Propofol EC$_{50}$ for inducing loss of consciousness is lower in the luteal phase of the menstrual cycle

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Background. Varying levels of female sex hormones during the menstrual cycle were found to influence the central nervous system. The goal of the present study was to investigate whether the median (50%) effective effect-concentration (EC$_{50}$) of propofol inducing loss of consciousness (LOC) varies between the luteal and the follicular phases of the menstrual cycle.

Methods. Twenty-two patients (follicular phase) and 20 patients (luteal phase) undergoing gynaecological procedures under general anaesthesia were enrolled in the study. Anaesthesia was conducted with a target-controlled infusion (TCI) of propofol. The initial target effect-site propofol concentration (C$_{e_{prop}}$) was 3.5 $\mu$g ml$^{-1}$ and was adjusted stepwise by 0.5 $\mu$g ml$^{-1}$ at 4 min intervals by an up–down sequential method to reach LOC. Anaesthesia was maintained with a propofol TCI guided by the bispectral index. The correlation between female sex hormones and predicted C$_{e_{prop}}$ at the time of LOC was analysed and emergence time from anaesthesia was recorded.

Results. Propofol EC$_{50}$ to induce LOC was higher in patients in the follicular phase than those in the luteal phase (4.17 vs 3.58 $\mu$g ml$^{-1}$, $P<0.05$). Progesterone correlated significantly with C$_{e_{prop}}$ at LOC. Emergence time was also longer in the follicular group than in the luteal group (6.5 vs 5.0 min, $P<0.05$).

Conclusions. During general anaesthesia, patients in the luteal phase of the menstrual cycle had a lower propofol EC$_{50}$ for LOC and a shorter emergence time compared with those in the follicular phase. Differences in progesterone levels between menstrual phases may contribute to these anaesthetic effects.

Registry number of clinical trial. ChiCTR-RCH-12002755.

Keywords: anaesthesia, general; anaesthetic i.v., propofol; hormones, progesterone; menstrual cycle

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From menarche to menopause, there are cyclical changes in endogenous sex hormone levels in women that create the follicular and luteal phases of their menstrual cycles. Besides the reproductive behaviour function, female sex hormones, which are all steroid-structured substances, have been proven to have an important influence on the central nervous system (CNS).\textsuperscript{1,2} Of the female sex hormones, progesterone and its metabolites show functions related to sedation, anxiolysis, analgesia, and anticonvulsant through direct action on the $\gamma$-aminobutyric acid (GABA) type A receptor,\textsuperscript{3–8} while oestrogen is thought to have the opposite effect by suppressing GABA$_A$ receptor-mediated inhibition.\textsuperscript{9} Hence the fluctuation of the female sex hormones during different phases of the menstrual cycle could have an influence on anaesthetic requirements and on anaesthetic onset and recovery times. A previous study\textsuperscript{9} showed that sevoflurane requirements were higher in patients in the follicular phase compared with patients in the luteal phase during maintenance of anaesthesia, suggesting that the luteal phase with high progesterone levels could reduce anaesthetic requirements. Since there are differences in the mechanism of action between inhaled and i.v. anaesthetic agents, it is warranted that i.v. anaesthetic agents during different phases of the menstrual cycle also be investigated.

Therefore we performed this prospective, double-blinded study to investigate whether the median (50%) effective effect-site concentration (EC$_{50}$) of propofol for inducing loss of consciousness (LOC) varies between the luteal phase and the follicular phase using an up–down sequential method. We also investigated the relationships between the level of female sex hormones (oestrogen, progesterone, follicle-stimulating hormone) and the anaesthetic requirements.
hormone (FSH), and luteinizing hormone (LH)) and the predicted effect-site concentration of propofol ($C_{\text{e, prop}}$) at the time of LOC. Finally, we studied the anaesthetic requirements and recovery times between different phases of the menstrual cycle in patients undergoing general anaesthesia for gynaecological procedures.

Methods

Study subjects

This study was approved by the ethical review board of the Women’s Hospital, School of Medicine, Zhejiang University (approval number 20120031), and registered in a Chinese Clinical Trial Registry (ChiCTR) (registration number ChiCTR-RCH-12002755). With written informed consent, 42 adult female patients with regular menstrual cycles (a regular cycle was defined as lasting 23–35 days with no variations in the length of cycle of more than 2 days),\textsuperscript{10} ages 18–40 yr, ASA I–II, undergoing elective gynaecological laparoscopy, were enrolled on the study. The exclusion criteria included pregnancy; receiving hormones and medications that affected ovulation during the 6 weeks before surgery; chronic or acute (within 48 h) intake of psychotropic drugs; hepatic, renal, or neurological dysfunction; alcoholism or use of benzodiazepines, anticonvulsants, or opioids; and irregular menstrual cycles. In addition, those patients with a BMI \textless 18 or a BMI \textgreater 33 were also excluded.

Patients were assigned to two groups based on the phase of their menstrual cycle, which was confirmed by measuring the progesterone level. Patients with menstrual cycle days from 1 to 10 were assigned to the follicular group and those with menstrual cycle days from 18 to 24 to the luteal group (X.C. was responsible for the study grouping). Sample size (patient number for each group) was determined by the requirement of the up–down method developed and modified by Dixon.\textsuperscript{11}

Before induction of anaesthesia

Patients received no premedication. On arrival in the operating theatre, an i.v. line was inserted for administration of Ringer’s lactate solution, and standard monitoring measures were applied, including non-invasive arterial pressure (NIAP), five-lead electrocardiogram, and pulse oximetry (SPO\textsubscript{2}) (S/S\textsuperscript{TM} compact monitor, GE Healthcare, Finland). All the patients were also monitored with the Bispectral Index (Model A-2000, BIS\textsuperscript{®} Aspect Medical Systems, Natick, MA, USA). The BIS\textsuperscript{®} sensor electrode (Aspect Medical Systems) was positioned over the temporal–frontal area of the forehead after careful cleaning with alcohol as recommended by the manufacturer and the electrode impedance was kept below 7.5 k\Omega to ensure optimal contact. The BIS was calculated with a smoothing rate of 15 s.

Induction of anaesthesia

Anaesthesia was induced with propofol and remifentanil via a target-controlled infusion (TCI) (Base Premera, Orchestra\textsuperscript{®}, Fresenius Company, Brézins France) with the pharmacokinetic and pharmacodynamic (PK–PD) model introduced by Schnider and colleagues\textsuperscript{12} for propofol and Minto and colleagues\textsuperscript{13} for remifentanil. The attending anaesthetists (F.F. and Y.F.) were blinded to the patient grouping.

To explore the EC\textsubscript{50} of propofol inducing LOC in patients during the luteal or the follicular phase, in each group we started induction using a series of predicted effect-site concentrations of propofol ($C_{\text{e, prop}}$) with an equal spacing of 0.5 \mu g ml\textsuperscript{-1}, according to the up–down method of Dixon.\textsuperscript{11} The initial TCI $C_{\text{e, prop}}$ for the first patient of each group was set at 3.5 \mu g ml\textsuperscript{-1}, which can produce LOC for most patients based on our clinical experience and a previous study in which the $C_{\text{e, prop}}$ for 95% of patients (EC\textsubscript{95}) was reported to be 3.8 \mu g ml\textsuperscript{-1} in a Chinese population.\textsuperscript{14} The initial TCI $C_{\text{e, prop}}$ for a patient in each group was determined by the response (positive or negative) of the previous patient to the initial dose of propofol (positive response was defined as LOC within 4 min of propofol infusion and negative response was defined as no LOC within 4 min of propofol infusion; LOC was defined as loss of response to verbal commands). If the response of a patient was positive, then the initial TCI $C_{\text{e, prop}}$ for the next patient in the same group was reduced by 0.5 \mu g ml\textsuperscript{-1}; if the response was negative, the initial TCI $C_{\text{e, prop}}$ for the next patient was increased by 0.5 \mu g ml\textsuperscript{-1}. In patients with a negative response, we increased $C_{\text{e, prop}}$ by 0.5 \mu g ml\textsuperscript{-1} stepwise at 4 min intervals until the patient showed LOC. An interval of 4 min was based on the PK–PD character of propofol to ensure that steady-state effect-site concentrations were obtained.\textsuperscript{12 15–17}

After LOC, remifentanil infusion was started with an initial predicted effect-site concentration ($C_{\text{e, remi}}$) of 4 ng ml\textsuperscript{-1}. Then, 0.6 mg kg\textsuperscript{-1} rocuronium was given to facilitate tracheal intubation.

Maintenance of anaesthesia

Anaesthesia was maintained with propofol and remifentanil. Immediately after intubation, $C_{\text{e, prop}}$ was adjusted in steps of 0.5 \mu g ml\textsuperscript{-1} in order to keep the BIS value at 50 (between 40 and 60) in both groups throughout surgery. In order to avoid intraoperative awareness, $C_{\text{e, prop}}$ of 2.0 \mu g ml\textsuperscript{-1} was set as the lower limit. $C_{\text{e, remi}}$ was adjusted stepwise by 1 ng ml\textsuperscript{-1} to reach an adequate anaesthesia (criteria showed in Table 1). The upper limit of $C_{\text{e, remi}}$ was 15 ng ml\textsuperscript{-1}. Upon reaching the upper limit of $C_{\text{e, remi}}$, patients with hypertension were treated with 10 mg urapidil i.v. Hypotension was treated initially by speeding Ringer’s solution infusion, then decreasing $C_{\text{e, remi}}$ by 1 ng ml\textsuperscript{-1} stepwise until the lower limit of 2 ng ml\textsuperscript{-1}, and finally giving 5 mg ephedrine i.v. Bradycardia was treated with 0.5 mg atropine i.v.

Recovery period

The TCI of both propofol and remifentanil was stopped at the end of surgery, which was defined as the final surgical suture. Emergence time from anaesthesia was defined as the duration between the time of discontinuation of anaesthetics and the time of spontaneous opening of eyes.

In the recovery room, pain intensity, postoperative nausea, and vomiting were evaluated and recorded using a visual analogue score of 0–10. On the first postoperative day, all patients
were visited by a nurse who was blinded to the study protocol. Any memory or awareness during anaesthesia and satisfaction level (using a 0–10 scale) during the surgical procedure were also recorded.

**Data collection**

Venous blood samples were obtained from all the patients at the time of arrival in the operating theatre (8 a.m.–9 a.m.). Blood concentrations of female sex hormones (oestrogen, progesterone, FSH, and LH) were measured with a competitive chemiluminescent enzyme immunoassay method (Roche E170 Diagnostics, Germany).

The values of NIAP, HR, and 

were recorded every 5 min. The BIS value was recorded at the beginning of induction (baseline), at the time of LOC, and at the time of emergence from anaesthesia. Predicted Ceprop and predicted Ceremi were recorded at the time of LOC and emergence from anaesthesia.

**Statistical analysis**

The modified Dixon’s up–down method\(^1\)\(^\text{11}^\) was used for calculating propofol EC\(_{50}\) for LOC. EC\(_{50}\) was determined by calculating the mean of the midpoints of pairs of Ceprop in successive patients in which an ineffective response of LOC was followed by an effective response. Data are expressed as mean and 95% confidence interval [95% CI, mean (1.96 so)]. Six pairs of effective–ineffective responses are necessary for a statistical analysis for each group. Data were also analysed using a quantitative response model (probit analysis) to determine the effective Ceprop inducing LOC in 5% and 95% of patients (EC\(_5\) and EC\(_{95}\), respectively).

GraphPad Prism software (version 5.0; GraphPad Software Inc., San Diego, CA, USA) was used for statistical analysis.

For numerical data, the Kolmogorov–Smirnov method was used to test for normal distribution, followed by a Student t-test for normally distributed data and a Mann–Whitney U-test for non-normally distributed data between the groups. For nominal data, statistical analysis was performed by means of a \(\chi^2\) test. The correlation between Ceprop at LOC and the level of the sex hormones was analysed using Spearman’s rank correlation.

The BIS level at which 95% of patients reached LOC or at which 95% emerged from anaesthesia was calculated using probit analysis. The emergence time between the groups was compared using the Kaplan–Meier log-rank survival analysis (calculating the cumulative probability of patients remaining unconscious after discontinuation of anaesthetics).

All tests were two-tailed and a \(P\)-value < 0.05 was considered statistically significant.

**Results**

**Patient characteristics**

Twenty-two patients in the follicular group and 20 patients in the luteal group were included into the final analysis. Patients’ characteristics are presented in Table 2. The two groups were similar in terms of age, weight, height, ASA physical status, duration of surgery, baseline BIS, oestrogen, and LH (all \(P>0.05\)), whereas they differed significantly in terms of progesterone and FSH levels (\(P<0.05\)).

**Propofol EC\(_{50}\) for LOC**

The propofol EC\(_{50}\) for LOC, determined using the up–down method of Dixon,\(^\text{11}^\)\(^\text{18}\) was 4.17 (95% CI: 3.77–4.57) \(\mu\text{g ml}^{-1}\) in the follicular group and 3.58 (95% CI: 3.08–4.09) \(\mu\text{g ml}^{-1}\) in the luteal group (\(P<0.05\)). Individual responses to propofol at corresponding effect-concentrations (Ceprop) are shown in Figure 1.

**The predicted Ceprop at the time of LOC and at the time of emergence from anaesthesia**

The mean predicted value of Ceprop at the time of LOC was significantly higher in the follicular group (3.06 \(\mu\text{g ml}^{-1}\), 95% CI: 2.80–3.31 \(\mu\text{g ml}^{-1}\)) compared with the luteal group (2.23 \(\mu\text{g ml}^{-1}\), 95% CI: 1.96–2.52 \(\mu\text{g ml}^{-1}\) (\(P<0.01\), Table 3). The mean predicted values of Ceprop at the time of emergence from anaesthesia were significantly higher in the follicular group and 3.58 (95% CI: 3.08–4.09) \(\mu\text{g ml}^{-1}\) in the luteal group (\(P<0.05\)). Individual responses to propofol at corresponding effect-concentrations (Ceprop) are shown in Figure 1.

**Table 2** Patient characteristic data. Values are mean (so) or absolute numbers. ASA, American Society of Anesthesiologists physical status; BIS, bispectral index; LH, luteinizing hormone; FSH, follicle-stimulating hormone; E2, oestrogen; P, progesterone. *Age is expressed as mean (range)*

<table>
<thead>
<tr>
<th></th>
<th>Follicular group (n = 22)</th>
<th>Luteal group (n = 20)</th>
<th>(P)-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>28.6 (20–36)</td>
<td>27.8 (4.6)</td>
<td>0.51</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>51.2 (4.7)</td>
<td>51.8 (6.2)</td>
<td>0.74</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>160.2 (3.2)</td>
<td>159.5 (4.9)</td>
<td>0.57</td>
</tr>
<tr>
<td>ASA I/II</td>
<td>20/2</td>
<td>19/1</td>
<td>0.61</td>
</tr>
<tr>
<td>Duration of surgery (min)</td>
<td>45.1 (10.3)</td>
<td>48.3 (9.2)</td>
<td>0.31</td>
</tr>
<tr>
<td>Baseline BIS</td>
<td>97.2 (0.9)</td>
<td>97.4 (0.7)</td>
<td>0.50</td>
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<tr>
<td>LH (IU ml(^{-1}))</td>
<td>7.5 (2.7)</td>
<td>6.2 (3.2)</td>
<td>0.17</td>
</tr>
<tr>
<td>FSH (IU ml(^{-1}))</td>
<td>5.8 (3.0)</td>
<td>4.1 (1.9)</td>
<td>0.04</td>
</tr>
<tr>
<td>E2 (pmol litre(^{-1}))</td>
<td>538.2 (320.6)</td>
<td>423.1 (202.4)</td>
<td>0.18</td>
</tr>
<tr>
<td>P (nmol litre(^{-1}))</td>
<td>2.6 (1.0)</td>
<td>24.4 (10.3)</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>
Menstrual cycle and propofol anaesthesia

The BIS value at which the patient had a 95% possibility for LOC and for emergence from anaesthesia

The BIS value at which the patient had a 95% probability for LOC was 44 (95% CI: 40–47) in the follicular group and 51 (95% CI: 47–53) in the luteal group. No differences between the groups were found (P > 0.05).

The BIS value at which patients had a 95% probability for emergence from anaesthesia (eyes opening) was 80 (95% CI: 78–85) in the follicular group and 79 (95% CI: 77–82) in the luteal group. No differences between the groups were found (P > 0.05).

Unwanted events during maintenance of anaesthesia and the postoperative period

For all patients, no movement was recorded in the present study. The incidence of unwanted events (hypertension, hypotension, tachycardia, and bradycardia) did not differ between the groups (P > 0.05) (data are not presented). No patient in both groups had intraoperative awareness. Postoperative modified Aldrete score, pain (visual analogue scale), nausea and vomiting, and total satisfaction in the recovery room and on the first day after surgery are presented in Table 4. The

Correlation between the predicted Ce prop at the time of LOC and female sex hormones

We also analysed, using the complete data of both groups, the correlation between the predicted values of Ce prop at LOC and the level of the female sex hormones. Of the four female sex hormones we measured in the present study, only progesterone had a significant correlation with the Ce prop at the time of LOC (Spearman’s r: -0.49, P < 0.001) and the others (FSH, LH, and oestradiol) had no significant correlation with the Ce prop at the time of LOC (P > 0.05) (Fig. 2).

Emergence time from anaesthesia

Emergence time, defined as the time from discontinuation of propofol and remifentanil infusion to eyes opening, was longer in the follicular group than in the luteal group [6.50 (95% CI: 3.95–9.05) vs 5.00 (95% CI: 2.45–7.55) min (P < 0.05)]. The cumulative percentages of patients remaining unconscious after discontinuation of propofol and remifentanil infusion for both groups are displayed in Figure 3.

Anaesthetic requirements

Propofol requirements (average normalized infusion rate calculated from induction of anaesthesia to discontinuation of propofol, which refers to total propofol dose/duration of anaesthesia/body weight) were significantly less in the luteal group compared with the follicular group [0.128 (95% CI: 0.121–0.136) vs 0.148 (95% CI: 0.136–0.159) mg kg⁻¹ min⁻¹, P < 0.001], whereas remifentanil requirements (average normalized infusion rate, which is calculated by total remifentanil dose/duration of anaesthesia/body weight) were comparable between the follicular group [0.176 (95% CI: 0.163–0.189) µg kg⁻¹ min⁻¹] and the luteal group [0.186 (95% CI: 0.174–0.199) µg kg⁻¹ min⁻¹, P > 0.05].

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Table 3 Predicted effect-site concentration of propofol (Ce prop) at certain time points. Values are mean (SD). LOC, loss of consciousness; DPI, discontinuation of propofol infusion; Emergence, emergence from anaesthesia or recovery of consciousness

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<td>3.06 (0.57)</td>
<td>2.23 (0.60)</td>
<td>&lt; 0.0001</td>
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<tr>
<td>DPI</td>
<td>2.71 (0.37)</td>
<td>2.60 (0.48)</td>
<td>0.43</td>
</tr>
<tr>
<td>Emergence</td>
<td>1.87 (0.30)</td>
<td>1.93 (0.42)</td>
<td>0.61</td>
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Fig 1 Individual responses to propofol at corresponding effect-concentrations (Ce prop). Unfilled squares represent ineffective responses to the corresponding Ce prop for achieving LOC. Filled squares represent effective responses to the corresponding Ce prop for achieving LOC. Arrows represent the midpoint Ce prop when crossing ineffective to effective response for LOC. The average Ce prop of crossing is represented by the horizontal dashed line. Ce prop, effect-site concentration of propofol.

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incidence of postoperative nausea and vomiting (PONV) was higher in the follicular group than in the luteal group (45% vs 15%, \( P < 0.05 \)). There were no significant differences in the postoperative pain intensity, modified Aldrete score, and total satisfaction level between the groups (\( P > 0.05 \)).

**Discussion**

In the present study, using the up–down method described by Dixon,\(^{11}\) we demonstrated that (i) patients in the luteal phase of the menstrual cycle have a lower median (50%) propofol effect-site concentration (EC\(_{50}\)) required for inducing LOC compared with patients in the follicular phase and that the mean predicted propofol effect-site concentration (Ce\(_{\text{prop}}\)) at LOC was significantly lower in the luteal phase; (ii) the predicted Ce\(_{\text{prop}}\) at LOC was inversely correlated with progesterone levels but had no correlation with LH, FSH, and oestrogen; and (iii)

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**Table 4** Postoperative data. Data are median (range) or number (proportion). Aldrete score, modified Aldrete score; PONV, postoperative nausea and vomiting; VAS, visual analogue scale, scaled from 0 to 10 (0 means no pain and 10 means the maximum intensity of pain). Satisfaction was graded on a scale from 0 to 100, where 0 represents the worst level and 100 represents the best level.

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<td>Aldrete score</td>
<td>6.7 (2–10)</td>
<td>6.5 (2–10)</td>
<td>0.32</td>
</tr>
<tr>
<td>VAS (pain)</td>
<td>3.3 (1–10)</td>
<td>3.5 (1–10)</td>
<td>0.36</td>
</tr>
<tr>
<td>PONV</td>
<td>10 (45%)</td>
<td>3 (15%)</td>
<td>0.047</td>
</tr>
<tr>
<td>Satisfaction</td>
<td>95 (80–100)</td>
<td>96 (80–100)</td>
<td>0.05</td>
</tr>
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the time of emergence from anaesthesia was significantly shorter in patients in the luteal phase of the menstrual cycle.

Propofol is an i.v. anaesthetic agent that has been widely adopted for induction and maintenance of anaesthesia due to its rapid onset and recovery characteristics. Previous studies have found that its anaesthetic effects vary with gender—women under propofol anaesthesia require more propofol to maintain equivalent bispectral index (BIS) levels and awoke faster after discontinuation of propofol. However, no published studies have investigated the effect of the anaesthetic characteristics of propofol during different phases of the menstrual cycle.

EC50 is a concept analogous to the minimum alveolar concentration (MAC) for volatile anaesthetics, aimed at estimating how much i.v. drug is needed to obtain an effect, for example, LOC, in 50% of the population. Owing to the fact that the i.v. drug concentration cannot be measured in real time, a PK–PD model is needed for prediction. In our study we used Schneider's PK–PD model for predicting Ce prop. The predicted Ce prop, using this model has been evaluated by several previous studies and the value of the predicted Ce prop has been verified to determine the PD effect of propofol in the individual patient. In addition, we tried to achieve a steady-state Ce prop to better evaluate the pharmacodynamic effects in the individual, by maintaining target Ce prop at least 4 min between two consecutive adjustments of the predetermined target concentration based on Schneider's model. Therefore the propofol EC50 for LOC obtained in the present study should be reliable and could be used to compare the anaesthetic effect between the luteal and the follicular phases of the menstrual cycle.

The finding in the present study that propofol EC50 for LOC was lower in the luteal phase compared with the follicular phase is similar to the findings in a previous study where decreased anaesthetic requirements were also found in the luteal phase compared with the follicular phase of the menstrual cycle. However, in the previous study, sevoflurane was chosen for comparison of anaesthetic requirements using end-tidal sevoflurane concentration calculated as MAC-hours between the luteal and the follicular phases during maintenance of anaesthesia. Owing to the difference in the mechanism of action of anaesthetics existing between volatile and i.v. agents, we were interested in the behaviour of propofol. In addition, the previous study was performed only during maintenance of anaesthesia, and the reported results with respect to the anaesthetic requirements may have been influenced by the anaesthetics used during induction of anaesthesia and the anaesthetics co-administered during maintenance of anaesthesia. Our study investigated the EC50 for LOC only during anaesthesia induction with no premedication and no other anaesthetics administered. Hence our results could be closer to the real requirement of an anaesthetic for achieving a certain anaesthetic effect, for example, LOC.

Mechanisms for reduced anaesthetic requirements in the luteal phase, such as the decreased propofol EC50 for LOC found in the present study, remain unclear. It is well known that the menstrual cycle is characterized by periodic fluctuations of the female sex hormones, which is suggested to be involved in the mechanisms of the different anaesthetic requirements in the menstrual phases. In the present study, we analysed the correlation between the predicted Ce prop at LOC and female sex hormones and showed that only progesterone levels had a significant negative correlation, while the other three female sex hormones (LH, FSH, and oestrogen) had no, or only a poor, correlation with the predicted Ce prop at LOC. This suggests that the decreased propofol EC50 for LOC in the luteal phase may result from the higher progesterone levels in the luteal phase of the menstrual cycle. Several previous studies indicated that female sex hormones, especially progesterone, may influence the central nervous system, and subsequently influence the effect of anaesthetics. Both animal and human studies demonstrated that the MAC of volatile anaesthetics was decreased during pregnancy, during which there are normally high levels of progesterone. A recent study demonstrated that administration of exogenous progesterone decreased the sevoflurane requirement as defined by rolling response in male mice. Although no studies up to now have directly investigated the effect of progesterone on propofol for a specific anaesthesia effect, we could speculate that progesterone might enhance propofol's effect and subsequently decrease the propofol requirement for achieving a certain anaesthesia depth, such as LOC, by the fact that propofol and progesterone have a similar central effect via direct action on the GABA receptor complex, which is known to be a major substrate for the effects of several general anaesthetics. Additionally, because of this progesterone was thought to influence the oxidative metabolism of drugs. The potential PK interaction between propofol and progesterone is likely to contribute to the lower propofol requirements for LOC in patients in the luteal phase.

Interestingly, we found that both the BIS value at which 95% of patients had LOC and the BIS at which 95% awoke from anaesthesia did not differ between the follicular phase and the luteal phase, suggesting, to a certain extent, that the different levels of female sex hormones during the menstrual cycle do not alter the sensitivity of BIS as a measure of anaesthetic depth, and BIS could also be used to guide administration of anaesthetics to reduce the risk of awareness during general anaesthesia with propofol in different phases of the menstrual cycle.

More interestingly, we found that patients in the luteal phase emerged faster from general anaesthesia than those in the follicular phase, while the levels of Ce prop and Ce remi at the time of awakening were similar between the groups. This may seem counter-intuitive at first. However, emergence from general anaesthesia is dependent on factors influencing both drug sensitivity and drug deposition in the brain (effect site). One possible explanation for this phenomenon is that the decline of anaesthetic concentration at the effect site might be different between the groups, that is to say, more exactly, Ce prop or Ce remi in patients in the luteal phase might decline more rapidly than in the follicular phase. This difference with respect to drug metabolism or distribution is not accounted for in the Schneider model, because the Schnider model does not
include menstrual cycle as a covariate. Given that in the present study lower mean propofol requirements (average normalized infusion rate from induction to discontinuation of propofol) were found in the patients in the luteal phase compared with the follicular phase, we could also hypothesize that patients in the luteal phase had less accumulation of propofol in the body, which might have contributed to the faster emergence from anaesthesia for patients in the luteal phase. However, further studies of this phenomenon are needed.

During the first postoperative day, pain ratings and satisfaction ratings were similar between the luteal phase and the follicular phase, whereas patients in the luteal phase had a lower incidence of PONV than those in the follicular phase, which is in accordance with the findings of a previous study in which patients in the luteal phase were found to have a decreased risk of PONV after laparoscopic gynaecological surgery during the early postoperative period. This finding could also be explained by the different level of female sex hormones between the luteal and follicular phases of the menstrual cycle.

Our study has limitations. First, menstrual cycle length depends on the rate and quality of follicular growth and development. Most women have regular menstrual cycles with a length from 24 to 35 days. But there are at least 20% of women whose menstrual cycles are irregular, making it difficult to be certain in which phase of the menstrual cycle a woman may be at the beginning of the study.9 However, we excluded patients whose menstrual cycle was <22 days or >36 days and finally confirmed patient assignment by measuring the sex hormones levels, thus avoiding the possibility that a patient was allocated to the wrong group. Second, we did not measure the plasma concentration of propofol (\(C_{P_{prop}}\)). \(C_{P_{prop}}\) calculated by the measured \(C_{P_{prop}}\) more accurately reflects real \(C_{E_{prop}}\) than the predicted \(C_{E_{prop}}\) calculated by the PK–PD model. Given that both progesterone and propofol bind highly to albumin, the accuracy of the PK–PD model–derived \(C_{P_{prop}}\) and consequently \(C_{E_{prop}}\) in patients in the luteal phase with higher levels of progesterone might be impaired. However, during general anaesthesia, the blood concentration of propofol is usually more than 100 times that of progesterone in patients in the luteal phase. Therefore the effect of progesterone on the accuracy of the predicted \(C_{P_{prop}}\) or \(C_{E_{prop}}\) is most likely negligible. Moreover, Cavaliere and colleagues suggested that hypoaalbuminaemia does not impair Diprifusor (a TCI pump integrated with a propofol PK–PD model) performance during propofol sedation. In addition, any possible errors resulting from factors other than progesterone in the predicted \(C_{E_{prop}}\) would have affected both groups equally and therefore most probably would cancel each other out. Third, we only studied propofol EC50 for LOC groups equally and therefore most probably would cancel with those in the follicular phase. The difference in progesterone levels between menstrual phases may contribute to some of these anaesthetic differences.

Authors’ contributions
F.F. helped in designing and conducting the study, collecting the data, and writing the manuscript. X.C. helped in designing and writing the manuscript. Y.F. helped in conducting the study and collecting the data. Y.S. helped in conducting the study and collecting the data. Z.F. helped in designing the study. B.B. helped in designing and writing the manuscript.

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Declaration of interest
None declared.

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