

Does the phase of the menstrual cycle really matter to anaesthesia?

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ABSTRACT

The menstrual cycle is a physiological phenomenon that is accompanied by several hormonal fluctuations involving oestrogen and progesterone. Oestrogen and progesterone exert several physiological effects. There are many questions pertaining to the influence of the physiology of menstruation on anaesthesia. We attempted to find out whether the phase of the menstrual cycle can alter the physiological functions during anaesthesia, the perioperative management and outcomes. We performed a literature search in Google Scholar, PubMed and Cochrane databases for original and reviewed articles on the phases of the menstrual cycle and their relation to anaesthesia-related physiological parameters to find an answer to these questions. Many studies have shown that women, perimenstrually, may have increased pain perception, exacerbation of systemic diseases, vocal cord/peripheral oedema and post-operative nausea and vomiting (PONV). Some of the other notable findings in most studies were sleep disturbances in the luteal phase (LP), increased occurrence of PONV in the ovulatory phase and a lower requirement of intravenous sedative and anaesthetic drug requirements in the LP. We found contradictory results concerning pain perception and PONV in relation to the follicular and LPs. However, we found that literature regarding the phase of the menstrual cycle and the haemodynamic response to intubation, anaesthesia-induced hypnosis and perioperative blood loss is relatively scarce. Thus, there is a need to conduct good quality research on these topics.

Key words: Follicular phase, luteal phase, menstruation, nausea, ovulation, pain, physiology, vomiting

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INTRODUCTION

The eminent endocrinologist Estelle Ramey once said 'in man, the shedding of blood is always associated with injury, disease or death. Only the female half of the humanity is seen to have the magical ability to bleed profusely each month and still rise phoenix-like from the gore'. Human menstruation has been regarded both negatively and positively in different aspects.^[1] Menstruation is the visible manifestation of cyclic physiologic uterine bleeding due to shedding of the endometrium following an invisible interplay of hormones.^[2] Menstruation is often least revealed by women preoperatively; nevertheless, as anaesthesiologists, we can perioperatively encounter women patients in different phases of the menstrual cycle and are expected to ask leading questions about menstruation during the pre-anaesthetic evaluation. Fluctuations in many physiological functions occur

throughout the different phases of the menstrual cycle due to hormonal fluctuations.^[3] Considering this, one cannot help wondering whether the physiological changes due to the menstrual cycle can have a positive or negative impact on anaesthesia. Should surgical procedures be scheduled according to the menstrual phase? In this article, we detail the physiological changes during the menstrual cycle relevant to the anaesthesiologist and discuss various research studies conducted on this subject in relation to anaesthesia

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with a goal to find out how and whether the phase of the menstrual cycle could alter anaesthesia-related perioperative management and outcomes.

Literature search and selection

We performed an electronic search in Google Scholar, PubMed and Cochrane databases for original and review articles on phases of the menstrual cycle and their relation to anaesthesia-related physiological parameters published in humans until March 2018. The search terms included phases of the menstrual cycle and sedation, sleep and menstruation, menstruation and anaesthesia, pain and the menstrual phase, menstruation and post-operative vomiting, menstrual phases and anxiety, menstrual phase and pharmacokinetics. We also searched for information on this topic in textbooks of gynaecology and anaesthesiology in our institutional library. From the 75 articles retrieved in the first few search rounds, additional articles were found among the cross-references cited. The articles for potential inclusion included both full-text articles and abstracts. We excluded articles that were not written in English. We eventually included the results of 126 articles.

THE MENSTRUAL CYCLE

The menstrual cycle includes the ovarian cycle and the endometrial cycle [Figure 1]. The 4 stages of the endometrial cycle include the phase of regeneration (2–3 days after the end of menstruation), the phase of proliferation (5th–6th day to 14th day till ovulation), the secretory phase (15th day to menstruation) followed by the menstrual phase.^[2] The menstrual cycle is divided into three phases: menstrual or follicular, ovulatory and luteal.^[3] The pre-ovulatory phase is known as follicular phase (FP), and the post-ovulatory phase is known as luteal phase (LP). The oestrogen level is at its peak during the proliferative phase, high during ovulation; progesterone is high during the secretory phase, and the early LP and both oestrogen and progesterone are low due to withdrawal

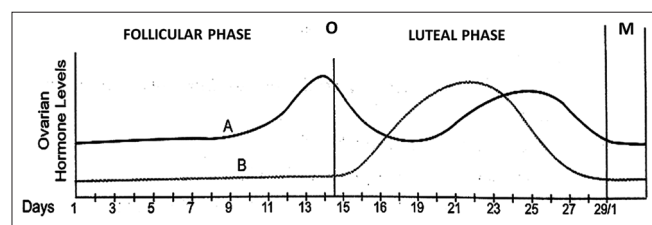


Figure 1: Phases of the menstrual cycle and associated hormonal fluctuations. A – Oestrogen; B – Progesterone; O – Ovulation; M – Menstruation

in the menstrual phase.^[2,4] Blood progesterone starts to increase on the 18th day, reaches a peak on the 21st day and starts to decrease on the 24th day of the menstrual cycle.^[5]

PHYSIOLOGICAL CHANGES IN THE MENSTRUAL CYCLE OF INTEREST TO THE ANAESTHESIOLOGIST

Haemodynamic changes

In healthy women, plasma norepinephrine levels and sympathetic activity have been found to be significantly higher in the LP than in the FP.^[6] Higher levels of heart rates and systolic blood pressure and lower diastolic pressure have been observed in the LP.^[7] During ovulation there is an oestrogen-induced increase in nitric oxide production which leads to an increase in the cardiac output and a decrease in systemic vascular resistance, systolic and diastolic blood pressure.^[8] Researchers have found a significant decrease in the arterial stiffness indices like reflection index, stiffness index and pulse wave velocity during the mid-cycle probably because of oestrogen.^[9] The haemodynamic response to physiological and psychological stress is elevated during the LP.^[7] The QTc interval might be influenced and may change with the phase of the menstrual cycle, and a prolonged QTc may predispose to cardiac arrhythmias.^[10] A prolongation of the QTc interval in the FP has been reported by some researchers.^[11]

Systemic diseases

Idiopathic or cyclic oedema characterised by excessive diurnal weight gain with peripheral oedema especially when the patient is in the upright position, headache and increased irritability can occur in obese women just before menstruation.^[12]

Some studies have found an exacerbation (21%–50%) of acute bronchial asthma during the pre-ovulatory (33%) and premenstrual phases.^[13–15] Seizures in women with epilepsy can increase in frequency perimenstrually. Several reports have documented fluctuations in the symptom severity of systemic diseases such as glaucoma, bipolar illness and allergies during menstruation.^[16–18]

Catamenial pneumothorax includes spontaneous and recurrent episodes of pneumothorax occurring within 72 h from the onset of menstruation. It accounts for 3%–6% of the causes of spontaneous pneumothorax in women. Catamenial haemothorax, too, can occur as a part of thoracic endometriosis.^[19]

Respiratory system

Several researchers have found that the pulmonary function significantly improves in the luteal or secretory phase of the menstrual cycle, probably due to the bronchodilatory effect of progesterone.^[20] A significant increase in the cardiorespiratory efficiency has been found to occur in the LP in normal weight women.^[21] Skeletal muscle contractile characteristics and muscle strength do not change with different phases of the menstrual cycle.^[22]

Vocal cords

The larynx is affected by fluctuations in the level of oestrogen and progesterone in the menstrual cycle. Swelling of the vocal folds due to water retention and engorgement of subepithelial capillaries leading to laryngeal oedema are seen in the FP and premenstrually leading to hoarseness of voice and a change in vocal tones. The increase in oestrogen and progesterone during ovulation produces thick and dry vocal folds which reduces the tonicity of the laryngeal muscles.^[23,24]

Physiological sleep

Ovarian hormones can modulate the sleep-wake cycle. Disturbed sleep, a decrease in rapid eye movement (REM) sleep, increased microarousals per hour and a less percentage of slow wave (non-REM) sleep have been observed during the LP.^[25-27]

Nervous system and psychology

Soliz-Ortiz S *et al.* while investigating the neuropsychological performance of healthy women with regular menstrual cycles found that sustained attention showed an increase in the early LP while visuospatial memory was increased and verbal fluency was decreased during the ovulatory phase.^[4] Studies have found that diseases such as migraine, preexisting mental health disorders including anxiety, bipolar, psychotic and eating disorders exacerbate premenstrually. Premenstrual dysphoric disorder affects 6% of premenopausal women.^[18]

The changes in drug pharmacokinetics and dynamics, renal, coagulation, gastrointestinal, immune and haematological systems are variable and not very conclusive.

RESEARCH STUDIES ON THE INFLUENCE OF VARIOUS MENSTRUAL CYCLE PHASES ON ANAESTHESIA

In most of the research studies that we analysed, women on the 20th–24th day after the first day of the

last menstruation were considered to be in the LP and those on the 1st–12th day or 8th day –12th day after the 1st day of the last menstrual cycle were considered to be in the FP.^[5] The premenstrual phase was 7–8 days before menstruation or on the 25th and 26th day of the menstrual cycle. The menstrual phase was considered as the period between 1–7/8 days or 1-3 days from the beginning of menstrual bleeding; days 13–15 were considered as the ovulatory phase. The menstrual cycle ranged from 23 to 35 days in most of the studies. Patients with irregular menstrual cycles were excluded in most of the studies. Plasma oestrogen and progesterone levels were monitored in most of the studies. There were only limited studies on most of the topics except on pain and vomiting. Although we tried to select standard journal articles, the studies probably had design problems; nevertheless, most of the studies were conducted on only one menstrual cycle and the sample size was very small in some studies.

Pain

Oestradiol and progesterone have shown promising pro-nociceptive and antinociceptive actions, respectively.^[28] It has been suggested by some researchers that the fluctuations in sex hormones during the menstrual cycle can cause fluctuations in pain perception.^[29]

Several studies have been conducted on this topic.^[30-45] The parameters tested included experimental pain sensitivity, cold pressor, heat and ischaemic pain perception, test pain intensity suppression, pain inhibition during conditional pain modulation, injection pain and post-operative pain scores [Table 1]. The results of these studies were variable and not very conclusive; nevertheless, many studies showed lowered pain perception in the FP and increased pain perception perimenstrually. We found only one study on local anaesthetic requirement which found that the injection discomfort and clinical effectiveness of local anaesthetics were not related to the phases of the menstrual cycle.^[40]

Anaesthesia-induced hypnosis, sedation and anaesthetic drug requirements

Only four studies have tried to directly study the influence of the phase of the menstrual cycle on anaesthetic requirement [Table 2].^[43,46-48] Erden *et al.* found a decreased sevoflurane requirement in the LP compared to the FP. The minimum alveolar anaesthetic concentration (MAC)-hour value of sevoflurane was 1.55 ± 0.18 MAC-h in patients in the FP and was 1.3 ± 0.13 MAC-h in patients in the LP.^[46] Zhou *et al.*

Table 1: Studies on pain and menstrual phases

Parameters observed	Findings as per phase of menstrual cycle				References
	Follicular	Ovulatory	Luteal	Menstrual	
Pain perception				Increases*	Ozçaka <i>et al.</i> , ^[30] Collins <i>et al.</i> , ^[31] Fatima <i>et al.</i> , ^[32] Ileri <i>et al.</i> , ^[33]
Thermal/pressure/ischaemic pain	Decreases		Increases		Stening <i>et al.</i> , ^[34] Viana Ede <i>et al.</i> , ^[35] Klatzkin <i>et al.</i> , ^[36]
Pain inhibition		Increases			Rezaei <i>et al.</i> , ^[37]
Morphine analgesia and its side effects	Increases				Ribeiro-Dasilva <i>et al.</i> , ^[38]
Injection discomfort to propofol			Higher		Hanci <i>et al.</i> , ^[39]
Injection discomfort to local anaesthetic and local anaesthetic clinical effectiveness	No changes				Tófoli <i>et al.</i> , ^[40]
Injection discomfort to rocuronium			Higher		Honca <i>et al.</i> , ^[41]
Post-operative pain	No changes				Sari <i>et al.</i> , ^[29] Ahmed <i>et al.</i> , ^[42] Fu <i>et al.</i> , ^[43]
Post-operative pain in PMS			Lesser		Arab <i>et al.</i> , ^[44]
12 h post-operative pain			Higher		Arab <i>et al.</i> , ^[44]
Pain score			Higher		Ahmed <i>et al.</i> , ^[42]
			Lesser		Lenzmeier <i>et al.</i> , ^[45]

*Perimenstrual. PMS – Premenstrual syndrome

Table 2: Details on studies on anaesthetic drug requirements in different menstrual phases

Study	Sample size	Type of surgery	Parameters recorded	Values calculated	Study limitations	Study findings according to menstrual cycle phase
Erden <i>et al.</i> , ^[46]	40	Septorhinoplasty/ tympanomastoideotomy	BIS (pre-induction, during surgery), EtCO ₂ , HR, NIBP, SaO ₂ , sevoflurane concentration (inspiratory and end-tidal), serum progesterone levels	Sevoflurane requirement, MAC-h (average value of MAC over an hour)	BIS used instead of MAC to calculate sevoflurane requirement	Sevoflurane requirement reduced in LP
Zhou <i>et al.</i> , ^[47]	64	Elective gynaecological surgery	BIS, NIBP, HR, SaO ₂	Duration and propofol consumption from propofol administration to loss of eyelash reflex and to reduce BIS to 50	Serum estrogen/ progesterone levels not measured	Dexmedetomidine with propofol sedation effect better in LP
Fu <i>et al.</i> , ^[43]	42	Elective gynaecological laparoscopy	BIS (pre-operative, at LOC, at emergence), NIBP, ECG, SaO ₂ , post-operative pain and vomiting Propofol EC50 for LOC, predicted Ce (prop), Ce (remi) at LOC and emergence	Propofol requirement, remifentanyl requirement, BIS value at 95% cases reaching LOC	Plasma propofol concentration not measured	Propofol EC50 for LOC and emergence time higher in FP
Han <i>et al.</i> , ^[48]	40	Selective gynaecological laparoscopies (myomectomy/ oophorocystectomy)	BIS (basic, intraoperative values), HR, NIBP, apnoea, SaO ₂ , EtCO ₂ , serum estradiol concentration and progesterone concentration	Time for BIS score reduce to 70 and 60 Number of patients whose BIS could reach 50 Lowest BIS values	Plasma dexmedetomidine concentration not measured	Time for BIS score to reduce to 70 less in LP; number of patients whose BIS could reach 50 higher in LP group BIS value lowest in LP

EtCO₂ – End tidal carbon dioxide levels; HR – Heart rate; NIBP – Non-invasive blood pressure; SaO₂ – Arterial oxygen saturation; ECG – Electrocardiogram; EC50 – Median effective concentration; Ce (prop) – Effect site propofol concentration; Ce (remi) – Effect site remifentanyl concentration; LOC – Loss of consciousness; LP – Luteal phase; FP – Follicular phase; BIS – Bispectral index; MAC – Minimum alveolar concentration

showed that in patients during the LP, pre-operative intravenous dexmedetomidine 1 µg/kg for 10 min followed by induction with propofol target controlled infusion could lead to a more significant sedative effect than in those during the FP, with or without dexmedetomidine. The propofol requirement was least and the duration of action was shortest with the

use of pre-operative intravenous dexmedetomidine in women in the LP.^[47] Fu *et al.* found that the median effective effect concentration (EC50) of propofol to induce loss of consciousness during general anaesthesia was higher in the FP than in the LP. The propofol requirement in the LP group was 0.128 mg/kg/min whereas it was 0.148 mg/kg/min in

the FP patients. The emergence time was longer in the follicular group than in the luteal group.^[43]

In another study on dexmedetomidine sedation in surgical patients, the lowest bispectral index value in the LP was lower than that in the FP. Thus, the sedative effect of dexmedetomidine was more significant during the LP than during the FP.^[48] Hoshino *et al.* found in a study that the passive collapsibility of the upper airway was higher in the mid-LP than in the FP during propofol anaesthesia. The active collapsibility decreased more in the FP.^[49] The decreased sedative requirements in the LP in all the studies were attributed to the sedative effect of progesterone and its metabolites through action on the GABA receptor complex and a decrease in the oxidative metabolism of anaesthetic drugs in the LP. In all the studies, women of the American Society of Anaesthesiologists grade 1–2 with regular menstrual cycles and aged between 18 and 40 years were included. Women receiving hormones affecting ovulation/psychotropic drugs/steroids, breastfeeding women and women having pregnancy/obesity/renal impairment were excluded from the study. The studies had some unique parameters monitored along with some limitations [Table 2]. This subject of the accentuation of the hypnotic effects of different anaesthetic agents in the LP is an area which warrants serious research.

The haemodynamic response to laryngoscopy and tracheal intubation

A single study on this topic has demonstrated that the rate-pressure product at 1 min after tracheal intubation is significantly more in the LP than in the FP.^[5] There was a statistically significant higher blood pressure

during the 1st min after intubation [Table 3]. Although there is an increased vulnerability to sedation in the LP, some studies have shown that there is an increased pain perception in the LP. Furthermore, there is an increased sympathetic activity in the LP. All this could account for the increase in the rate pressure product at intubation; nevertheless, we recommend further studies on this topic.

Post-operative nausea and vomiting

A number of studies have been conducted on the effect of the menstrual cycle phase on PONV [Table 3].^[50-57] Most studies have revealed that females subjected to general anaesthesia for surgery had more nausea and vomiting in the FP compared to the LP with the greatest risk during menstruation.^[50-52] In contrast, a few studies have found the highest incidence of PONV during the LP^[53] and in the periovulatory and premenstrual periods, while a few studies have shown that no relationship exists between the menstrual phase and the incidence of emesis.^[56,61] No conclusions can thus be drawn. As mentioned in some studies, the increase or decrease in vomiting could have been due to the effect of the changing concentrations of follicle stimulating hormone and oestrogen on sensitising the chemoreceptor trigger zone or vomiting centre;^[51] nevertheless, whether an increased requirement of anaesthetic drugs in the concerned menstrual phase leads to an increased incidence of vomiting is not known because this aspect has not been investigated. Fu *et al.* did notice a decrease in post-operative nausea and vomiting along with a decrease in the hypnotic drug requirement in the LP, but they have attributed this to the changing levels of sex hormones in the cycle.^[43] We suggest that this topic is open for research.

Table 3: Studies on post-operative nausea and vomiting; perioperative blood loss and haemodynamic response

Parameters observed	Findings as per phase of menstrual cycle				References
	Follicular	Ovulatory	Luteal	Menstrual	
Haemodynamic response to laryngoscopy and tracheal intubation					
Rate pressure product	Increases				Hanci <i>et al.</i> ^[5]
PONV					
PONV	Higher		Higher		Panditrao and Panditrao, ^[50] Beattie <i>et al.</i> , ^[51] Šimurina <i>et al.</i> ^[52]
		Higher†		Higher**	Honkavaara <i>et al.</i> ^[53]
PONV in OCP taking patients		Higher			Bacić <i>et al.</i> ^[54]
PONV in non-OCP taking patients				Increases*	Matchock <i>et al.</i> ^[55]
	No changes				Matchock <i>et al.</i> ^[55]
					Ramsay <i>et al.</i> , ^[56] Gratz <i>et al.</i> ^[57]
Effect on perioperative blood loss					
Perioperative blood loss					Sariguney <i>et al.</i> ^[58]
	No difference				Baron <i>et al.</i> , ^[59] Findikcioglu <i>et al.</i> , ^[60] Lin <i>et al.</i> ^[61]
	Higher†				Findikcioglu <i>et al.</i> ^[62]

*Perimenstrual; **Premenstrual; †Periovulatory. PONV – Post-operative nausea and vomiting; OCP – Oral contraceptive pills

Perioperative blood loss

Very few studies have addressed this topic.^[58-62] Surgery on hormonally sensitive female tissues such as the breast and uterus may produce more perioperative blood loss depending on the menstrual phase; however, there are conflicting results. Among studies on surgery in hormonally independent organs too, like the nose and abdomen, there are conflicting results [Table 3].

CONCLUSION

Based on the limited data available, the anaesthesiologist should keep in mind the possibility of the occurrence of unfavourable physiological and systemic events in the surgical patient in the premenstrual, menstrual, preovulatory and ovulatory phases. A decreased requirement of intravenous sedative and anaesthetic drug requirements and an improvement in pulmonary function in the LP are noteworthy findings. As regards the question of choosing a favourable phase (FP/LP) for anaesthesia and surgery, the evidence is currently scarce with mixed results suggesting a few favourable points and a few drawbacks in both phases. We cannot really suggest any phase favourable for surgery and anaesthesia; nevertheless, we urge anaesthesiologists to conduct good quality research including randomised clinical trials on this very promising subject.

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Conflicts of interest

There are no conflicts of interest.

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