



A study of menstrual cycle effects on pain perception, haemodynamic response to laryngoscopy, and postoperative outcome in gynaecological laparoscopy

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ABSTRACT

Background: The physiological alterations that occur during the females' reproductive age due to hormonal fluctuations throughout the menstrual cycle may affect the perioperative period and impact the postoperative outcome. This study evaluated the impact of menstrual cycle phases on pain perception, haemodynamic response to laryngoscopy, postoperative agitation, nausea, and vomiting in women undergoing laparoscopic gynaecological procedures.

Methods: This prospective observational study included 60 women who were randomly assigned to have diagnostic gynaecological laparoscopy during their menstrual cycle's luteal or follicular phases. Patients were divided into two groups: follicular and luteal group. Preoperatively a blood sample was withdrawn for measurement of norepinephrine, estradiol, and progesterone levels. Anaesthetic techniques were standardized in both groups. In the postoperative period, another blood sample was withdrawn from all patients and sent for norepinephrine measurement.

Before induction of anaesthesia, baseline HR, SBP, DBP, and MAP were measured. Then, following endotracheal intubation at 1, 3 and 5 minutes. Pain perception was assessed using Numerical Rating Scale (NRS); in response to IV cannulation, then postoperative abdominal pain and shoulder referred pain were assessed every 15 minutes till the end of 1st hour, then every 6 hours till discharge. The incidence of postoperative nausea and vomiting was recorded at the same time points of pain assessment. Postoperative agitation was assessed using Richmond Agitation-Sedation Scale (RASS).

Results: Women in the follicular phase showed higher postoperative pain, higher incidence of postoperative nausea, and more increase in HR and delayed return to baseline value post tracheal intubation as compared to luteal phase.

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1. Introduction

The menstrual cycle is distinguished by multiple hormonal swings involving oestrogen and progesterone. The physiological effects of oestrogen and progesterone are diverse. The impact of the menstrual cycle physiology on anaesthesia is a subject of much debate [1]. The premenstrual syndrome (PMS) [2,3] which is most probably disregarded in clinical studies, has an effect on pain perception. The sex steroids: estrogens, androgens, and progesterone are largely produced in the ovaries, adipose tissue, and the brain in women. They exert their actions through either the classical (intracellular) pathway, or a non-classical (membrane) pathway [4,5]. Steroid hormones with nervous system action are referred to as "neurosteroids" or "neuroactive steroids" [4,6,7]. They may be produced de novo by neurons and glial cells in the central and peripheral nervous systems, or they may be peripherally synthesised and subsequently cross the blood-brain barrier [8]. Neurosteroids control several

brain regions that are important in the regulation of mood, behavior, and cognition [9,10]. There are two types of oestrogen receptors, ER α and ER β , which are widely distributed throughout the body. [11]. As a result, estrogens regulate and affect a wide range of transmitters and functions in the central nervous system such as glutamate [12,13], dopamine [14], serotonin [15], and norepinephrine [16]. Regarding the processing of pain, the impact of estrogens on the control of endogenous opioids, such as enkephalins, is of great interest and affects several parts of the brain [17] as well as the spinal cord [18]. There are two isoforms of progesterone receptors: PR-A and PR-B [19]. Progesterone affects not just its own receptors but also other systems. Allopregnanolone, a well-known metabolite of it, is a GABA-A receptor agonist [20]. Acute postoperative pain is complicated and affected by a number of variables, including gender. [21]. Pain is modulated at several sites, including the primary afferents, spinal cord, brainstem, and cerebrum. [22].

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Since gonadal hormone receptors are present all across the neurological system [23], it is possible that these hormones will affect a variety of locations to control the perception of pain [24–27]. Menstrual cycle changes in female sex hormones may affect pain sensitivity, presumably through interactions with serotonergic and noradrenergic neurons in the nucleus raphe magnus and locus coeruleus, which have oestrogen and progesterone receptors [28], that affect sensory neurons and inhibitory pain pathways [29–31]. In conclusion, the balance between these hormones' pronociceptive and antinociceptive effects [32] will likely determine their overall impact on pain sensitivity. Gynaecological laparoscopy is one of the most common surgeries performed in women [33]. Although the duration of the recovery time and length of hospital stay are usually shorter after laparoscopic surgery, postoperative pain is the most common complaint. Following laparoscopic surgery, postoperative pain include; incisional pain which is a parietal pain, deep intra-abdominal pain which is a visceral pain, and shoulder pain which is a referred pain [34]. Laryngoscopy and endotracheal intubation are two of the most stressful medical procedures that result in immediate hemodynamic reactions [35]. This was first described by Reid and Brace [36]. After laryngoscopy, the reaction begins within five seconds, peaks in one to two minutes, and then recovers to normal within five minutes [37]. According to certain research, it has been linked to higher plasma concentrations of catecholamines, namely norepinephrine and to a lesser extent epinephrine [38]. With the assumption that, the menstrual cycle's ovarian hormonal changes are linked to neurohumoral changes that control the cardiovascular system [39,40]. Several attempts remaining to clarify the influence of different phases of menstrual cycle, and gonadal hormones on plasma norepinephrine level and haemodynamic response to laryngoscopy and tracheal intubation. Postoperative nausea and vomiting (PONV) is one of the common and distressing problem in the postoperative period [41–45]. The high rate of PONV in women, which begins during the reproductive period and rises at the start of and during pregnancy, emphasizes the part that sex hormones play a role in this process [46]. According to certain research, vomiting syndromes are influenced by hormonal changes, particularly oestrogen [47–49].

Emergence agitation during the immediate post-anaesthetic period is common [50]. Despite being brief in duration, postoperative agitation (POA) is potentially harmful to the patient and the recovery staff [51]. Similarly, profound sedation in the post-anaesthesia care unit has been associated with increased adverse events, including respiratory complications [52,53]. Progesterone is thought to have a sedative effect via directly acting on the GABAA receptor through its metabolites (5 α - and 5 β -pregnanolone) [54]. Compared to progesterone, oestrogen seems to have the opposite effect on the GABA system in the central

nervous system. It has been discovered that oestrogen has excitatory effects on the cerebellum and cerebral cortex and reduces GABAA-mediated inhibition in the hippocampus [55].

2. Patients and methods

After approval from the Ethics Committee of the Faculty of Medicine, this prospective observational observer blinded study was conducted during the year of 2021 in El Shatby Alexandria University Hospital and included 60 adult women aged 18 to 35 years with a body mass index (BMI) between 18.5 and 30 kg/m², physical status grades I or II according to the American Society of Anesthesiologists (ASA) and scheduled for diagnostic gynaecological laparoscopy under general anaesthesia. The sample size was calculated by Medical Research Institute, Department of Medical Statistics.

The consultant gynaecologist who was participating in the study recruited the patients. Seventy women were assessed for eligibility to participate in this study, 60 patients were enrolled, with 10 patients excluded for failing to satisfy the inclusion criteria, and there were no dropouts over the duration of the study. A total of 60 women completed the 24 hours of study period (Figure 1). Women were randomly assigned to have surgery during either the luteal or follicular phases of their menstrual cycle. The anaesthesiologist and the research staff involved in the collection of data were blinded to the menstrual cycle phase.

Patients were divided into two groups: follicular (F) and luteal (L) group, and all patients have given their informed consent.

The menstrual cycle phase was determined according to:

Days counted from day one of the previous menstrual period. Days 6–12 have been designated as follicular, and days 20–24 as luteal.

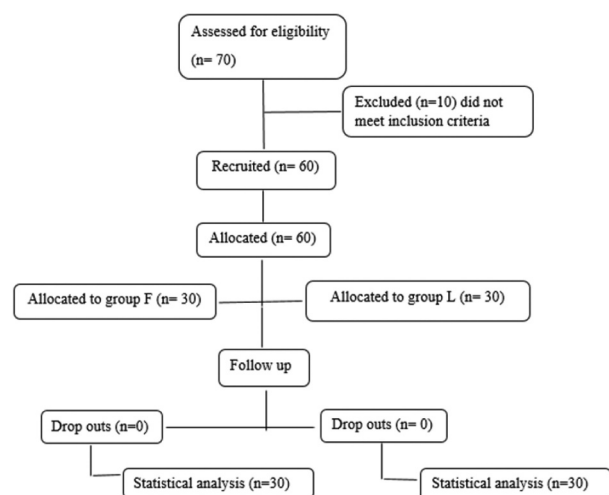


Figure 1. Flow chart of patients.

- (1) Measurement of estradiol and progesterone level on the day of surgery [56].

The gynaecologist participating in the study, performed vaginal ultrasonography on the same day of surgery to confirm the menstrual cycle phase [56].

Evaluation of the patients was carried out through history taking, clinical examination, routine laboratory investigations, and the concept of a numerical rating scale (NRS) for pain was explained to the patient.

On the morning of the procedure: At 6 am, in the ward, all patients were placed in a rest supine position and a large 18 gauge antecubital IV line was inserted to allow blood sampling without a tourniquet. Blood samples were sent to the laboratory for measurement of norepinephrine levels.

In the preoperative holding area: blood samples were collected from each patient and sent to the laboratory for measurement of estradiol and progesterone levels. Then, all patients received premedication with 0.1 mg/kg midazolam. Prophylactic antiemetics were not given to the patient, which was the standard of care in our hospital. Preloading was done with ringer lactate fluid 15 ml/kg.

Anaesthetic technique: Upon entering the operating room, all standard monitors were attached. Both groups' anaesthesia techniques were standardised. All patients received general anaesthesia; following preoxygenation with 100% oxygen, induction of anaesthesia was performed using fentanyl 1 mcg/kg, propofol 2 mg/kg, and atracurium 0.6 mg/kg, and trachea has been intubated using the appropriate size of ETT after 2 minutes of mask ventilation. Isoflurane 1.2% in oxygen was used to maintain anaesthesia. End-expiratory CO₂ partial pressure was kept between 34 and 40 mmHg using mechanical ventilation. Throughout the procedure, arterial blood pressure, heart rate, oxygen saturation, and ETCO₂ were continuously monitored. A highly skilled gynaecologist performed all laparoscopic surgeries using the same instrumentation. Pneumoperitoneum was maintained constant to 12 mmHg. Before skin closure, an IV infusion of 1 g paracetamol was given for analgesia. In the postoperative period, after 30 minutes of recovery, all patients had another blood sample withdrawn and sent to the laboratory for measurement of norepinephrine level. Then, all patients have received ketorolac 30 mg/8 hours.

3. Measurements

A. Demographic data: age, weight in kg, and body mass index.

B. Hormonal level: preoperative oestradiol and progesterone levels. Pre- and post-operative norepinephrine level.

C. Haemodynamic response to laryngoscopy: Before induction of anaesthesia; a baseline heart rate (HR), systolic blood pressure (SBP), diastolic blood pressure

(DBP), and mean arterial blood pressure (MAP) were measured. Then following laryngoscopy and endotracheal intubation, the same parameters were measured again at 1, 3 and 5 minutes.

D. Pain perception: was assessed using an 11 point numerical rating scale (NRS). Assessment of pain in response to IV cannulation was done just after the insertion of the IV line. Assessment of postoperative pain, including abdominal pain and shoulder referred pain was done every 15 minutes till the first hour, then every 6 hours till discharge. When postoperative pain is NRS4, patients have received nalbuphine 0.15 mg/kg IV. The time to first analgesic request and total doses given was recorded.

E. Postoperative nausea and vomiting (PONV): postoperative nausea (PON), vomiting (POV), and the use of rescue antiemetic were all assessed at the same time points as pain. A 10 cm visual analogue scale (VAS) was used to determine the severity of PON. Rescue antiemetic (Ondansetron 4 mg IV) was administered to patients who had two or more bouts of vomiting and/or retching within 30 min, any nausea lasting longer than 15 min or nausea VAS score 5 or higher. Both the total number of antiemetic dosages provided and the time it took before the first request were noted.

F. Postoperative agitation (POA): The Richmond Agitation-Sedation Scale (RASS) [57] was used to assess the incidence of postoperative agitation (Table 1).

4. Results

Age, body weight, and body mass index did not statistically differ between the two groups.

The preoperative oestradiol and progesterone levels were significantly higher in the luteal group (Figure 2, 3).

The preoperative norepinephrine level and the postoperative one did not statistically differ between the two groups (Figure 4a).

Upon comparing the postoperative norepinephrine level with the preoperative level (Figure 4b); there was a high statistically significant increase in the postoperative norepinephrine level in both groups (group F: $P_1 = 0.001$), (group L: $P_1 = 0.002$) which is most probably due to surgical stress. However, there was no statistically significant difference between the two groups in this percent change from the pre to the postoperative value ($P\%$ change = 0.918).

The baseline HR, SBP, DBP, or MAP did not statistically differ between the two groups. By comparing the values of these haemodynamic parameters at different times of measurement to the baseline values in both groups: There was a statistically significant increase in HR (Figure 5) in group F at 1 min post-intubation ($p_1 = 0.004$) then this difference became not significant at 3 min ($p_1 = 0.508$), then at 5 min. ($p_1 = 1.000$) the majority of cases returned to baseline value. By comparing the heart rate values at different times of measurement to

Table 1. Richmond agitation–sedation scale [57].

Score	Term	Description
+4	Combative	Overtly combative or violent; immediate danger to staff
+3	Very agitated	Pulls on or remove tube(s) or catheter(s) or has aggressive behavior toward staff
+2	Agitated	Frequent non purposeful movement or patient–ventilator dyssynchrony
+1	Restless	Anxious or apprehensive but movements not aggressive or vigorous
0	Alert and calm	
-1	Drowsy	Not fully alert, but has sustained (more than 10 seconds) awakening, with eye contact, to voice
-2	Light sedation	Briefly (less than 10 seconds) awakens with eye contact to voice
-3	Moderate sedation	Any movement (but no eye contact) to voice
-4	Deep sedation	No response to voice, but any movement to physical stimulation
-5	Unarousable	No response to voice or physical stimulation

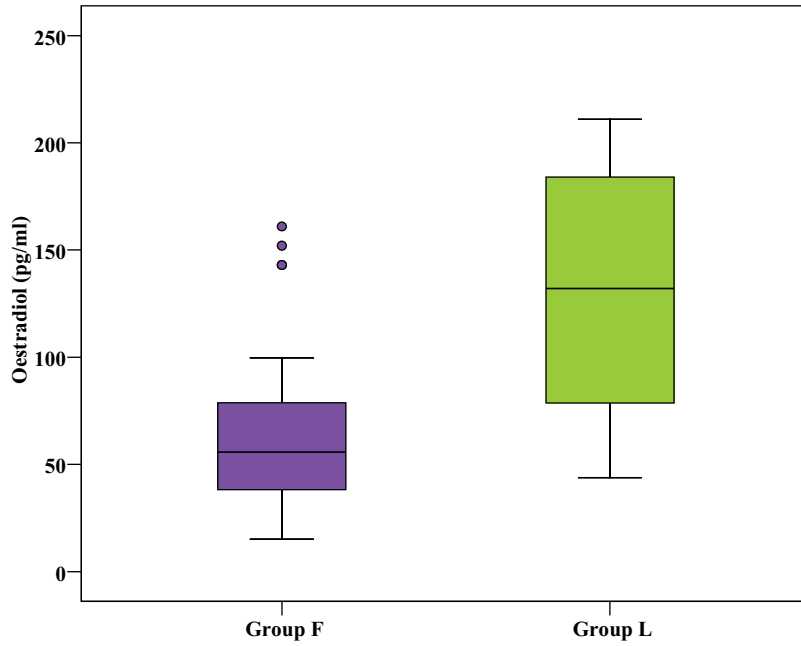


Figure 2. Comparison of the two studied groups based on preoperative oestradiol levels.

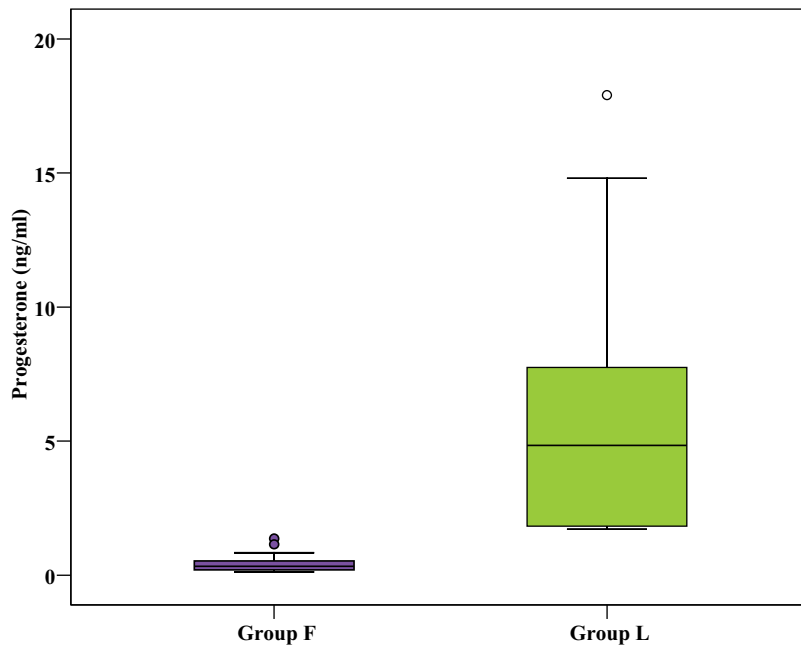
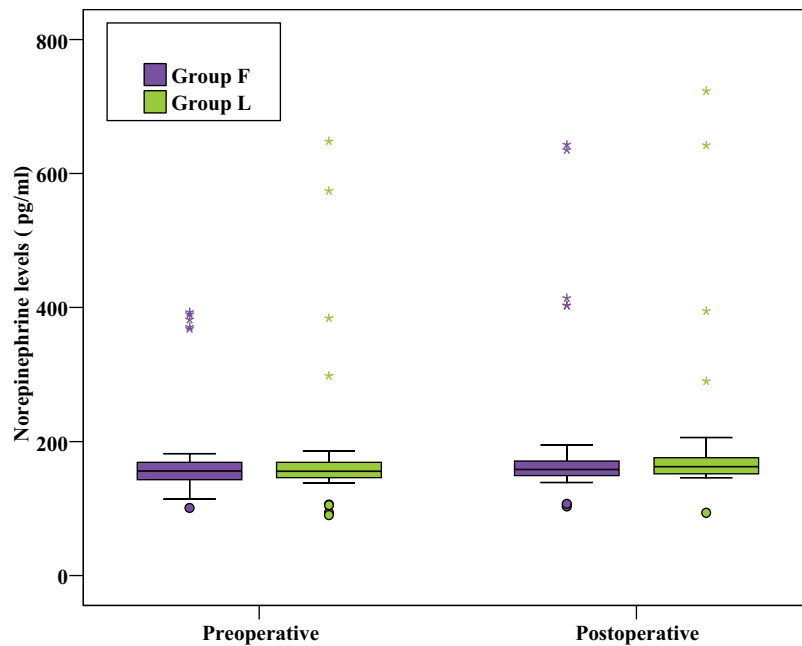
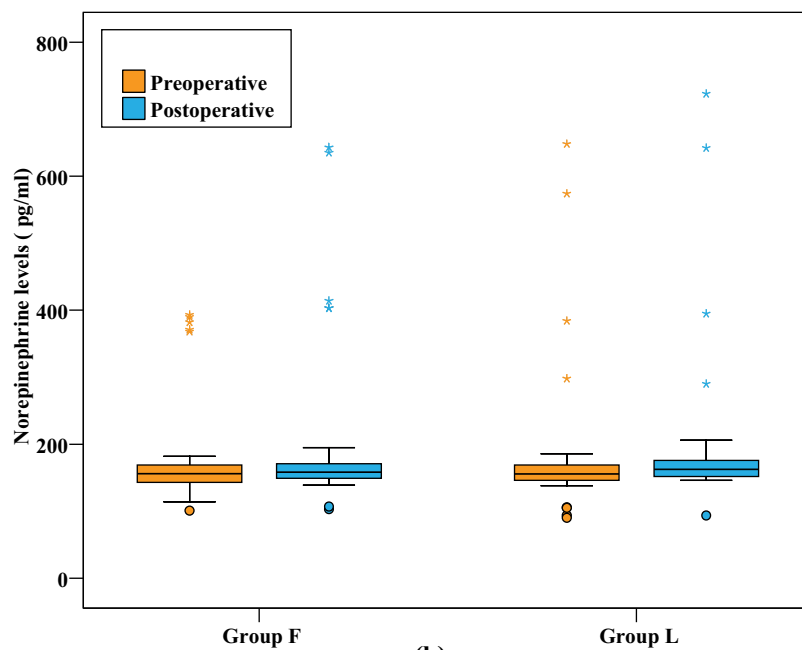


Figure 3. Comparison of the two studied groups based on preoperative progesterone levels.



(a)



(b)

Figure 4. Comparison of the two studied groups based on preoperative and postoperative norepinephrine levels.

the baseline value in group L, there was an increase in HR at 1 min post-intubation, but this was not statistically significant ($p_1 = 0.086$). At 3 min, the majority of cases returned to baseline value ($p_1 = 1.000$). By comparing the two groups; there was a statistical increase in HR in group F at 3 min ($p = 0.024$) and at 5 min ($p = 0.034$).

This means that females in group F experienced a significant increase in HR at 1 min after intubation and delayed return to baseline value till 5 min after intubation, while females in group L do not experience a significant increase in HR after endotracheal intubation.

The SBP, DBP, and MAP post-endotracheal intubation did not statistically differ compared to the baseline values in both groups and also these values did not statistically differ between both groups at different study times.

Pain perception has been assessed using Numerical Rating Scale (NRS) several times; NRS in response to IV cannulation did not statistically differ between the two groups (p value = 0.626), as in group (F) it ranged from 0 to 6 with a mean value of 3.27 ± 1.95 and in group (L), it ranged from 0 to 7 with a mean value of 3.10 ± 2.12 . The postoperative abdominal pain NRS, There were

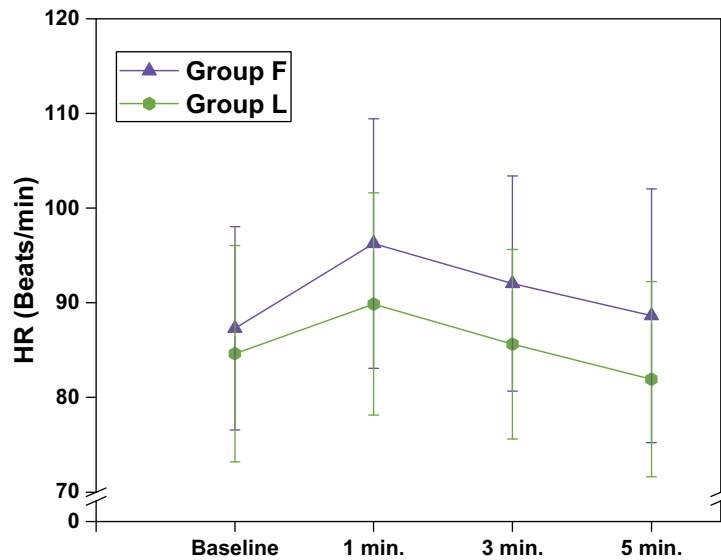


Figure 5. Comparison of the two studied groups based on heart rate changes.

statistically significant differences in postoperative abdominal pain NRS between both groups at 15 minutes in the recovery room, then at 6, 12, and 24 hours in the ward (p values were 0.030, 0.001, 0.035, and 0.048, respectively) showing that pain scores were higher in group (F) than group (L) in these time points (Figure 6). The NRS for postoperative shoulder pain did not statistically differ between the two groups. This means that the follicular group experienced more postoperative abdominal pain than the luteal group.

The time to first postoperative analgesic (nalbuphine) request did not statistically differ between the two groups (p value = 0.178). However, the total number of postoperative nalbuphine dosages required was higher in the follicular group (p value = 0.033) (Figure 7a, 7b).

The incidence of postoperative nausea (PON) and vomiting (POV) were recorded at the same time points of pain assessment. Severity of PON was evaluated using visual analogue scale (VAS) for nausea. POV was recorded as any episode of vomiting or retching. The incidence of POV did not statistically differ between the two groups (Figure 8). However, the follicular group's nausea score (the VAS for nausea) was statistically significantly greater than the luteal group's at 15 minutes postoperatively only (p = 0.043) (Figure 9)

There was no statistically significant difference in the time to first postoperative rescue antiemetic (ondansetron) request (p = 0.109) or total postoperative doses administered to the patients (p = 0.832) between the two studied groups.

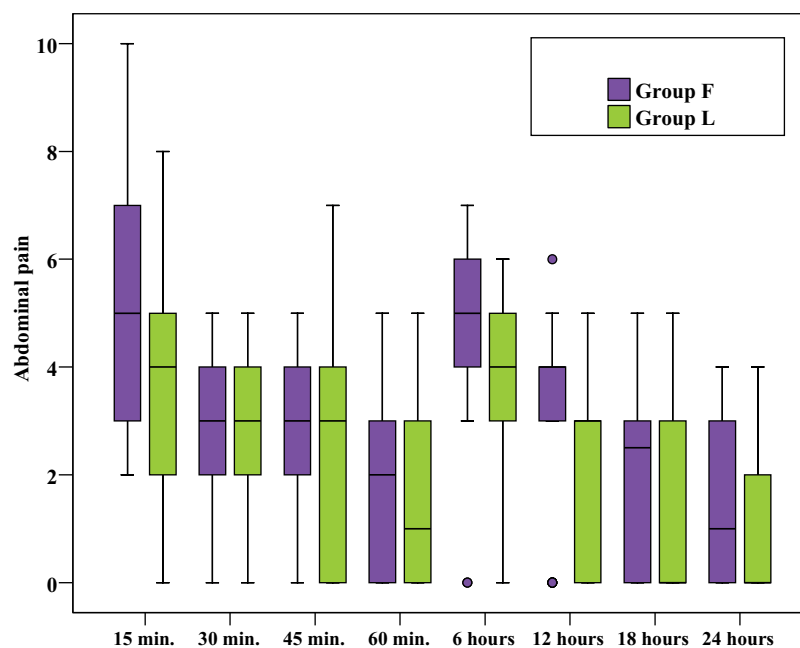
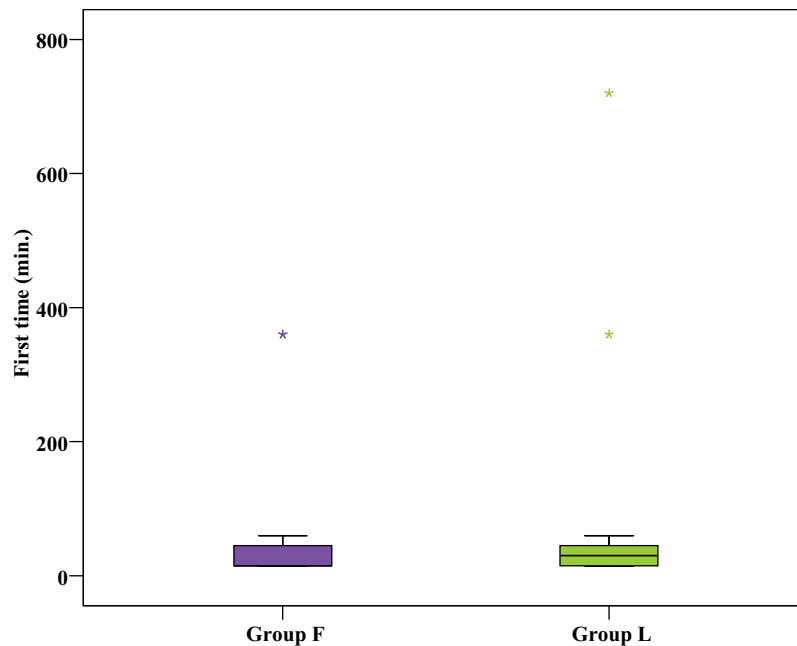
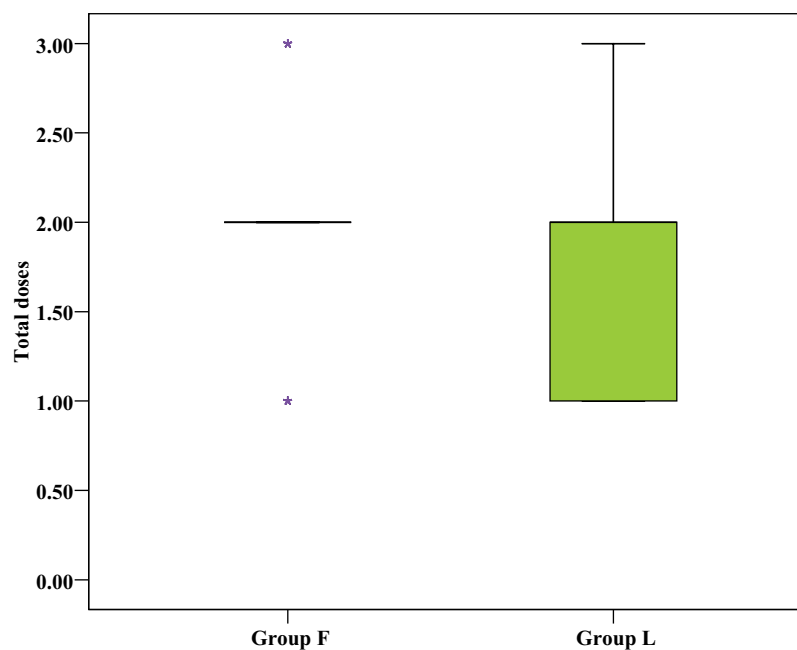


Figure 6. Comparison of the two studied groups based on postoperative abdominal pain NRS.



(a)



(b)

Figure 7. Comparison of the two studied groups based on postoperative abdominal pain NRS.

The emergence agitation-sedation score did not statistically differ between the two groups as all patients' RASS ranged from -2 to $+2$ (Figure 10).

5. Discussion

Acute postoperative pain is complicated and influenced by a number of factors, including gender. The gonadal hormones may have a complicated effect on pain perception, through influencing cognition,

emotions, context, and the biological condition of the neural structures or acting directly on pain mechanisms [58]. Since gonadal hormone receptors are present all across the neurological system [23], it is possible that these hormones will affect a variety of locations to control the perception of pain.

Oestrogen appears to affect cardiovascular function via a variety of pathways, including stress-induced stimulation of the hypothalamic-pituitary-adrenal and sympatho-adrenomedullary systems [39,40,59].

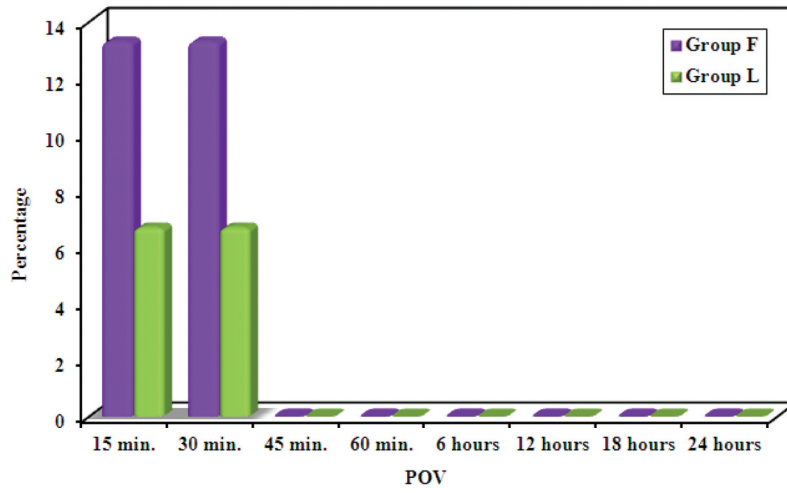


Figure 8. Comparison of the two studied groups based on POV.

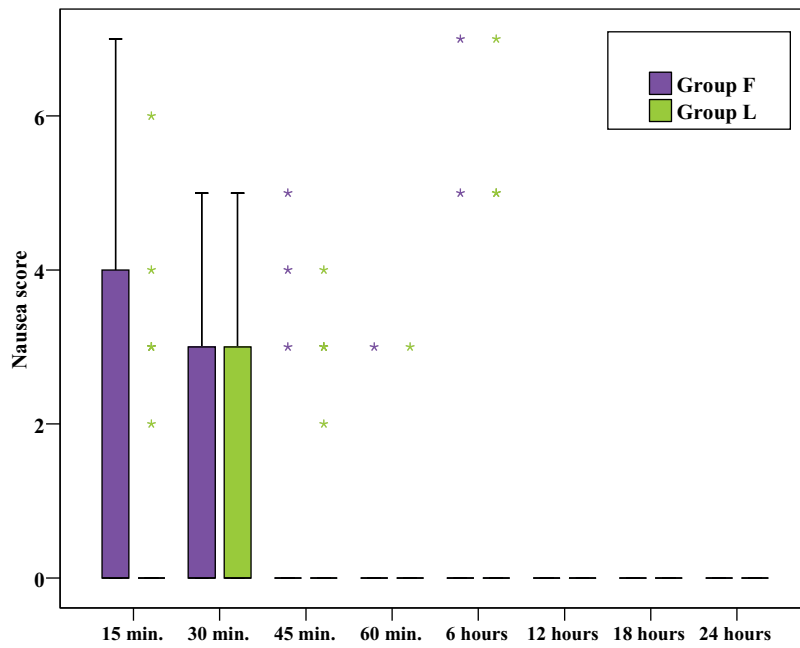


Figure 9. Comparison of the two studied groups based on VAS for nausea (PON).

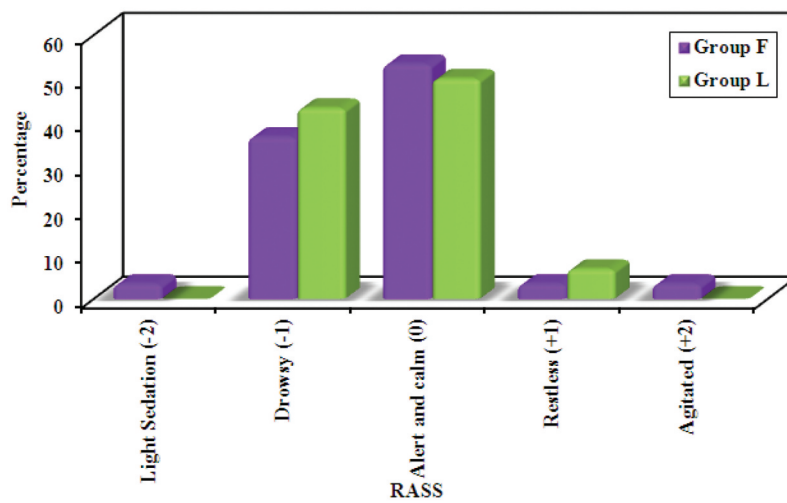


Figure 10. Comparison of the two studied groups based on RASS.

Oestrogen levels fluctuate during the course of the menstrual cycle; hence, cardiac autonomic nervous system activity may also change [60].

The incidence of PONV is two to three times greater in females than in men, with female gender continuously being the main risk factor for PONV [41,61]. The incidence of PONV following laparoscopic gynaecological procedures under general anaesthesia may be as high as 71% [62]. The menstrual cycle has been linked to PONV in a number of research; however, the findings from those studies have been inconsistent [63–66]. These differences have been linked to variations in female sex hormone levels throughout the menstrual cycle.

Emergence agitation during the immediate postanaesthetic period is common [50] and associated with increased adverse postoperative outcome [67]. Indisputably, calm patient is the ideal recovery outcome. There is mounting evidence that patient sex influences postoperative results, particularly the speed with which patients recover from general anaesthesia [68–70]. It is unclear if this is related to pharmacokinetic or pharmacodynamic differences between sexes [71].

The aim is to determine the relationship between menstrual cycle, postoperative pain, PONV, postoperative agitation, and analgesic/antiemetic requirements.

The demographic values in the current study, such as age, body weight, or body mass index, did not statistically differ between groups.

Current results showed that postoperative abdominal pain perception was higher in the follicular group than the luteal group, specifically at these time points; 15 minutes in the recovery room, and at 6, 12, and 24 hours in the ward.

Previous studies done on experimental pain have demonstrated diverse results, in the follicular phase, they demonstrated higher thermal pain threshold and thermal sensation of cold threshold; nevertheless, pressure pain threshold and ischemic pain threshold were higher in the luteal phase than in the other stages of the cycle [72–75]. This finding implies that stimulation modality is crucial when assessing how the menstrual cycle affects pain.

There is very little research on the effect of menstrual cycle phases on acute postoperative pain perception.

In agreement with our study, Piroli et al. [76] have found that the follicular group showed a pain score that is higher than the luteal group at the time of venous cannulation and late postoperative period (in the ward 12 to 24 hours). Also, Hellström and colleagues [77] examined the impact of menstrual cycle on chronic pain; they showed that women rated pain slightly higher in the follicular phase than the luteal phase. In a meta-analysis conducted by Iacovides and colleagues [78] on effect of menstrual hormones on

chronic pain; they have found that, when oestrogen levels were low or declining, such as during menstruation, pain sensations seemed to be more intense than during the mid-luteal period, when sex hormone levels were at their peak.

However, in a study conducted by Hanci and colleagues [79] have noticed that propofol injection pain was significantly lower during the follicular phase compared to the luteal phase. The lack of measurement of oestrogen and progesterone levels was a weakness of their research. Comparably, Honca et al. [80] evaluated how the menstrual cycle affected the perception of pain associated with rocuronium injection, and found that women scored more withdrawal movements during the luteal phase than during the follicular phase. In a study by Ahmed et al. [81] between two groups of women (follicular and luteal) undergoing total abdominal hysterectomy, there were no differences in pain perception or analgesic requirements at different time points studied, with the exception of rest pain at 12 hours postoperative, which was significantly higher in the luteal group.

On the other hand, Kumar et al. [82] discovered a negative association between postoperative analgesia duration and serum oestrogen levels in women undergoing elective surgical procedures, suggesting that high serum oestrogen levels may be linked to higher pain perception.

Sari et al. [83] evaluated the effects of the menstrual cycle phases on postoperative pain in women who underwent laparoscopic cholecystectomy during either follicular or luteal phase and discovered no difference in acute postoperative pain scores or analgesic consumption over a 24-hour period.

Differences in the type of pain stimulus, the lack of measurement of female hormonal levels, the small sample size used in previous studies and that they sometimes missed to exclude females with premenstrual syndrome, and discrepancies in testing situations (experimental pain versus acute pain versus chronic pain), all these can explain these contrasting results.

Regarding the potential changes in the norepinephrine level with menstrual cycle phases, the preoperative norepinephrine level and the postoperative one did not statistically differ between the two groups.

which is not comparable with the results of Goldstein et al. [84], Blum et al. [85], Nakagawa et al. [86], Minson et al. [87] and Davidson et al. [88], who all have found that noradrenaline was greater in the luteal than in the follicular phase. In healthy women, Feichtinger and associates [89] found increased norepinephrine excretion during menstruation and around the time of ovulation, as well as increased epinephrine excretion in the premenstrual period. Wasilewska and associates [90] discovered that premenstrual urine excretion of both norepinephrine and epinephrine

was increased. Childs and colleagues [91] suggested that the catecholamine stress reactivity was higher in the luteal more than the early to mid-follicular phase. On the other side, a research by McFetridge & Sherwood [92] discovered that women in the luteal phase responded to laboratory stressors less strongly than women in the follicular phase in terms of catecholamine release.

Upon comparing the postoperative norepinephrine level with the preoperative level; there was a high statistically significant increase in the postoperative norepinephrine level in both groups.

This is similar to the findings of Pernerstorfer and colleagues [93] who found that after laryngoscopy and intubation, serum norepinephrine levels were noticeably higher, while epinephrine levels were slightly decreased after induction and remained unchanged after intubation. Similar findings were made by Russell et al. [38] and Shribman et al. [35] about significant increases in norepinephrine and epinephrine serum levels following laryngoscopy and tracheal intubation. Hassan and colleagues [94] came to the conclusion that laryngoscopy and endotracheal intubation considerably contribute to the sympathoadrenal response elicited by supraglottic stimulation.

Regarding the potential effects of the menstrual cycle phases on haemodynamic response to laryngoscopy, there was no statistically significant difference between the basal HR in both phases, but there was a significant increase in HR at 1 min after intubation in group F and delayed return to baseline value till 5 min after intubation, while females in group L did not experience a significant increase in HR after endotracheal intubation.

Sato et al. [95], Bai et al. [96] and McKinley et al. [40] observed contradictory findings to ours. They observed that sympathetic nervous activities are more prevalent in the luteal phase than the follicular phase. On the contrary, the luteal phase showed a larger rise in parasympathetic activity, according to Princi et al. [97] and Chung and Yang [98]. On the other side, Leicht et al. [99] were unable to uncover any proof that changes in autonomic nervous activity as evaluated by HRV spectral analysis were significantly correlated with normal cyclic fluctuations in endogenous ovarian hormone concentrations during the menstrual cycle; this result was similar to that of Kondo and colleagues [100] and Yildirim et al. [101]. Equivalently, according to Teixeira et al. [102], the different menstrual cycle phases did not affect healthy women's resting heart rates, regardless of whether they used oral contraceptives.

In a study conducted by Manhem et al. [103], they concluded that resting levels of heart rate and blood pressure were comparable during the two phases of the menstrual cycle, which were similar to our results,

but at the contrary they found that during mental stress, the luteal phase had much higher heart rate responses, blood pressure, plasma catecholamine concentrations, and subjective stress experiences than the follicular phase did. Minson et al. [104] have demonstrated that no differences were observed between phases for resting heart rate and mean arterial pressure despite the reported higher catecholamine levels and sympathetic activity in the luteal phase than the follicular phase.

In a recent study conducted by Moldovanova and colleagues [105] have demonstrated that in most cases, the hemodynamics across cycle phases were the same both at rest and in response to various stresses. Similarly, Hirshoren et al. [106] observed that the menstrual cycle phases had no impact on resting supine BP and HR.

These earlier researches' contradictory findings on the association between the menstrual cycle and haemodynamics could be attributed to variations in sample size, subject age and physical condition, ECG recording time, and phase investigated (menstruation, follicular phase, ovulation, luteal phase).

Tada et al. [107] in a recent research found that changing sympathetic nervous system activity over the menstrual cycle was not unaffected by major lifestyle variables (diet, physical activity, and sleep). This suggests that future research should take these parameters into account when evaluating the cardiac autonomic function in menstruating women.

By studying the effect of laryngoscopy and endotracheal intubation on blood pressure, there were no statistically significant changes in SBP, DBP, and MAP post-endotracheal intubation in comparison to baseline values in both groups and also there was no difference between both groups in all time periods. This supports other researchers' findings that there is no connection between ambulatory blood pressure and the menstrual cycle phase [39,108]. This result is different from that of Chapman and colleagues [109] who found that blood pressure is lower during the luteal phase and this discrepancy in result may be due to the fact that they did their study under normal circumstances not in perioperative period and they used a small sample size.

However, the absence of consistent evidence argues against female sex hormones having a significant direct influence on blood pressure regulation. It is more plausible that sex hormones' hemodynamic effects are mediated indirectly through interaction with other circulatory regulators [105].

Concerning the potential impact of the menstrual cycle phase on PONV, there was no statistically significant difference in the incidence of POV between the two groups. However, regarding the nausea score (the VAS for nausea), it was statistically significantly higher in the follicular group compared to the luteal group at

15 minutes postoperatively only. However, there was no statistically significant difference in the time to first rescue antiemetic ondansetron request or total delivered doses between the two groups.

In agreement with our study, Gratz et al. [110] and Lee and colleagues [111] have concluded that there are no significant differences in the incidence of PONV among women who underwent surgeries under general anaesthesia in different menstrual phases. Simurina and colleagues [112] have concluded that luteal phase had a lower incidence of PONV in the early postoperative period following gynecologic laparoscopy than follicular and ovulatory phases. In the same way, Sener and colleagues [113] conducted a recent study where they showed that, in the early postoperative time (the second hour), nausea was higher in the follicular phase than in the other phases, and the luteal phase was a predictor for retching.

However, in a study conducted by Honkavaara et al. [66], they investigated the relationship between menstrual cycle and PONV in women who underwent gynaecological laparoscopy using three different anaesthetic techniques without combining the measurement of estradiol and progesterone levels in their study. They concluded that incidence of PONV, and antiemetic consumption were higher during the luteal phase of the menstrual cycle than in the premenstrual, menstrual, and follicular phases.

Jalili and Rashtchi [114] have demonstrated in their study that; the incidence and severity of PONV are unaffected by the menstrual phase.

In our study, the risk of postoperative agitation has been assessed using Richmond Agitation-Sedation Scale (RASS) and there was no statistically significant difference found between the two studied groups.

Studies conducted on this scope in the literature are very limited. Sener and colleagues [113] have found that the frequency of agitation was similar in all groups, and their results were comparable to our findings.

6. Conclusions

- (1) The intensity of postoperative pain perception was greater in the follicular phase, at least following laparoscopic gynaecological surgeries.
- (2) The plasma norepinephrine level did not change throughout the cycle but it increased in response to laryngoscopy and surgical stress in all candidates.
- (3) Haemodynamic response to laryngoscopy and tracheal intubation was higher in the follicular group in the form of increase in HR and delayed return to baseline values.

- (4) The follicular group had a higher prevalence of postoperative nausea.
- (5) The postoperative agitation was not found to be significantly present in any phase of the cycle.
- (6) According to these results, it is better to schedule elective surgeries in the luteal phase (days 20–24) of the cycle.


7. Recommendations

- (1) It may be better in the future to select a larger sample size and use a multicenter study.
- (2) In order to get more knowledge on the subject, it can be advised that future research on various surgical procedures and their relative impact on postoperative pain, nausea, and vomiting during different phases of the menstrual cycle be encouraged.
- (3) Other aspects like behavioural, psychological, and social factors were mentioned as potential factors that might affect patient's response to pain. Therefore, more study is needed to improve our comprehension of the connection between pain, hormonal status, and psychosocial aspects during different phases of the menstrual cycle

Disclosure statement

No potential conflict of interest was reported by the author(s).

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