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ORIGINAL RESEARCH ARTICLE

Association of menstrual cycle and postoperative quality of recovery in premenopausal women: a prospective cohort study

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Abstract

Background: Women have poorer quality of postoperative recovery from general anaesthesia than men. This persists for at least 3 days postoperatively, and is more pronounced in premenopausal women. Studies of menstrual cycle effects on pain or postoperative nausea and vomiting report conflicting results. Our aim was to determine whether menstrual cycle phase is associated with quality of recovery after surgery in premenopausal women.
Methods: Eligible women aged 18–45 yr undergoing wisdom teeth extraction or laparoscopic cholecystectomy under general anaesthesia with volatile agents were recruited from Epworth HealthCare Richmond in Melbourne, Australia from 2019 to 2021. Menstrual history and progesterone levels were used to determine cycle phase (luteal or non-luteal). Linear mixed and generalised linear regression models were fitted to examine differences in Quality of Recovery-15 (QoR-15) score on postoperative days 1 (primary outcome) and 3, and secondary outcomes (pain, analgesic effectiveness, postoperative nausea and vomiting, prolonged hospital admission), between groups, adjusting for confounders.
Results: A total of 177 women were recruited (74 luteal, 103 non-luteal). Six (3%) underwent laparoscopic cholecystectomy. Estimated mean differences (95% confidence interval; *P*-value) in adjusted QoR-15 scores between luteal and non-luteal groups were −0.05 (−5.86 to 5.76; *P*=0.986) and 1.40 (−4.41 to 7.21; *P*=0.636) on postoperative days 1 and 3, respectively. Secondary outcomes were not different between groups.
Conclusions: There was no significant difference in postoperative QoR-15 score or other outcomes between women in the luteal and non-luteal phases of their cycle. Women can be reassured that cycle phase does not impact postoperative quality of recovery when undergoing minor surgery under general anaesthesia.
Clinical trial registration: ACTRN12618000240246.

Keywords: hormonal cycle; menstrual cycle; postoperative nausea; postoperative pain; postoperative recovery; premenopausal; quality of recovery

Women generally have a poorer quality of postoperative recovery from general anaesthesia than men, in part because of higher pain scores and increased postoperative nausea and vomiting (PONV).[1–6] This finding persists for at least 3 days postoperatively, and is more pronounced in premenopausal compared with postmenopausal women.[1] The reasons for this are not fully elucidated, although differences in sex steroid

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levels including progesterone and oestrogen may be responsible.

Clinical studies have attempted to delineate the relationship between menstrual cycle and PONV, but have shown conflicting results.[7–11] A systematic review suggested that there is no effect on PONV,[12] but it was limited by the quality of the included studies. A blinded, randomised controlled trial found that women in the luteal phase have significantly higher pain scores in response to propofol injection,[13] and a brain imaging study has shown significantly different pain responses and brain activation patterns between the two cycle phases.[14] However, a meta-analysis of the experimental pain literature concluded that inconsistent nomenclature and methodological problems made it difficult to draw any inferences on pain sensitivity across the hormonal cycle.[15] Two small clinical studies have shown no significant relationship between cycle phase and postoperative pain scores and analgesic consumption.[16,17]

The majority of these studies concerning pain and PONV have a moderate to high degree of misclassification bias and other methodological problems including suboptimal study designs, small sample sizes and confounding. Furthermore, no study has attempted to determine the effect of cycle phase on overall postoperative quality of recovery (pain, PONV, functional and emotional recovery) in this population. Quality of postoperative recovery is a patient-centred outcome frequently assessed in perioperative medicine studies. Assessing the relationship between cycle phase and quality of recovery will assist in determining whether cycle phase is an unmeasured confounder of recovery in studies of other exposures involving premenopausal women.

We hypothesised that menstrual cycle phase is associated with the quality of postoperative recovery in premenopausal women undergoing general anaesthesia.

Methods

Study design and setting

This single-centre prospective cohort study was conducted from May 2019 to October 2021 at Epworth HealthCare Richmond, a university-affiliated tertiary private hospital in metropolitan Melbourne, Australia. Ethical approval was obtained from the Epworth HealthCare Human Research Ethics Committee (EH2017-205) and on its dissolution, from the Alfred Ethics Committee (691/18). Written informed consent was obtained from all participants. The study was prospectively registered with the Australian New Zealand Clinical Trials Registry (ACTRN12618000240246). This manuscript adheres to the applicable Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines.[18]

Participants

Eligible participants were women aged from 18 to 45 yr scheduled to have general anaesthesia for wisdom teeth extraction or laparoscopic cholecystectomy. Women were excluded if they were using hormone contraception, receiving sex hormone therapy, pregnant, lactating, had undergone a bilateral oophorectomy, or were known or suspected to be peri- or post-menopausal. They were also excluded if they were unable to provide informed consent or complete the 15-item Quality of Recovery-15 (QoR-15) score, or had previously participated in this study. Women with active cancer, regular opioid use, or systemic disease affecting daily function were excluded as these conditions may unduly affect quality of recovery. Dexamethasone is frequently administered during these procedures; thus, any participant with diabetes mellitus (in whom dexamethasone may raise blood glucose levels), a contraindication to dexamethasone, or receiving systemic steroid treatment for any condition, was also excluded.

Exposure variables

Menstrual cycle phase cannot be reliably classified according to patient history alone; therefore, it was determined using a combination of patient-reported menstrual cycle history and preoperative blood progesterone level. Blood for progesterone level testing was taken at the time of routine preoperative intravenous cannula insertion. Samples were collected into a BD Vacutainer® Serum Separating Tube (SST) II Advance, allowed to clot, then centrifuged before analysis. Samples were transported and analysed at 20–25°C. Progesterone levels were analysed using the Roche Elecsys Progesterone competitive immunoassay on the Roche Diagnostics (cobas e801), Mannheim, Germany. The laboratory's progesterone reference range was 5.3–86 nmol L^{-1} for the luteal phase and 0.6–4.7 nmol L^{-1} for the follicular phase. At progesterone concentrations of 2.65, 39.6, and 85.5 nmol L^{-1}, the coefficient of variation was 6.43%, 3.53%, and 3.35%, respectively.

Cycle phases are traditionally grouped into follicular, mid-cycle/ovulation (luteinising hormone peak), and luteal (progesterone peak) (Supplementary Fig. S1). Patients are unlikely to be able to anticipate and book surgery for the brief mid-cycle phase; therefore, classification into two groups – luteal and non-luteal – was most clinically relevant.

Group classification for all study participants was determined by one author (SL), who was blinded to all study outcomes. To determine menstrual phase on the day of surgery, we compared each participant's progesterone level to her menstrual cycle history (regularity of cycle and first date of last menstrual period). Participants with regular cycles, known date of last menstrual period, and confirmatory progesterone levels were assigned to luteal or non-luteal groups. Participants with irregular cycles or unknown first date of last menstrual period, whose progesterone levels could not be correlated with their cycle phase, were excluded from analysis.

Outcome variables

Primary outcome

The concept of a 'good recovery' is patient-centred; thus, it is the patient's assessment of their recovery that is of interest. The QoR-15 score is a reliable, well-validated, multidimensional patient-reported quality of recovery scale.[19] Fifteen questions assess the domains of pain, physical comfort, physical independence, emotions, and psychological support (Supplementary Fig. S2). The continuous scale ranges from 0 (extremely poor recovery) to 150 (excellent recovery). QoR-15 was measured at admission on the day of surgery and 24 h postoperatively (measured from arrival in the post-anaesthetic care unit), when participants were expected to have been discharged home.

Secondary outcomes

1. The QoR-15 score on Day 3 after surgery.

2. Pain Numeric Rating Scale (NRS) — the worst NRS at rest and on movement, in the past 24 h, as reported by the patient. NRS is a commonly used simple and effective method of assessing perioperative pain intensity,[20] ranging from 0 (no pain) to 10 (worst pain imaginable).
3. The subjective analgesic effectiveness scale — in the past 24 h, as reported by the patient. To the question, 'How effective was your medication in relieving the pain?', the response options included 'poor', 'fair', 'good', 'very good', and 'excellent'.
4. PONV Impact Scale — in the past 24 h, as reported by the patient (Supplementary Fig. S3). Assessment of PONV is complex; the PONV Impact Scale is the only currently validated scale in the postoperative setting[21] that assesses intensity, duration, and impact of PONV. Clinically important PONV is present if the summed score of two questions (each question is scored from 0 to 3) is 5 or more out of 6.
5. Unplanned or prolonged hospital admission owing to pain or PONV, according to standard durations of admission in Australia.

Other variables

The two surgical procedures (wisdom teeth extraction and laparoscopic cholecystectomy) were chosen because they each have defined but differing surgical and anaesthetic techniques, analgesic requirements, and recovery phases, and are common in this group of participants. Extraction of wisdom teeth is considered minor extra-cavity surgery, involving general anaesthesia of approximately 30 min, intraoral local anaesthetic blocks, and simple intraoperative analgesia. Patients are admitted and discharged on the day of surgery, with an expected return to daily function within 1–2 days. Postoperative analgesia consisted of paracetamol, a non-steroidal anti-inflammatory analgesic, and an opioid as required. Laparoscopic cholecystectomy is considered intermediate intra-abdominal surgery, involving relaxant general anaesthesia of approximately 1.5 h and multimodal analgesia including opioids. Patients are admitted on the day of surgery and discharged the following morning, with an expected return to daily function within 3–5 days. The use of two surgical models was planned to allow exploration of effect modification by degree of surgery (minor and intermediate).

General anaesthesia was maintained with volatile anaesthesia in an air/oxygen mixture. There was no restriction on use of analgesics or antiemetic prophylaxis.

Participant age, BMI, smoking status, motion sickness, medical comorbidities, and anaesthetic technique (neuromuscular blocking agents, use of opioid analgesia and antiemetic prophylaxis) were collected. Mental health status was not considered as a potential confounder as QoR-15 score includes the domains of emotional state, and specifically asks about feelings of anxiety and depression, so mental health was captured in the outcome. Furthermore, mental health status may be a mediating factor of the phase of menstrual cycle and QoR-15 relationship, rather than a confounder.

Scheduling of elective surgery at the study hospital is determined by patient choice of available times on their chosen surgeon's operating list. This choice is often determined by study, work, and family commitments. Preoperatively, participants were asked whether scheduling of surgery was determined by menstrual cycle phase, and their willingness to schedule future surgery around timing of cycle if an effect was found.

Data sources/measurement

Potential participants were identified from elective surgical lists and telephoned by a research coordinator 1–2 days preoperatively, to discuss the study. A research coordinator obtained written informed consent on the day of admission for surgery, then collected preoperative data. Intraoperative data were prospectively collected by research coordinators and the treating anaesthetist. These data were recorded in a paper case report form, and subsequently entered into a secure electronic database.

On receipt of a text and email reminder on postoperative days 1 and 3, participants self-reported the primary and secondary outcomes via a webpage link which directly entered the data into the electronic database.

Study size

Based on a power analysis for a two-sample means test, a total of 170 women undergoing either minor or intermediate surgery allowed us to detect a minimum clinically important difference of 8 points[22] in mean QoR-15 score (primary outcome) 24 h postoperatively (primary time point) between women in the luteal phase and women in the non-luteal phase of their cycle, with 80% power at the two-sided 5% level of significance. This assumes an imbalance in sample size between the two cycle phase groups of 40/60 (i.e. 68 *vs* 102), an equal standard deviation of 18 points[5] in both groups, and no correlation between the QoR-15 score at admission on the day of surgery and 24 h postoperatively (conservative).

To account for an anticipated 5% missing data in the primary outcome, a total of 180 participants was required. With approval from the overseeing Ethics Committee, the sample size was increased to 191 participants in July 2021 to account for anovulatory patients who cannot be classified into luteal or non-luteal groups.

Statistical methods

The statistical analysis plan was approved by the primary and statistical authors before analysis began. A linear mixed model was used to examine the association between QoR-15 score 24 h postoperatively and the menstrual cycle phase (luteal or non-luteal) with a random intercept to account for the clustering of observations within patients. The response consisted of all scores (baseline, 24 h, and 3 days postoperatively) and the model included factors representing exposure group (luteal and non-luteal), time point, and exposure by time-point interaction. The absolute difference in mean QoR-15 between luteal and non-luteal cycle phase was estimated (including two-sided 95% confidence interval) at 24 h (primary time-point) and 3 days (secondary time-point) postoperatively. The difference in the effect between the two types of surgery (minor, intermediate) was explored by including an interaction term between surgery and menstrual cycle phase in the model if the numbers within each surgery type allowed for this analysis. Unadjusted models and models adjusted for the following pre-specified potential confounders, were fitted for all analyses: age (yr), BMI (kg m^{-2}), surgery type (minor/intermediate), current smoker (Yes/No), history of PONV (Yes/No), history of motion sickness (Yes/No), number of antiemetics in theatre (0, 1, or 2), number of antiemetics in recovery (0, 1, or 2), opioids in theatre (Yes/No), and opioids in recovery (Yes/No).

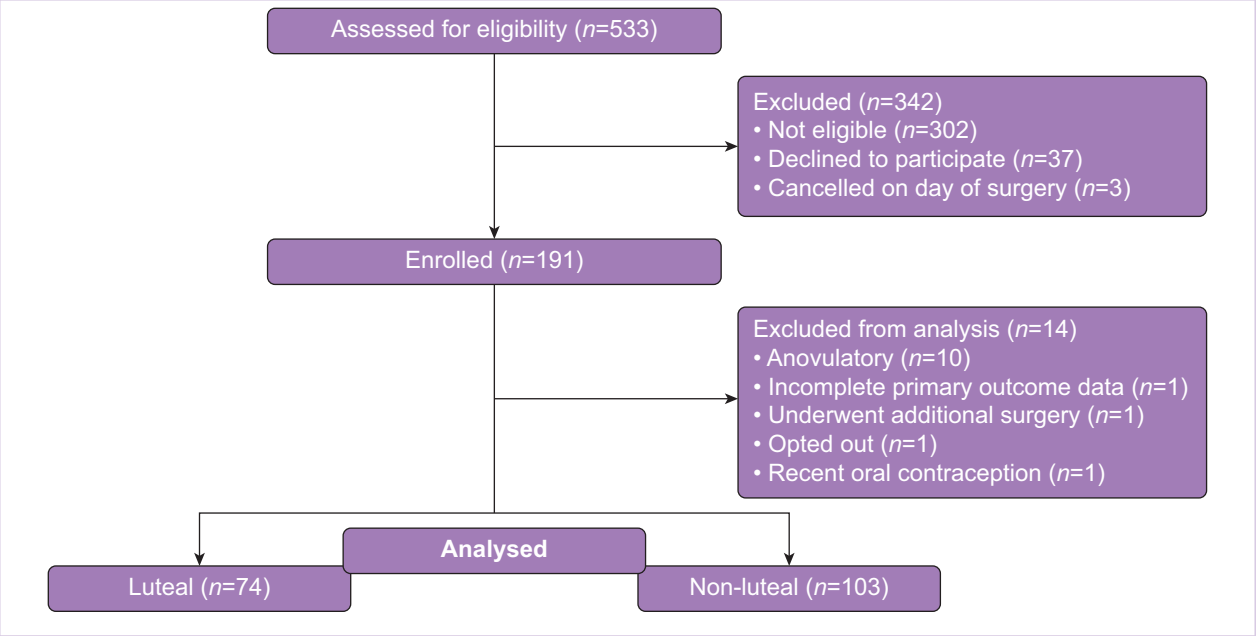

Fig 1. Study flow diagram.

Unadjusted and adjusted linear, ordinal logistic and logistic regression models were fitted for the secondary outcomes of pain Numeric Rating Score (continuous), Subjective Analgesic Effectiveness scale (ordinal), impact of PONV (binary), and unplanned or prolonged hospital admission owing to pain or PONV (binary). The Brant test was used to assess the validity of the proportional odds assumption for the ordinal logistic regression model. Appropriate diagnostics plots, such as residual *vs* fitted values, were used to assess modelling assumptions for linear regression models, linear mixed-effects models, and logistic regression models.

Table 1 Participant characteristics by exposure group (luteal and non-luteal cycle phase). Continuous variables presented as median [25th percentile, 75th percentile]. Categorical variables presented as absolute value (percentage). PONV, postoperative nausea and vomiting.

Variable	Category	Luteal (*n*=74)	Non-luteal (*n*=103)
Progesterone (nmol L^{-1})		31.2 [17.5, 40.8]	0.6 [0.3, 1.0]
Age (yr)		25 [21, 32]	23 [19, 30]
Height (cm)		165 [162, 170]	165 [160, 170]
Weight (kg)		61.5 [52.2, 68.0]	65.0 [57.5, 72.0]
ASA physical status	1	64 (86.5)	83 (80.6)
	2	10 (13.5)	20 (19.4)
BMI (kg m^{-2})		22.1 [19.9, 24.2]	23.5 [21.3, 26.6]
Surgery	Wisdom teeth extraction	71 (96.0)	100 (97.1)
	Laparoscopic cholecystectomy	3 (4.1)	3 (2.9)
Smoker		6 (8.1)	11 (10.7)
History of PONV		9 (12.2)	7 (6.8)
History of motion sickness		24 (32.4)	33 (32.0)
Opioid analgesia in theatre		65 (87.8)	86 (83.5)
Opioid analgesia in recovery unit		14 (18.9)	12 (11.7)
Number of antiemetic(s) in theatre (in addition to dexamethasone)	0	34 (46.0)	45 (43.7)
	1	39 (52.7)	54 (52.4)
	2	1 (1.4)	4 (3.9)
Number of antiemetic(s) in recovery unit	0	70 (94.6)	95 (92.2)
	1	4 (5.4)	6 (5.8)
	2	0	2 (1.9)
Reversal with neostigmine		2 (2.7)	1 (1.0)

Results

Of 533 women approached to participate in this study, 191 women were eligible and consented to participate (Fig. 1). Overall, 177 (93%) women were included in the primary and secondary analyses. Very few participants (n=6; 3%) underwent laparoscopic cholecystectomy, meaning analyses exploring differences in relationships by surgery type were not possible.

Participant characteristics were similar in the luteal and non-luteal groups (Table 1); excluded participants also had similar characteristics (data not shown).

QoR-15 scores for luteal and non-luteal groups at each time-point are reported in Table 2 and Figure 2. We found no significant difference in the QoR-15 score between women in the luteal or non-luteal menstrual cycle phase on either Day 1 or Day 3 postoperatively. These findings were unchanged after adjusting for confounders (Table 3).

There was no significant difference between groups in the unadjusted and adjusted secondary outcomes of pain NRS at rest or on movement at 1 day postoperatively, or the Subjective Analgesic Effectiveness Scale (Table 3). Only one and two women, respectively, in the luteal and non-luteal groups had clinically significant PONV. No women had an unplanned or prolonged hospital admission.

Preoperatively, 95.5% of included participants said that scheduling of their surgery was not determined by menstrual

Table 2 Outcomes by exposure group (luteal and non-luteal cycle phase). Continuous variables presented as median [25th percentile, 75th percentile]. Categorical variables presented as absolute value (percentage). *Subjective Analgesic Effectiveness scale: 1, poor; 2, fair; 3, good; 4, very good; 5, excellent. NRS, Numeric Rating Scale; QoR-15, 15-item Quality of Recovery.

Outcomes	Category	Luteal (n=74)	Non-luteal (n=103)
QoR-15 on admission		141.5 [135.0, 147.0]	140.0 [132.0, 146.0]
QoR-15 on Day 1		100.0 [91.2, 115.8]	103.0 [87.0, 120.5]
QoR-15 on Day 3		113.0 [99.2, 129.0]	111.0 [97.0, 125.0]
Worst pain NRS at rest		5.4 [3.2, 7.0]	5.5 [2.9, 6.3]
Worst pain NRS on movement		6.0 [4.1, 7.4]	6.1 [3.9, 7.8]
Subjective Analgesic Effectiveness scale*	1	0	9 (1.0)
	2	7 (9.5)	12 (11.7)
	3	24 (32.4)	24 (23.3)
	4	28 (37.8)	46 (44.7)
	5	15 (20.3)	20 (19.4)
Clinically significant PONV		1 (1.4)	2 (1.9)
Discharge delay		0	0

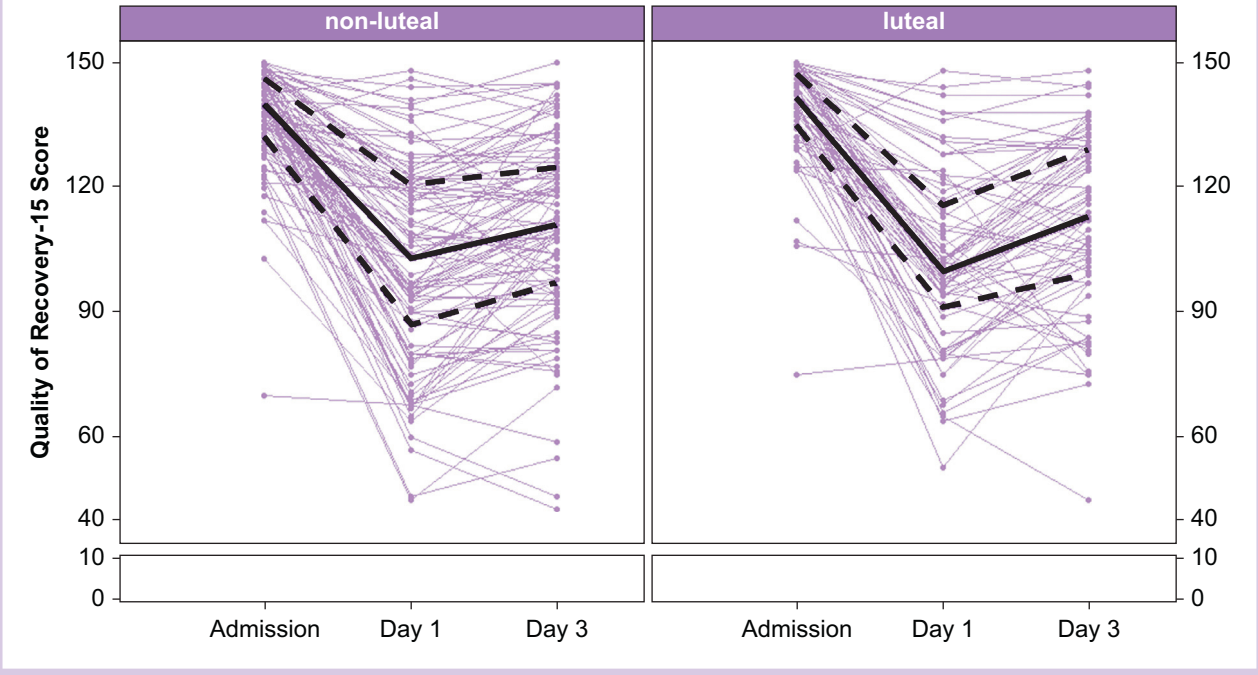

Fig 2. Patient 15-item quality of recovery scores, with median (solid line), and 25th and 75th percentiles (dashed lines) at each time point by cycle phase.

Table 3 Estimates (95% confidence intervals) of the association between outcomes and cycle phase (luteal *vs* non-luteal) derived from unadjusted and adjusted models. Models were a linear mixed model (outcome: QoR-15 on Day 1 and Day 3; estimate is the mean difference), linear regression (NRS; estimate is the mean difference) and ordinal logistic regression (Subjective Analgesic Effectiveness scale; estimate is the odds ratio). *Adjusted for patient age, BMI, surgery type (minor/intermediate), smoking status, history of postoperative nausea and vomiting, history of motion sickness, number of intraoperative antiemetics, number of antiemetics in recovery, intraoperative opioids, opioids in recovery. NRS, Numeric Rating Scale; QoR-15, 15-item Quality of Recovery.

Outcomes	Unadjusted	P-value	Adjusted*	P-value
QoR-15 on Day 1	0.29 (−5.55, 6.14)	0.92	−0.05 (−5.86, 5.76)	0.99
QoR-15 on Day 3	1.74 (−4.1, 7.59)	0.56	1.4 (−4.41, 7.21)	0.64
Worst pain NRS at rest	0.03 (−0.71, 0.77)	0.94	0.12 (−0.61, 0.85)	0.75
Worst pain NRS on movement	−0.11 (−0.84, 0.62)	0.77	−0.11 (−0.81, 0.59)	0.76
Subjective Analgesic Effectiveness scale	0.92 (0.53, 1.60)	0.78	0.92 (0.51, 1.65)	0.78

cycle phase; 86.4% were willing to schedule future surgery around timing of menstrual cycle if an effect was found.

Discussion

In premenopausal women undergoing minor surgery, there was no significant difference in postoperative quality of recovery, pain or analgesic effectiveness between women in the luteal and non-luteal phases of their menstrual cycle. The remaining two outcomes (clinically significant PONV and prolonged hospital admission owing to pain or PONV) could not be analysed because too few women experienced these outcomes.

QoR-15 is used as a measure of postoperative recovery in perioperative medicine studies. Our findings suggest that menstrual cycle phase in premenopausal women is unlikely to be an unmeasured confounder in studies involving minor surgery. The results of this study do not support a clinically meaningful difference in quality of recovery, with the upper 95% confidence limit of the difference in QoR-15 scores being less than the pre-specified minimal clinically important difference of 8. Since undertaking this study, the developers of the QoR-15 score revised the minimal clinically important difference from 8 to 6.[23] In total, 314 participants would be required to detect this difference under the specifications outlined in our sample size calculation. Therefore, our study was underpowered for this difference. However, the upper 95% confidence limit for the difference at postoperative day 1 (primary outcome) was less than 6, suggesting that differences were not important.

In terms of limitations, selection bias is unlikely because women were enrolled in the study before cycle history and hormone blood samples were obtained, that is before exposure group was known. About 5% of women experience spontaneous menopause before the age of 45.[24] Patients older than 45 yr, and those who were peri- or post-menopausal, were excluded. This was determined by a history of cycle irregularity and menopausal symptoms. Blood testing would also have identified an undetected early pregnancy.

Misclassification error is unlikely because women were classified into cycle phases based on menstrual cycle history and progesterone levels on the day of surgery. Many women were likely to be aware of their cycle phase, and this may have affected their responses to questions regarding postoperative quality of recovery. However, it was not known whether cycle phase affects quality of recovery (and if it did, in which direction); therefore, this is also unlikely to be a source of bias.

We collected and statistically adjusted for variables known to affect postoperative quality of recovery such as surgery type, smoking status, predictors of PONV, and the number of antiemetics and opioids administered in theatre and PACU. Surgical and anaesthetic techniques were standardised by choosing operations with defined surgical techniques and standardising the anaesthetic technique. Dexamethasone has been shown to reduce pain[25–27] and PONV,[28,29] and improve overall postoperative quality of recovery as measured by QoR-15 and Quality of Recovery-40 scores.[30,31] To control for its effect on pain and PONV, dexamethasone 8 mg was administered intraoperatively to all participants.

One of our objectives was to explore whether any effect of cycle phase on quality of recovery was modified by the degree of surgery. Here, 97% of women underwent wisdom teeth extraction, which is classified as minor surgery. We were therefore unable to explore any potential effect in moderate or major surgery. In our study, 86.4% of women said they would schedule elective surgery around their cycle timing if an effect was found; this is an area for future investigation.

There is a plausible biological mechanism by which changing progesterone levels during the menstrual cycle may impact the quality of postoperative recovery in premenopausal women. Two described mechanisms of action of progesterone and oestrogen are via intracellular receptors that act to alter the rate of gene transcription, and rapidly acting neurotransmitter-gated ion channels such as the gamma-aminobutyric acid$_A$ ($GABA_A$) receptor. GABA is the major inhibitory neurotransmitter in the central nervous system; $GABA_A$ receptors contain distinct binding sites for anaesthetic and other hypnotic drugs such as propofol, benzodiazepines, barbiturates, and etomidate.[32]

Administration of exogenous progesterone has a strong hypnotic effect on animals and humans of both sexes.[33,34] A-ring-reduced metabolites of progesterone function as neuroactive steroids, with anaesthetic, sedative-hypnotic, anxiolytic, and antiepileptic actions.[35] Increased endogenous progesterone production in pregnancy is believed to be the underlying mechanism by which there are reduced requirements for inhalation anaesthetic agents.[36,37] Similarly, increased progesterone levels in the luteal phase of the menstrual cycle are associated with a lower dose of propofol to achieve loss of consciousness[38] and lower anaesthetic volatile concentrations to maintain anaesthesia.[39]

Along with progesterone, oestrogen plays a role in cyclical variation of metabolic rate and physiological variables via suppression of $GABA_A$-mediated inhibition and increased glutamate binding to *N*-methyl-D-aspartate (NMDA) receptors. The role of oestrogen in a potential link between cycle phase and quality of recovery is likely to be less important because

levels are similar across the cycle except in the brief mid-cycle surge.

We found no significant difference in postoperative quality of recovery, pain, or analgesic effectiveness between women in the luteal and non-luteal phases of their cycle. Women can be reassured that menstrual cycle phase does not impact postoperative quality of recovery when undergoing minor surgery under general anaesthesia with volatile agents.

Authors' contributions

Study conception: NT.
Study design: NT, HT, PM.
Data collection: DD, NT.
Data analysis and interpretation: NT, SL, KL, SZ.
Draft revisions: NT, SL, KL, SZ, DD, HT, PM.
Patient recruitment: DD.

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Declarations of interest

The authors declare that they have no conflicts of interest.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.bjao.2022.100102.

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