Patient sex and its influence on general anaesthesia

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SUMMARY

Physiological and pharmacological differences exist between men and women. Women wake faster than men following general anaesthesia. Women also differ from men in their postoperative recovery as reflected by differences in postoperative pain, nausea and vomiting and overall quality of recovery. These gender differences seem to be more pronounced in premenopausal women, suggesting hormonal mechanisms are a major contributing factor.

Key Words: gender, anaesthesia, analgesia, outcome

Men and women differ physiologically and in their responses to some drugs1,2, but are these clinically relevant in anaesthesia? Women have historically been excluded from many drug development studies because of the variability induced by reproductive hormone flux and a concern for potential teratogenicity1,2. This selective exclusion of women from clinical studies may have missed opportunities to identify sex-specific differences in drug metabolism and efficacy3.

There is growing evidence to suggest that patient sex is an independent factor influencing postoperative outcomes and, in particular, speed of recovery from general anaesthesia5-9. Whether this is due to sex-related differences in pharmacokinetics or pharmacodynamics remains unclear10, with some investigators suggesting that the influence of patient sex on anaesthesia requirements and side-effects is clinically insignificant11. This review highlights the physiological and pharmacological differences between women and men relevant to general anaesthesia and recovery after surgery.

PHYSIOLOGICAL DIFFERENCES

Hormonal variability

Many of the physiological differences between women and men could be the result of the direct or indirect actions of female sex hormones. Endogenous female sex hormones are steroid-based substances released in a cyclical manner from the age of menarche to menopause (Figure 1). In the early follicular phase, plasma concentrations of oestrogen, progesterone, follicle-stimulating hormone (FSH) and luteinising hormone are at their lowest, with the oestradiol concentration at levels comparable to males12. Progressively increased oestrogen secretion by the ovaries from mid-to-late follicular phase culminates in a sharp rise in oestrogen concentration; this in turn triggers surges in luteinising hormone and FSH just prior to ovulation.

In the early luteal phase, plasma concentrations of oestrogen decrease while that of progesterone continues to increase and plateau. In the late luteal phase, plasma concentrations of oestrogen and progesterone fall rapidly while FSH concentrations increase until the onset of menses, which then heralds the start of another cycle.

Body composition differences

Women and men have differences in body mass index, waist circumference and body fat composition13. Women typically have higher percentages of body fat (~5 to 10%) and lower muscle mass (~10%) compared with men14. A consequence of increased body fat is that women have a 15 to 20% decrease in total body water compared with men15. Furthermore, the extracellular fluid volume, to which total body water contributes, varies in women during the menstrual cycle as a result of changes in plasma volume16. This is due to
Electrolyte balance in women fluctuates during the menstrual cycle. Plasma sodium levels increase during the mid-follicular and ovulatory stages and decrease throughout the luteal phase\textsuperscript{17}. The decrease in plasma sodium can be attributed to progesterone-enhanced natriuresis during the luteal phase\textsuperscript{17}, as progesterone is a competitive antagonist to aldosterone\textsuperscript{18}.

**Cardiovascular differences**

Although males and females are born with the same number of cardiac myocytes, cardiac mass increases substantially more in men post-adolescence\textsuperscript{19,20}. Despite this, younger women have better diastolic function and a larger left ventricular ejection fraction compared with men\textsuperscript{21,22}. The average resting heart rate is three to five beats faster in women, and this varies during the menstrual cycle, being least during menses\textsuperscript{9}. These cyclic fluctuations in heart rate are not autonomic in nature and persist despite complete autonomic blockade\textsuperscript{23}.
When compared with men, women have a lower 24-hour mean blood pressure, in the order of 6 to 10 mmHg. This changes after menopause and, in fact, blood pressure exceeds that of men by the age of 70 years.

Female sex hormones and androgens are likely to play a role in the cardiovascular differences between the sexes. Oestrogens cause vasodilation due to enhanced production and secretion of the endogenous vasodilator nitric oxide. As with heart rate, blood pressure in women is affected by the fluctuating levels of oestrogen that occur during the menstrual cycle, pregnancy and with exogenous oestrogen supplementation. Like oestrogen, progesterone also lowers blood pressure, but synthetic progestins have been shown to increase blood pressure.

**Respiratory differences**

Women have smaller lung volumes, maximal expiratory flow rates and diffusion surfaces, independent of body size. Women also have reduced ventilatory response to exercise. This is due to smaller diameter airways relative to lung size in women. When women with normal lung function and varying fitness levels are subjected to incremental exercise tests to maximal oxygen consumption, they experience exercise-induced hypoxaemia at levels of maximal oxygen consumption that are substantially lower than those of men. The ventilatory response to CO₂ and hypoxia, and the apnoeic threshold, are greater in men than women. Progesterone is a known respiratory stimulant, with women mildly hyperventilating during the luteal phase of the menstrual cycle and during pregnancy. The luteal phase is associated with an increase in minute ventilation, a reduction in P₅₀ and an increased hypercapnoeic ventilatory response. Increased levels of progesterone also stimulate ventilation at rest and during exercise. Interestingly, despite having a lower P₅₀ during the luteal phase of the menstrual cycle, no change in pH occurs throughout the menstrual cycle. Instead, phase-related changes in acid-base balance occur to ensure hydrogen ion concentrations remain relatively constant.

**Renal differences**

Although women appear to have a lower glomerular filtration rate and renal blood flow compared with men, this difference is accounted for by body size. Varying concentrations of plasma oestrogen have no measurable effect on renal blood flow, renal vascular resistance and filtration fraction, but may play a role in modulating renal tubular function. Plasma renin activity levels are higher in men than in women, and in postmenopausal women compared with younger women.

**Metabolic differences**

Men have a higher basal metabolic rate than women, but this is due to their larger body size. Sedentary energy expenditure has been found to be about 5 to 10% lower in women than men after adjusting for differences in body composition, age and activity. Metabolism also fluctuates with the stage of the menstrual cycle, with progesterone secretion mediating a 9% increase in 24-hour energy expenditure during the luteal phase.

In women, core body temperature fluctuates by 0.3 to 0.5°C during the menstrual cycle. It increases during the luteal phase, reaching peak levels mid-phase due to the thermogenic effects of progesterone. Women and men differ in their thermal responses to exogenous and endogenous heat load and loss during rest and exercise because of their larger ratio of body surface to body mass, greater subcutaneous fat content and lower exercise capacity. Women, though, still maintain similar core body temperatures as a result of greater evaporative efficiency of sweating.

**Table 1**

<table>
<thead>
<tr>
<th>Physiological variable</th>
<th>Female</th>
</tr>
</thead>
<tbody>
<tr>
<td>Body fat</td>
<td>5-10% higher¹³¹³²³</td>
</tr>
<tr>
<td>Muscle mass</td>
<td>10% lower²</td>
</tr>
<tr>
<td>Total body water</td>
<td>15-20% less¹⁴</td>
</tr>
<tr>
<td>Cardiac mass</td>
<td>Lower⁶²³¹</td>
</tr>
<tr>
<td>Diastolic function</td>
<td>Better²¹²²</td>
</tr>
<tr>
<td>Left ventricular ejection fraction</td>
<td>Higher²¹</td>
</tr>
<tr>
<td>Stroke volume</td>
<td>Higher²¹²</td>
</tr>
<tr>
<td>Resting heart rate</td>
<td>Higher⁸¹⁻⁵²</td>
</tr>
<tr>
<td>Cardiac cycle length</td>
<td>Shorter²⁴</td>
</tr>
<tr>
<td>Blood pressure</td>
<td>Lower (6-10 mmHg) premenopause³⁶</td>
</tr>
<tr>
<td>Lung volumes</td>
<td>Lower³¹⁻³⁴</td>
</tr>
<tr>
<td>Expiratory flow rates</td>
<td>Lower³¹⁻³⁵</td>
</tr>
<tr>
<td>Lung diffusion surface</td>
<td>Lower³⁶</td>
</tr>
<tr>
<td>Exercise-induced hypoxaemia</td>
<td>Higher³¹⁻³⁴</td>
</tr>
<tr>
<td>Ventilatory response to hypercapnia</td>
<td>Less³⁶⁻⁶⁰</td>
</tr>
<tr>
<td>Ventilatory response to hypoxia</td>
<td>Less³⁸⁻⁶⁰</td>
</tr>
<tr>
<td>Apnoeic threshold</td>
<td>Less³⁶⁻⁶⁰</td>
</tr>
</tbody>
</table>
Neurological differences

There are many sex differences in brain structure and function\textsuperscript{54-57}. Male brains are on average larger and have a higher neuronal density, but with similar cortical thickness, yet there is more neuronal processing in females\textsuperscript{55}. Some regions of the brain have been found to be proportionally larger in females than males and other regions larger in males\textsuperscript{54}. There are also regional sex differences in cerebral glucose metabolism\textsuperscript{56}, including the amygdala, a key region involved in emotionally-influenced memory\textsuperscript{57}. This might explain the apparent increased risk of awareness during surgery in women.

PHARMACOLOGICAL DIFFERENCES

Pharmacokinetics

Bioavailability

Of the major factors influencing drug absorption, only gastrointestinal motility has been shown to have sex-based differences\textsuperscript{2,58-80}. These are likely to be due to female sex hormones\textsuperscript{59}. Women have lower activity of the enzyme \textit{alcohol dehydrogenase} than men, resulting in higher blood alcohol concentrations in women following ingestion of an equivalent amount of alcohol\textsuperscript{65}. Although sex-based differences in gastrointestinal motility and some gastric enzymes do exist, these are not considered to be clinically significant\textsuperscript{58}.

Volume of distribution

Body fat increases in both sexes with age\textsuperscript{10}. For water-soluble drugs used in anaesthesia (such as muscle relaxants), the volume of distribution can be expected to be lower in women\textsuperscript{10}. Indeed, numerous studies have confirmed that women require less vecuronium\textsuperscript{66-71}, rocuronium\textsuperscript{2}, pancuronium\textsuperscript{72} and atracurium\textsuperscript{73} to produce an equivalent effect to that of men. At equivalent doses plasma concentrations of muscle relaxants are higher in women\textsuperscript{68-72}. For lipid-soluble drugs used in anaesthesia, women can be expected to have a larger volume of distribution. This has been shown with benzodiazepines such as diazepam\textsuperscript{74-76} and midazolam\textsuperscript{77}, and hypnotic drugs such as propofol\textsuperscript{78,79} and etlanolone\textsuperscript{80}.

Sex differences in volume of distribution may be secondary to the physiological changes in water and electrolyte balance that occur during normal and abnormal fluctuations of the menstrual cycle\textsuperscript{75}. To date, few studies have examined the effect of this variability on drug volume of distribution. If changes in drug volume of distribution do occur with the menstrual cycle, they are not likely to be large enough to alter plasma drug concentration and thus are unlikely to be of clinical significance\textsuperscript{7}.

Protein binding

Any sex differences in plasma protein binding will alter the free fraction of available drug and this may contribute to pharmacokinetic differences in drug action between men and women\textsuperscript{8}. Studies investigating the role sex hormones play on plasma albumin levels are inconsistent. In one study, comparing the protein binding of the drugs chlorpromazine, propranolol, meperidine, desipramine, salicylic acid and phenytoin in the plasma of 64 healthy volunteers (35 males and 29 females), patient sex was not an independent factor influencing plasma albumin levels\textsuperscript{8}. However, a study examining the effect of supra-physiological levels of oestrogen on the protein binding of bupivacaine in women undergoing in vitro fertilisation procedures found that oestrogen decreased the concentrations of serum albumin and \textit{alpha}-acid glycoprotein, resulting in higher concentrations of free bupivacaine\textsuperscript{8}. A similar effect was observed with exogenous oestriol lowering levels of \textit{alpha}-acid glycoprotein when propranolol was studied\textsuperscript{8}. During pregnancy the concentration of several plasma proteins decrease, resulting in an increased free fraction of drugs with high protein binding, for example lignocaine, diazepam and propranolol\textsuperscript{8}. However, it is believed that protein binding is not a major contributor to differences in drug activity between men and women\textsuperscript{2,10}.

Drug metabolism

Sex differences in drug metabolism are believed to play the greatest role in pharmacokinetic differences between the sexes\textsuperscript{8}. Although cardiac output and therefore hepatic blood flow is lower in women, it is sex differences in hepatic enzyme activity that is largely responsible for differences in hepatic metabolism and therefore clearance of drugs\textsuperscript{8}. Both phase I and II reactions are likely to be involved\textsuperscript{8}.

Although sex differences in CYP 450 activity have been proposed to exist\textsuperscript{4,5}, current evidence supporting this is limited, non-existent\textsuperscript{6} or conflicting\textsuperscript{4}. Using in vitro techniques, female livers have been shown to have a significantly higher CYP3A4 content\textsuperscript{8} and activity\textsuperscript{8} compared with males, although a later study could not confirm this finding\textsuperscript{8}. Such in vitro studies are limited, however, as they lack the systemic hormonal environment of males and females and this may lead to erroneous results\textsuperscript{8}.

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In vivo studies have also revealed similarly conflicting results. For example, the metabolism of the antibiotic erythromycin is widely used to assess CYP3A4 activity in vivo and one study has found that CYP3A4 activity is significantly greater in women than in men. Verapamil, a non-dihydropyridine calcium channel blocker, is another drug whose metabolism has been used as a marker of CYP3A4 activity and for which hepatic metabolism is greater in women than in men. Midazolam, being a substrate of CYP3A4, has also been used to measure CYP3A4 activity. Most studies have failed to find any significant sex differences in midazolam activity, with the exception of a greater clearance in women.

One reason which may help to explain the conflicting results obtained for CYP3A4 substrates in terms of sex-based differences in hepatic metabolism is the presence of the transporter p-glycoprotein. This is a membrane-bound transport protein which lowers intracellular concentrations of many types of drugs by promoting drug efflux. As a drug needs to be intracellular in order to be metabolised by CYP3A4, higher numbers of the transporter p-glycoprotein at the hepatocyte membrane will decrease the rate of drug metabolism. Men have been found to have more hepatic transporter p-glycoprotein. This results in higher intracellular drug concentrations in female hepatocytes, with subsequent increased CYP3A4-specific drug metabolism and clearance in women for drugs that are both CYP3A4 and transporter p-glycoprotein substrates. Hence this can explain sex-based differences in CYP3A4 activity between midazolam and verapamil. Verapamil is a substrate for both CYP3A4 and the transporter p-glycoprotein; midazolam is only a substrate for CYP3A4.

A possible hormonal effect of oral contraceptive use, menstrual cycle variations and pregnancy, has been postulated as probable components of sex-related differences in drug disposition. Sex hormones influence enzyme activity in hepatocytes by determining the type and quantity of enzymes produced and they do this both in an acute and chronic basis. The use of oral contraceptives may modulate CYP 450 activity. Pregnancy has been shown to increase the activity of the hepatic enzyme CYP2D6. There is also some evidence that drug clearance may vary with the day of the menstrual cycle. For example, the clearance of theophylline and caffeine are highest during the early follicular phase and most prolonged during the mid-luteal phase.

Menstrual variations in the clearance of intravenous anaesthetic drugs have not been studied. Previous studies examining the influence of the menstrual cycle on midazolam, alprazolam and alfentanil metabolism have found no correlation between the time of the cycle and drug clearance. Alfentanil clearance, which is almost entirely dependent on hepatic CYP3A4 activity, is sex-dependent with clearance higher in women than in men. Hormonal influences may be involved as clearance is approximately 70% higher in women less than 50 years compared with older women, implying differences between pre- and post-menopausal women.

Of the phase II reactions involved in drug metabolism, only glucuronidation may be sex-dependent with higher activities found in women. Drugs such as oxazepam, temazepam and paracetamol are cleared faster in men. Possible hormonal influences may occur as the oestrogen component of the oral contraceptive pill has been associated with increased conjugation activity.

From an anaesthetic point of view, propofol is a drug whose clearance depends on both metabolism and distribution. Its rapid metabolism is linked to glucuronidation of the parent drug to form the propofol glucuronide (62%) and via cytochrome P450 to form other minor conjugates (38%). Numerous studies have shown a higher clearance of propofol in women, but these differences are thought to be of limited clinical importance.

Renal clearance of drugs

Renal clearance of drugs is dependent on glomerular filtration and/or tubular secretion. As the glomerular filtration rate is proportional to body weight, any sex differences in the rate of renal excretion of most drugs would reflect differences

<table>
<thead>
<tr>
<th>Pharmacological variable</th>
<th>Females</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bioavailability</td>
<td>Decreased gastric emptying time</td>
</tr>
<tr>
<td>Volume of distribution</td>
<td>Decreased for non-depolarising muscle relaxants, increased for diazepam, midazolam, propofol, etanolone</td>
</tr>
<tr>
<td>Protein binding</td>
<td>Increased oestrogen decreases albumin and alpha, acid glucoprotein</td>
</tr>
<tr>
<td>Drug metabolism</td>
<td>Possible increased or decreased CYP3A4 activity, decreased glucuronidation</td>
</tr>
<tr>
<td>Renal clearance</td>
<td>No difference</td>
</tr>
</tbody>
</table>
in body size rather than true sex differences. Lower secretion rates for para-aminohippuric acid and frusemide have been measured in female rats and for amantadine in women. But more studies are needed to better understand the extent of sex differences on renal tubular secretion.

SEX DIFFERENCES IN ANAESTHESIA

Pharmacodynamics

Sex hormones probably play a role in modulating sex differences in anaesthesia. Oestrogen, progestin and androgen receptors have been identified in mammalian brains, with effects beyond that involved in reproductive behaviour and function. Oestrogen and progesterone bind to intracellular receptors that influence genomically-directed protein synthesis, as well as by altering neuronal excitability on neurotransmitter-gated ion channels such as the GABA<sub>A</sub> receptor complex. Of the sex hormones, progesterone and its metabolites are known to have hypnotic, anxiolytic, anti-convulsant and analgesic effects. They have also been shown to increase the potency of inhalational anaesthetics, to demonstrate dose-dependent hypnotic effects, to induce sleep in humans and induce general anaesthesia in animals at higher doses. Indeed, progesterone and its metabolites have similar effects on sleep EEG patterns as the benzodiazepines.

Increased production of progesterone during the luteal phase of the menstrual cycle may decrease anaesthetic requirements. Women in the luteal phase of the menstrual cycle, when serum progesterone levels are at their highest, were found to have a significantly lower minimum alveolar concentration (MAC) value for sevoflurane during the maintenance phase of anaesthesia compared to women in the follicular phase. Progesterone is thought to exert its sedating effect through the direct action of its metabolites (particularly 5α-pregnanolone and 5β-pregnanolone) on the GABA<sub>A</sub> receptor, with comparable equimolar potency to that of benzodiazepines.

Unlike progesterone, oestrogen appears to have the opposite effect on the GABA system in the central nervous system. Oestrogen has been shown to suppress GABA<sub>A</sub>-mediated inhibition in the hippocampus, and have excitatory effects on the cerebral cortex and cerebellum. Oestrogens also potentiate the binding of glutamate to N-methyl-D-aspartate receptors. Furthermore, changes in plasma oestrogen levels are accompanied by changes in a variety of other neurotransmitters including acetylcholine, dopamine, serotonin and endorphins.

General anaesthetics affect a number of different neurotransmitter receptors including the GABA<sub>A</sub>, acetylcholine and glutamate receptors in the brain, and glycine receptors in the spinal cord. Furthermore, as distinct neuroanatomic sites correlate with distinct anaesthetic properties, it is possible that altered modulation of these same receptor complexes at these sites of anaesthetic action by sex steroid hormones may explain some of the reported sex differences in general anaesthesia. Few studies have specifically investigated possible sex differences in the pharmacodynamic effects of anaesthetic drugs.

Inhalational agents

The MAC of a volatile anaesthetic is a useful measure of pharmacodynamic effect and this may be sex dependent. In one small study, women required larger concentrations of desflurane to prevent movement in response to noxious electrical stimulation compared to men. Xenon, an inert gas used to maintain general anaesthesia, has sex differences in elderly patients with women requiring 26% less xenon than men to achieve MAC during laparotomy. Pregnancy is a time of hormonal flux with increased circulating levels of oestrogen and progesterone and characterised by a decrease in the MAC of the volatile agents isoflurane, halothane and enflurane.

The concept that MAC may be sex-dependent was not supported by a pooled analysis of 258 patients previously anaesthetised with desflurane, diethyl ether, halothane, methoxyflurane and sevoflurane. However, this retrospective analysis may have been underpowered: extrapolating from the standard errors of the MAC estimates in that study identifies a possible sex difference that would require a larger study to confirm or refute. To date, most studies have been too small and thus underpowered to clinically detect a difference and further properly designed studies are needed.

Propofol

Several studies have found that women recover more quickly from propofol-based anaesthesia compared with men. Although sex differences in pharmacokinetics, with a more rapid decline in plasma propofol concentration in women compared with men, could explain the faster emergence after propofol anaesthesia, sex differences in central sensitivity to propofol may also exist.

The available evidence supporting the influence of patient sex on propofol sensitivity is conflicting.
While one study has found women to be more sensitive to the effects of propofol based on lower plasma concentrations required to produce similar bispectral index (BIS) levels\(^{144}\), other studies have found no difference\(^{146}\) or the reverse to be true\(^{148,149}\). In the same studies, women required more propofol to achieve the same depth of anaesthesia as monitored by Narcotrend\(^{146,147}\). Reduced propofol sensitivity in women is supported by a requirement for more propofol to lose consciousness\(^{5,149,150}\) and to maintain anaesthesia during surgery\(^{149,150}\), when adjusted for body weight. Men are also more readily sedated (as measured by auditory evoked potentials) compared to women when given the same dose of propofol\(^{152}\). Women also respond to verbal stimuli more quickly than men following cessation of a propofol infusion\(^{1}\). Here, no differences in plasma propofol concentrations were observed either at the end of surgery or at the time of emergence\(^{3}\). However, this suggested sex difference in pharmacodynamic effect to propofol may be age-related. In elderly patients, the blood propofol concentrations were approximately 10% lower in female patients\(^{151}\). Interestingly, pharmacokinetic analysis demonstrated a larger volume of distribution and higher clearance in the female patients to account for this difference in plasma concentration\(^{151}\).

Patient sex has not consistently been shown to influence the hypnotic requirements for loss of consciousness. In one study, no sex differences were observed for loss of consciousness with sevoflurane or propofol\(^{146}\) when used with BIS\(^{144}\). This finding contrasts with previous studies which examined sex differences during general anaesthesia\(^{1}\), not just those occurring at loss of consciousness. As the mechanisms responsible for general anaesthesia are dependent not just on hypnosis, but also on amnesia, immobility and analgesia\(^{156}\), other effects of sex on anaesthesia may be occurring to explain these differences. Most victims of awareness under anaesthesia are women\(^{152}\); this suggests that sex may be an independent factor contributing to sensitivity to general anaesthesia. Recent evidence reinforces this view. In a large subset analysis comparing recovery characteristics from general anaesthesia of female and male patients at risk of awareness, women had higher BIS values during maintenance of general anaesthesia despite similar amounts of anaesthetic drug administration\(^{1}\). This suggests that women are less sensitive to the hypnotic effect of anaesthetic drugs than men and this may help explain the faster recovery times in women\(^{144}\).

The reported differences in intraoperative recall and emergence times between men and women appear to be related to lighter levels of hypnosis, as indicated by higher BIS values in women undergoing general anaesthesia\(^{1}\), but this apparent difference may be related to reduced autonomic responses (and generally lower blood pressure) in female patients. This is an alternative explanation as to why women appear ‘less sensitive’ to general anaesthetics. A study titrating anaesthetic drug administration to an objective validated endpoint of hypnotic depth, such as BIS monitoring\(^{1}\), should be able to resolve this issue.

**Clinical differences in men and women following general anaesthesia**

Despite a faster speed of awakening – suggesting a decreased sensitivity to the hypnotic effects of anaesthetic drugs – women do not appear to be discharged any faster after ambulatory surgery compared with men\(^{152}\). Indeed, quality of recovery may be slower in women. Perioperative sequelae such as anaphylactic and anaphylactoid reactions\(^{144}\), pain scores\(^{150}\), postoperative nausea and vomiting (PONV)\(^{156}\), sore throat\(^{157}\), headache and backache\(^{157}\) have also been reported to be significantly higher in women following general anaesthesia and would therefore influence patient quality of recovery.

Female sex has been shown to be associated with a worse outcome in terms of morbidity and mortality\(^{158}\), increased length of hospital stay\(^{158}\) and decreased functional outcome\(^{159}\), following some types of surgery. Also, there is evidence that a sex difference in quality of recovery may extend for months beyond the initial surgery, with female sex associated with more functional impairment after cardiac surgery\(^{160}\) and cholecystectomy\(^{161}\). Sex differences in quality of recovery also contribute to lower rates of patient satisfaction in women following general anaesthesia\(^{162}\).

PONV is a common problem and major contributing factor impairing a patient’s quality of recovery; it also prolongs recovery time and delays patient discharge\(^{163}\). PONV is influenced by many factors including site and duration of surgery, anaesthetic agents and patient sex\(^{164}\). Indeed, female sex is a known risk factor for PONV\(^{5,150,157,163}\); women have a two-fold increased risk, but this decreases after the age of 50 years\(^{165}\). This suggests that hormonal influences may be contributing to the PONV sensitivity. In one study of women undergoing laparoscopic tubal ligation, there was a correlation between the incidence of nausea and the day of the menstrual cycle\(^{166}\). Here, the incidence of
nausea was found to be greatest during the follicular phase compared to the luteal phase, with the peak incidence occurring during day five of the menstrual cycle\textsuperscript{163}. This observation was confirmed in another study involving women undergoing gynaecological laparoscopy and laparotomy\textsuperscript{164}. The greater study involving women undergoing gynaecological surgical procedures\textsuperscript{6,11,156,157,163}. in a wide range of anaesthetic regimens and incidence of PONV in women has been reported cycle\textsuperscript{163}. incidence occurring during day five of the menstrual phase compared to the luteal phase, with the peak nausea was found to be greatest during the follicular phase compared to the luteal phase, with the peak incidence occurring during day five of the menstrual cycle. This observation was confirmed in another study involving women undergoing gynaecological laparoscopy and laparotomy. The greater study involving women undergoing gynaecological surgical procedures in a wide range of anaesthetic regimens and incidence of PONV in women has been reported cycle. Incidence occurring during day five of the menstrual phase compared to the luteal phase, with the peak nausea was found to be greatest during the follicular phase compared to the luteal phase, with the peak incidence occurring during day five of the menstrual cycle. This observation was confirmed in another study involving women undergoing gynaecological laparoscopy and laparotomy. The greater study involving women undergoing gynaecological surgical procedures in a wide range of anaesthetic regimens.

### Table 3

*Summary of sex differences during and following anaesthesia*

<table>
<thead>
<tr>
<th>Anaesthetic variable</th>
<th>Female</th>
</tr>
</thead>
<tbody>
<tr>
<td>Propofol requirements</td>
<td>Decreased sensitivity\textsuperscript{5,6,8,10,16,155}</td>
</tr>
<tr>
<td>Intraoperative bispectral index</td>
<td>Higher\textsuperscript{9}</td>
</tr>
<tr>
<td>Time to eye-opening</td>
<td>Shorter\textsuperscript{5,6,11}</td>
</tr>
<tr>
<td>Postoperative pain</td>
<td>Higher\textsuperscript{155}</td>
</tr>
<tr>
<td>Postoperative nausea and vomiting</td>
<td>Higher (up to 3 times)\textsuperscript{5,6,8,11,156,157,163}</td>
</tr>
<tr>
<td>Sore throat</td>
<td>Higher\textsuperscript{156}</td>
</tr>
<tr>
<td>Headache</td>
<td>Higher\textsuperscript{156}</td>
</tr>
<tr>
<td>Backache</td>
<td>Higher\textsuperscript{156}</td>
</tr>
<tr>
<td>Functional postoperative outcome</td>
<td>Poorer\textsuperscript{5,15,18}</td>
</tr>
<tr>
<td>Hospital stay</td>
<td>Longer\textsuperscript{159}</td>
</tr>
<tr>
<td>Patient satisfaction</td>
<td>Less\textsuperscript{162}</td>
</tr>
</tbody>
</table>

### CONCLUSIONS

Women recover more rapidly from general anaesthesia. The extent and impact of pharmacokinetic and/or pharmacodynamic differences that could explain the apparent reduction in sensitivity to general anaesthetics remains unclear. The female sex hormones, oestrogen and progesterone, may play a role in modulating the beneficial and adverse effects of general anaesthesia in women, and this is likely to influence the rate and overall quality of recovery from general anaesthesia.

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