($r = -0.108$), and weak positive correlation was found between progesterone levels and tramadol requirement ($r = 0.246$). Correlations of oestradiol and progesterone levels with pain scores were also weak ($r = 0.200$ and 0.269 respectively).

**Discussion**

We did not find a significant difference between the groups in the recovery room or at 6 and 24 h post-operatively, as regards their pain scores or analgesic consumption. Most research on the effect of menstrual cycle phase on pain perception and response has been conducted using experimental pain, and there is relatively limited data for clinical pain. Pain threshold to cold pressor pain was found to be lower during the pre-menstrual (luteal) phase by Hapidou and De Catanzaro,$^{12}$ and Goolkasian demonstrated increased discrimination of noxious heat during the ovulatory phase.$^{13}$ No difference in responses to electrical or cold pressor pain was found in the different phases of menstrual cycle by Veith and colleagues.$^{14}$ Fillingim and colleagues have reported that women with pre-menstrual syndrome show increased pain sensitivity during the pre-menstrual period.$^{15}$ Rao and colleagues also demonstrated low pain threshold to mechanical stimulus during the pre-menstrual phase.$^{16}$ However, there is marked variability in the way different researchers have identified the phases of menstrual cycle. In addition, some studies have not measured plasma levels of gonadal hormones and have relied on menstrual history alone to determine the phase. The type of experimental pain stimulus also varies considerably. All these discrepancies in methodology make it difficult to compare results.

Effect of menstrual cycle has been studied in some chronic pain conditions.$^{17,18}$ Increased pain-related symptoms have been reported towards the end of the menstrual cycle and during menstruation in women with temporomandibular pain disorder by LeResche and colleagues.$^{17}$ Sherman and co-researchers also reported that women having temporomandibular disorder showed higher palpation pain intensity at mid-luteal phase and at menarche.$^{18}$ Very limited data are available on the effect of

### Table 2

<table>
<thead>
<tr>
<th>Time</th>
<th>Follicular group (n = 30)</th>
<th>Luteal group (n = 30)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recovery room On arrival</td>
<td>3.73 (2.47)</td>
<td>3.00 (2.87)</td>
<td>0.328</td>
</tr>
<tr>
<td>10 min</td>
<td>4.27 (2.46)</td>
<td>3.77 (2.20)</td>
<td>0.411</td>
</tr>
<tr>
<td>20 min</td>
<td>4.27 (2.14)</td>
<td>4.23 (2.22)</td>
<td>0.953</td>
</tr>
<tr>
<td>30 min</td>
<td>4.10 (2.05)</td>
<td>3.83 (2.16)</td>
<td>0.627</td>
</tr>
<tr>
<td>40 min</td>
<td>3.67 (2.10)</td>
<td>3.33 (1.91)</td>
<td>0.524</td>
</tr>
<tr>
<td>50 min</td>
<td>2.93 (1.74)</td>
<td>2.77 (1.92)</td>
<td>0.726</td>
</tr>
<tr>
<td>60 min</td>
<td>2.30 (1.31)</td>
<td>2.20 (1.54)</td>
<td>0.788</td>
</tr>
<tr>
<td>Ward (at rest) 6 h</td>
<td>1.43 (1.07)</td>
<td>1.73 (1.46)</td>
<td>0.368</td>
</tr>
<tr>
<td>12 h</td>
<td>0.70 (0.75)</td>
<td>1.17 (0.98)</td>
<td>0.043*</td>
</tr>
<tr>
<td>24 h</td>
<td>0.57 (1.13)</td>
<td>0.57 (0.73)</td>
<td>&gt; 0.999</td>
</tr>
<tr>
<td>Ward (on coughing) 6 h</td>
<td>2.67 (1.51)</td>
<td>2.93 (1.83)</td>
<td>0.542</td>
</tr>
<tr>
<td>12 h</td>
<td>1.90 (1.18)</td>
<td>1.18 (1.72)</td>
<td>0.488</td>
</tr>
<tr>
<td>24 h</td>
<td>1.50 (1.35)</td>
<td>1.30 (1.17)</td>
<td>0.545</td>
</tr>
</tbody>
</table>

*Significant difference.
menstrual cycle phases on perception of acute pain. Hanci and colleagues found that patients in their luteal phase reported significantly higher propofol injection pain scores compared with those in their follicular phase. They have explained this on the basis of changes in oestrogen and progesterone levels during the menstrual cycle as oestrogen levels may influence mood and well-being in a favourable manner, while progesterone levels, known to be high in the luteal phase along with low beta-endorphin levels, might cause the increased pain sensitivity during this phase.

In our study, the menstrual cycle phase was determined by history, and blood was drawn for hormone assays to verify the phase. The levels of oestradiol and progesterone correlated with phases determined by history. Oestradiol has been found to play a critical role in the pain modulation system of female mice. Administration of oestradiol and progesterone to mimic pregnancy in rats has shown to produce analgesia. LeResche and co-researchers have reported that temporomandibular pain in women is highest at times of lowest oestrogen. Sherman and LeResche have suggested that standardizing the timing of data collection to times of highest and lowest hormone levels is important to obtain reliable results. We found weak correlations between hormone levels, pain perception and tramadol requirements, but could not retrieve any study addressing the effect of oestradiol and progesterone on acute post-operative pain. Furthermore, other factors like behavioural, psychological and social factors might play a role in the patient’s response to pain, therefore, it is difficult to state that oestrogen and progesterone are alone responsible for any differences in pain perception.

In our study, the pain scores and the mean dose of tramadol used in the recovery room was similar in the two groups. Sener and colleagues studied the effects of menstrual cycle on post-operative analgesic requirements after gynaecological laparoscopy. They used fentanyl in the recovery room and metamizol in the ward. They also found similar fentanyl requirements in the recovery room. The mean pain score at 6 and 24 h was also similar in the two groups in our study, both at rest and on coughing. However, rest pain scores at 12 h were significantly higher in the luteal phase ($P = 0.043$), although they were similar on coughing. When measuring pain intensity at 13 different time points in each patient, as done in our study, the finding of statistically significant difference only at one point is very likely to be by random chance, especially when the pain score on coughing at the same time point was similar in the two groups. The mean pain scores at 12 and 24 h are low in our study. This could be due to the fact that all patients had a lower abdominal transverse incision and they effectively used PCA to an acceptable level of analgesia. Unlike our negative results with post-operative pain, Riley and colleagues, in their meta-analysis of studies done with experimental pain, reported enhanced pain sensitivity during the luteal phase for most painful stimuli. It has been suggested that mood changes and decrease in beta-endorphin levels in the late luteal phase may change the perception of pain.

The overall tramadol consumption during 24 h and use of morphine for rescue analgesia in our study was also similar in the follicular and the luteal phases, while Sener and colleagues found that metamizol consumption in the ward after gynaecological laparoscopy was highest in the luteal phase. In a recent study on experimental pain,
Ribeiro-Dasilva et al.\textsuperscript{24} report that in women with normal menstrual cycles, morphine analgesia for ischemic pain and morphine side effects were significantly greater in the follicular vs. the luteal phase. They conclude that sex hormones may influence opioid responses. A five-point Likert scale was used by us to assess the degree of improvement in pain relief 10 min after administration of additional tramadol or morphine boluses, when required. If an improvement was made, the patient was asked to again rate their pain on NRS of 0 to 10. Requirement of further boluses was decided on the NRS score. Therefore, to avoid confusion due to the use of two different scales after each analgesic intervention and to ensure uniformity in assessment and management of pain, which was our main aim, only pain scores on NRS were reported.

Ascertaining the phase of menstrual cycle by careful history taking and confirming it by assessing oestradiol and progesterone levels are the strengths of our study. As explained by Becker et al.,\textsuperscript{25} grouping study participants by stage of the menstrual cycle defined on the basis of timing or other criteria such as changes in basal body temperature could be unreliable, because there are large inter-individual differences at each stage. In addition, self-reports of menstrual cycle phase are often unreliable. They recommend that, because the menstrual cycle is only a rough index of the hormonal profile, it is therefore better methodology to directly measure ovarian hormones at the time of study and classify women into groups accordingly.

There are a few limitations in our methodology. Firstly, between-subject designs to study pain perception may make result interpretation difficult because there could be considerable inter-patient variability in the timing of the menstrual phases. This makes it very difficult to match the timing of the painful stimulus among patients. Sherman and LeResche,\textsuperscript{21} in their methodological review of experimental pain response across the menstrual cycle have concluded that standardized timing of painful sessions is important in the replication of significant findings. This has proved to be practically difficult even in experimental studies, where the researcher has much more control on the timing of the stimulus. Secondly, pain levels were generally quite low in our patients, which may have reduced the ability to detect the menstrual cycle effects. Lastly, because of our choice of surgical procedure, being total abdominal hysterectomy, our patients were aged 40 years or more, therefore, it was not possible for us to study younger patients in whom there is a likelihood of more marked hormonal variations during the menstrual cycle and differences could be better detected if present. More research is required in acute post-operative pain to further explore this interesting issue. We recommend that future research on this subject should include a surgical procedure other than total abdominal hysterectomy so that influence of menstrual cycle phases on post-operative pain perception and analgesic requirement could be studied in patients of relatively younger age group. In conclusion, a clinically significant effect of the menstrual cycle phase on post-operative pain scores and tramadol consumption was not demonstrated following total abdominal hysterectomy in our study.

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