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Sex and gender differences in anesthesia: Relevant also for perioperative safety?

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Sex (a biological determination) and gender (a social construct) are not interchangeable terms and both impact perioperative management and patient safety. Sex and gender differences in clinical phenotypes of chronic illnesses and risk factors for perioperative morbidity and mortality are relevant for preoperative evaluation and optimization. Sex-related differences in physiology, as well as in pharmacokinetics and pharmacodynamics of anesthetic drugs may influence the anesthesia plan, the management of pain, postoperative recovery, adverse effects, patient satisfaction, and outcomes. Further studies are needed to characterize outcome differences between men and women in non-cardiac, cardiac, and transplantation surgery in order to individualize perioperative management and improve patient safety. Transgender patients represent a vulnerable population who need special perioperative care. Gender balance increases team performance and may improve perioperative outcomes.

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Patient safety, a fundamental principle of medicine since Hippocrates' time (primum non nocere), has evolved dramatically, as medicine has shifted toward an evidence-based practice. However, most of what physicians of all specialties know about diseases is derived from data obtained from male populations, both in animals or in humans. In clinical research, one reason for excluding female subjects from studies on drug development has been the variability induced by reproductive hormonal flux and only recently policies mandating researchers to consider sex and gender in medical trials have become the norm [1]. Acknowledging differences between men and women relevant to anesthesia is of paramount importance to ensuring perioperative patient safety.

Sex and gender: definitions and general implications

The biological differences between men and women are defined by the sex, according to the reproductive organs and functions assigned by chromosomal complement and hormonal activities [2]. The genetic differences that start at conception, together with the testosterone surge at the end of the pregnancy in males, result in sex-differences in physiological patterns and susceptibility to diseases, which combined with hormonal sex-differences affect disease prevalence, symptoms, and response to treatment [3].

Conversely, gender defines the social differences between men and women. According to the WHO definition, gender includes "norms, behaviors and roles associated with being a woman, man, girl or boy, as well as relationships with each other" [4]. The social norms define, perpetuate, and justify different expectations and opportunities for men and women such as social and family roles, job segregation and limitations, dress codes, and health practices [3,5]. Gender also refers to the institutionalization of the norms through distribution of power among genders in the political, educational, and social institutions in society [5].

Gender is not a binary term, as a much broader spectrum exists: cisgender, transgender males and females, gender non-conforming, nonbinary, transitionary, and transexuals [2]. Interestingly, more than two-thirds of women and men report gender-related characteristics traditionally attributed to the opposite sex, and in transgender people, gender identity differs with the sex they were assigned at birth [2,5].

The differences between sex and gender are important for human health, as the associate behaviors lead to epigenetic modifications translated into different biological phenotypes [3]. However, an analysis of the literature found that approximately 9 out of 10 articles use these two terms interchangeably contributing to the confusion and lack of awareness of the importance of sex/gender differences for health [6].

Anesthesiologists, as guardians of patient safety throughout the perioperative journey, should consider relevant sex and gender differences for their practice.

Sex and gender differences and perioperative implications

Preoperative evaluation

Sex and gender differences have been observed in chronic illness, which can significantly impact many of the common causes of perioperative morbidity and mortality. The anesthesiologist has to integrate them into a clinical framework of risk assessment, in order to optimize the perioperative outcomes, decrease the length of hospital stay and readmissions. Preoperative evaluation and preparation are listed among the principal requirements of the Helsinki Declaration on Patient Safety in Anaesthesiology [7].

Cardiovascular diseases (*CVD*) represent the leading cause of death in women [3,8]. The risk factors include both common (i.e. hypertension, dyslipidemia, diabetes mellitus, smoking, obesity, sedentary life, etc.) and sex-specific factors (i.e. oral contraceptive use, premenstrual syndrome, polycystic ovarian syndrome, hysterectomy, etc.) [9]. Although common risk factors are associated with higher hazard ratios for acute myocardial infarction (AMI) in women than in men, endogenous estrogens protect women against CVD until the onset of menopause [8,10,11]. The presence of sex hormones leads to attenuated sympathoadrenal activation, which is further augmented because the pathways regulating the sympathetic nervous system are less sensitive to excitatory stimuli and more sensitive to inhibitory stimuli in women than in men [12].

Clinical phenotypes of ischemic heart disease (IHD) are different in men and women [13]. Men are prone to diseases of the large coronary arteries, while women suffer more from microvascular dysfunction, without obstructive disease, possibly related to increased sensitivity to vasoconstrictor stimuli or lack of vasodilator capacity [8,14]. Consequently, women with IHD have non-exertional pain and other than chest pain symptoms more frequently than men, which explain why they are more often underdiagnosed and influence noninvasive testing and management strategies [8,13]. Anesthesiologists should know that treadmill exercise testing has a higher false-positive rate in women and that coronary cardiac computed angiography (CCTA) may provide more prognostic information for women than for men [9]. However, CCTA exposes breast tissue to radiation, and from this point of view, stress echocardiography is preferred in women [9].

Women receive less evidence-based treatment, including reperfusion therapy, and they have worse outcomes and increased rated of readmission, reinfarction, and death in the first year after AMI, and higher in-hospital mortality after cardiogenic shock complicating AMI [13,15]. They also receive substandard pharmacological treatment, which may need to be optimized perioperatively [16].

Gender-related characteristics also impact adverse cardio-vascular outcomes. Feminine roles and personality traits were associated with higher rates of recurrent acute coronary syndromes (ACS) and major cardiac adverse events compared with masculine characteristics, and mortality one year after an ACS was more strongly associated with gender than with biological sex [17]. Gender determines access to health care, help-seeking behaviors, and individual use of the health-care system, including preventive measures and invasive therapeutic strategies [3].

Gender also influences health providers in decision-making processes. An implicit gender-bias may explain why women's IHD symptoms are often dismissed by doctors or assumed to be psychosomatic [5]. In one study, women with AMI treated by male emergency physicians had a higher mortality than those treated by female physicians, and male physicians were more effective at treating female patients when they worked with female colleagues and when they had experience in treating female patients [18].

Women have a shorter cardiac cycle and are more prone to develop arrhythmias and react differently to antiarrhythmic drugs [12]. As female sex is an independent risk factor for stroke in non-valvular atrial fibrillation (AF), oral anticoagulation for a CHA_2DS_2-VASc score 2 or higher and bridging of anticoagulant medications must be addressed preoperatively [8]. Importantly, aspirin provides greater benefit for women than for men in the primary prevention of ischemic stroke [19].

Women have higher rates of type 2 *diabetes mellitus* (DM) at younger ages, which negate the hormonal protection against CVD in reproductive-age women [20]. Due to sex-specific differences observed in glucose fasting and tolerance, more impaired in men and women, respectively, screening or diagnosis of type 2 DM should be based on the measurement of hemoglobin A1c [3]. There are also differences in the response to antidiabetic drugs, with better response to sulfonylureas (increase insulin secretion) and thiazolidinediones (increase insulin sensitivity) in men with low body mass index (BMI) and women with high BMI, respectively [21].

Chronic lung disease, mainly chronic obstructive pulmonary disease (COPD) and asthma, have significant sexually di-morphic phenotypes [3]. The female lung, due to anatomical characteristics, is more prone to COPD than the male lung, despite less prior smoking as a risk factor [22]. However, estrogens have protective effects that explain the accelerated decline in lung function in women with COPD after menopause [3]. In contrast, asthma is more frequent and has a higher mortality in middle-aged women, due to estrogens which increase inflammation, especially before menstruation [23]. As women exhibit greater expression of M2 over M3 muscarinic receptors, they show greater improvements in lung function than men in response to the muscarinic anticholinergic bronchodilator ipratropium [3].

Gender-differences in disease awareness, surveillance rates, and disparities in health-care access are responsible for the late diagnosis and initiation or lack of kidney replacement therapy among women with *chronic kidney disease* [24].

The adult male and female brains exhibit distinct cerebral anatomy, connectivity, and function, rendering men and women differently susceptible to *neuropsychiatric disorders* [25]. Alzheimer's disease, depression, post-traumatic stress and panic disorders are more frequent and usually undertreated in women [3].

Coagulation disturbances may be also sex-related, with women having a higher risk of venous thromboembolism (VTE) during fertile years and men having a 3.6-fold higher risk of recurrent VTE than women, with oral contraceptive use increasing the VTE risk 4-fold [26,27]. A modified Caprini risk assessment model is recommended to guide perioperative estrogen management [28].

Frailty, as a marker of homeostatic reserve of the organism, is an important predictive factor of postoperative complications, institutionalization, and mortality, especially for elderly patients [29]. Although women live longer than men, leading to a higher burden of morbidity and disability, aggregated as frailty, this does not translate in worse outcomes [30].

Risky behaviors are also sex and gender-related with smoking, alcohol drinking, and poor life-styles being more frequent in men than in women, and leading to progressive lung damage, higher risk of pulmonary bacterial and viral infections, including SARS-CoV-2 infections, chronic liver disease, and premature mortality in men, despite women being often misdiagnosed [3,5,8,31].

Anesthesia

Several physiological and pharmacological differences between men and women can modulate the effects of anesthesia. The physiological differences between men and women which are important for the anesthesiologist are summarized in Table 1. Some differences are related to the body size (i.e. glomerular filtration rate and basal metabolic rate) or hormonal fluctuations during the menstrual cycle [32]. Sympathetic activity is higher during luteal activity, as well as norepinephrine levels, heart

Table 1
Sex-differences in cardiac, respiratory, renal, neurocognitive, and metabolic physiology+ [12,25,32–34].

Cardiac		Respiratory	
Cardiac mass	↓*	Lung volumes	↓
Diastolic function	↓	Maximal expiratory flow rates	↓
Left ventricular ejection fraction	→	Lung diffusion surface	↓
Stroke volume	↓	Exercise-induced hypoxemia	↑
Cardiac output	→	Ventilatory response to hypercapnia	↓
Resting heart rate	↑ **	Ventilatory response to hypoxia	↓
Cardiac cycle length	↓***	Apneic threshold	↓
Blood pressure	↓$	Airway diameter	↓
Coronary arteries diameter	↓		
Collateral coronary circulation	↓		
Q-T interval	↑		
Baroreflex sensitivity	↑		

Neurocognitive		Metabolic		Renal	
Neuronal density	↓	Basal metabolic rate	↓$$	Creatinine clearance	↓
Neuronal processing	↑	Sedentary energy expenditure	↓	Glomerular filtration rate	↓→#
Stress glucocorticoid response	↑	Core body temperature	→↑++	Renal blood flow	→
Pain threshold	↑			Renal vascular resistance	→
Sleep	Disturbed			Filtration fraction	→
				Plasma renin	↓&

↑ higher, better ↓ lower, less. shorter → no difference.
+The changes presented are in women as compared to men.
*15–30% larger.
**Three to five beats, least during menses.
***↑ during menstruation.
$6–10 mmHg, premenopause.
$$dependent on body size and menstrual cycle.
++dependent on the menstrual cycle.
#dependent on body size.
&premenopause.

rate and blood pressure; pulmonary function improves in the luteal phase; the core body temperature fluctuates from 0.3 to 0.5 °C during the menstrual cycle, being higher during the mid-luteal phase [32,33]. Swelling of the vocal cords, hoarseness, and dysphoric disorders were noted premenstrually, while sleep disturbances during the luteal phase [33].

Sex-related differences in pharmacokinetics and pharmacodynamics of some anesthetics are also relevant for the safety of anesthesia. The sex-related differences in pharmacokinetics of common anesthetics and muscle relaxant are due to body composition and hormonal variability (Table 2) [32–34]. The smaller water content together with the larger proportion of body fat in women affects the volume of distribution and therefore the initial concentration of many drugs used in anesthesia and the optimal dosage of drugs given as one or few injections, but not on the concentration of drug at steady state [35]. The sex-specific requirements of induction of anesthesia are identifiable to each class of anesthetic agents and must be considered on a case-by-case basis [25].

Common lipid-soluble hypnotics, such as midazolam or propofol, have a larger volume of distribution in women and they need higher infusion rate to achieve the same plasma concentration [34,36]. Women have a higher distribution volume and clearance for propofol and require more of the drug to achieve the same depth of anesthesia, as measured by the bi-spectral index (BIS) [35]. In contrast, water-soluble drugs, such as neuro-muscular blocking agents (NMBAs), have lower volumes of distribution in women, and lower doses are needed for the same effect [34].

The bioavailability of oral drugs is reduced in women due to decreased gastric emptying time, whereas the protein binding is decreased due to decreased albumin and alpha 1-acid glycoprotein, induced by increased levels of estrogens [32].

Drug metabolism is either increased or decreased, depending on the hepatic enzyme activity, mainly the cytochrome P450 (CYP) system, which is modulated by pregnancy, menstrual cycle, and use of oral contraceptives (OC) [35]. A larger volume of distribution and more rapid rate of metabolism would facilitate faster cessation of drug action and faster rate of recovery seen in women after general anesthesia [37]. Glucuronidation and hydroxylation of drugs, i.e. propofol, are also increased in women [32].

There are also sex differences with the pharmacodynamic effects of drugs used in anesthesia. Women were less sensitive to general anesthetic drugs as assessed by BIS scores, which were higher at similar concentrations of anesthetics, and also wake faster from general anesthesia than men, suggesting an apparent resistance to the hypnotic effect of anesthetics [38]. Similarly, they were at risk for intraoperative awareness [39].

Progesterone, the dominant female hormone in the luteal phase, seems to modulate sex-related differences in general anesthesia, as it has sedative, anxiolytic, analgesic, and anticonvulsant effects and shares similar mechanisms of action with propofol through the gamma-aminobutyric acid type A (GABA-A) receptor [40]. Women in the luteal phase of the menstrual cycle had a lower calculated effect-site median effective concentration (EC_{50}, the concentration at which 50% of patients experience loss of consciousness, LOC) of propofol, inversely correlated with progesterone levels, and a shorter emergence time than those in the follicular phase [41]. Pre-treatment with different concentrations of dexmedetomidine can reduce further the effect-side EC_{50} of propofol for LOC during the luteal phase,

Table 2
Sex differences in pharmacokinetics, relevant for anesthesia [12,32–34].

Physiological and pharmacological variables in women as compared to men	
Body fat	↑ (5–10%)
Muscle mass	↓ (10%)
Total body water	↓ (15–20%)
Bone mass	↓
Bioavailability	↓
Volume of distribution	↓ for water soluble drugs ↑ for lipid soluble drugs
Protein binding	↓
Drug metabolism	↑↓
Renal clearance	→↓

↑ higher, better ↓ lower, less, shorter → no difference.

in contrast to men, due to a progesterone-additive effect [42]. The depth of anesthesia monitoring should therefore be the norm to avoid unnecessary deep anesthetic state as well as increased risk of awareness during combined propofol/dexmedetomidine anesthesia.

In contrast to hypnotic drugs to which women appear to be less sensitive, opiates have higher analgesic potency, slower action onset and offset, and more impact on ventilatory control [36]. It was found that women are more sensitive to μ receptor agonist morphine and κ receptor agonists (pentazocin, nalbuphine, butorphanol) [43]. In one study, male patients used up to 43% more morphine in the first three postoperative days (PODs) compared with female patients [44]. Less remifentanil was also needed for smooth extubation (without cough) in female compared to male patients [45]. One postulated explanation is that the difference is due to the higher μ-opoid receptor availability in women than in men [45].

The effects of NMBAs also appear to be influenced by sex, with women having ~30% greater sensitivity and a prolonged effect from atracurium, pancuronium, rocuronium, and vecuronium [35,36]. Importantly, women have a higher incidence of allergic reactions to NMBAs [34].

It seems that women are more susceptible to adverse drug reactions in general, including general anesthetics [34,46]. A relevant example for the anesthesiologist is the potentially fatal arrhythmia "torsade de pointes," which was found to be more frequent in women due to a sex difference in repolarization of heart muscle, reflected in a longer corrected QT interval in women at baseline [46]. Induction of general anesthesia also caused greater changes in blood pressure, with a reflex increase in heart rate in women compared with men, suggesting sex-related differences in pressor response [47]. In contrast, the prevalence of malignant hyperthermia was more than doubled in male patients than in female patients, probably related to the male muscular structure [48].

Data on sex differences in local anesthetics are scarce and contradictory [49,50]. Table 3 summarizes the general anesthesia sex/gender-related differences. They should be interpreted with caution and not lead to altered practice as pharmacokinetic difference might be counterbalanced by a pharmacodynamic difference in the opposite direction [35]. Moreover, some consider age effects more relevant than the sex-related differences [37]. As the interindividual variability is significant, the safe practice of anesthesia should be patient-centered and individualized.

Recovery after general anesthesia

Women recover after general anesthesia faster than men even when their measured BIS levels are equivalent, suggesting that both pharmacokinetic (faster clearance) and pharmacodynamic (less response at equal effect site concentrations) variables may be involved [35]. Plasma progesterone concentrations in women negatively correlated with the time to eye opening, supporting the role of pharmacodynamic sex-related differences [32]. Despite shorter time to eye opening after cessation of

Table 3
Sex differences during and following anesthesia [12,32,35,36].

Anesthetic variable in women compared with men	
Propofol requirements	↑ (30–40%)
Opiates requirements	↓ (30–40%)
Neuromuscular blocking agents' requirements	↓
Intraoperative bi-spectral index	↑
Time to eye-opening	↓
Postoperative pain	↑
Postoperative nausea and vomiting	↑↑
Sore throat	↑
Headache	↑
Backache	↑
Functional postoperative outcome	↓
Hospital-stay	↑
Patient satisfaction	↓

↑ higher, better ↓ lower, less, shorter.

anesthesia and duration of recovery room stay in women compared with men, these differences did not translate to quicker discharge from ambulatory surgery [32,37].

Acute postoperative pain

Acute postoperative pain is a major modifiable perioperative factor that can alter postoperative outcomes. Previous studies have identified differences between men and women in the perception, experience, report, duration, and management of pain, including higher rates of pain, enhanced sensitivity to painful stimuli, and a greater functional impact of pain among women compared to men [51,52]. The differences tend to worsen in the reproductive years and vary across a woman's menstrual cycle, being higher during the follicular phase than during the luteal phase, suggesting that elective surgery may be scheduled during luteal phase in premenopausal women to decrease the pain perception [53].

A systematic review of studies comparing sex differences in pain perception and modulation has confirmed that the pain threshold is higher and the overall activity of diffuse noxious inhibitory control mechanisms is more efficient in men [54]. Women have a lower endogenous inhibition of pain assessed by conditioned pain modulation (CPM), which is a consequence of the activation of descending inhibitory mechanisms. However, the age-effect on CPM of pressure and thermal pain seems to be larger than the sex-effect [55]. Ethnicity, preoperative pain, and psychological factors may also overshadow the sex-differences in pain [36,51].

Women are also more likely to report high levels of distress and pain-related negative affect, suggesting a possible gender-mechanism that may contribute to sex-differences in postoperative pain-related outcomes [56]. Different societal expectations toward pain behavior for men and women may account for discrepancies in pain reporting after surgery [51].

Postoperative pain is also affected by different responses to analgesia. Women appear to be more sensitive to both the analgesic and respiratory depressant effects of opioid analgesics [35,36]. In both experimental and clinical pain studies, morphine efficacy was greater in female subjects, and men needed higher morphine doses than women to achieve equivalent pain relief after surgery [43,57]. Consequently, from a safety point of view, women may be more vulnerable to opioid therapy than men. However, the direction of sex/gender-related differences in opioid efficacy is influenced by interaction of many variables, such as basal pain perception, sensitivity to opioids and interaction with gonadal hormones, all modulated by age [45]. Genetic variability and interindividual metabolic differences may be more important than the sex/gender-related disparities [53]. Individual-tailored approaches toward optimal postoperative pain management should be implemented to ensure patient safety.

Postoperative nausea and vomiting

Postoperative nausea and vomiting (PONV) are common and distressing complications following surgery. Women are 3 times more susceptible to PONV than men and the rate decreases after menopause, but still remains higher than that in men, which supports a significant role of sex hormones [36,58]. The incidence seems to be higher in the follicular phase than in the luteal phase, being highest during menstruation [33]. Scheduling elective surgery within the luteal phase of a patient's menstrual cycle, particularly for someone with a strong history of PONV, would be beneficial, especially in ambulatory surgery [36].

Postoperative outcomes

Women are at greater risk of adverse outcomes after surgery [59,60]. Compared with men, women also report worse patient-related postoperative outcomes related to satisfaction and health-related quality of life [61].

In *non-cardiac surgery*, most data on sex/gender-related differences in outcome come from vascular and orthopedic surgery. In carotid endarterectomy and abdominal aortic aneurysm surgery women experienced increased hospital length of stay, regardless of anesthesia type (regional or general), and higher mortality in both elective open and endovascular repair, respectively [62,63]. A variable effect of sex/gender was observed on the postoperative outcome in total joint surgery. In some studies, female patients had higher risk of blood transfusion and urinary tract infections [64,65], whereas male patients had more postoperative wound infections, higher return to the operating room, hospital readmissions and increased mortality rates [64].

Female sex/gender is also recognized as an independent risk factor in *cardiac surgery* and included in risk scores [60]. Women experience more urgent surgery with need for preoperative intra-aortic balloon pump support, and they have more coexistent congestive HF, DM, COPD, peripheral vascular disease, smaller body surface area, severe/unstable angina and lower preoperative hematocrit, which account for increased morbidity and mortality rates following cardiac surgery [60,66]. In contrast, in other studies, sex/gender did not significantly affect the observed 30-day, and 1-, 3-, and 5-year mortality rates after cardiac surgery, despite significant differences in the preoperative risk profiles between males and females [67–69]. The beneficial effect of surgery decreased after seven years in lower age women, and in patients undergoing aortic valve replacement (AVR) or other procedures compared with isolated coronary artery bypass grafting (CABG) surgery, suggesting that these groups of patients need closer attention and aggressive CVD preventive strategies in order to improve outcomes [68]. However, postoperatively, women were more likely to be admitted to the hospital in the first year and in the following years after surgery because of unstable angina and congestive HF, along with a significant decline in physical function and increase in depression [60]. Female sex/gender was also independently associated with major adverse cardiac and cerebral events after isolated mitral and aortic surgery [70]. In transcatheter aortic valve replacement (TAVR), women are at increased risk of intra- and postoperative complications such as bleeding and vascular complications, probably due to older age, higher frailty scores, and anatomical particularities, but tend to have improved mid- and long-term mortality compared to men [71,72], suggesting that TAVR may be offered over open AVR in women at a lower threshold than men [71].

Sex/gender-related differences in *organ transplantation surgery* are multifactorial and related to biological and social characteristics of men and women [73]. They influence all stages of the organ transplant process. Women are less likely of being listed for a transplant, less liver, kidney or heart-transplanted, whereas sex mismatch (female donor to male recipient) results in a worse outcome in kidney, liver, lung, and heart transplantation [74]. Generally, women have increased post-transplant psychological effects, poorer compliance, increased infections, and lower quality of life [73]. Social inequities may contribute to these disparities [74].

Transgender patients

With increased visibility and acceptance of transgender people, anesthesiologists should acquire knowledge about their particularities, skills, and cultural competence to safely mange them in the perioperative period. Transgender people are often socially and economically disadvantaged, underserved by the health system and carrying an excess morbidity, due to gender dysphoria, HIV infection and behaviors such as smoking or drug and alcohol consumption [2].

Preoperative evaluation is central to patient safety by creating a trustful environment for these vulnerable patients and should include a detailed risk assessment of perioperative cardiovascular events and a summary of current medication, including cross-sex hormone therapy (CSHT), which increases the risk of blood elevation, insulin resistance and lipid derangements, and anti-depressive medication [75]. Transgender patients have increased risk of CVD, MI, DM, VTE, pulmonary complications, depression and anxiety, and HIV infection, whereas their blood chemistry can vary depending on the drug and duration of CSHT [2]. Perioperative management of anti-thrombotics should be managed taking these factors into consideration.

A detailed history of surgical procedures should be recorded, especially of laryngoplasties or chondroplasties, as these could lead to an intraoperative higher risk for a difficult airway due to vocal cord damage, tracheal stenosis or perforation, scarring or loss of the cricothyroid membranous space, and equipment for the management of a difficult airway should be readily available [75,76]. Urinary catheter placement can be done by, or after consulting, a urologist, as urethral surgery is common in these patients [75].

Intraoperatively, the anesthesiologist should pay special attention to drug interactions with CSHT and, in case of HIV infections, to anti-retroviral therapy and the VTE prevention. Additional monitoring should be implemented where possible, especially monitoring of depth of anesthesia as algorithms for dosing iv. anesthetics may be altered [76].

Postoperatively, a multidisciplinary approach must be taken when managing pain, respecting privacy and ensuring mental well-being as this period is a vulnerable time for the transgender patient due to pain, depression, anxiety, and withdrawal [2].

Gender balance and perioperative team performance

The perioperative team is comprised of a multitude of health-care professionals, whose collaboration is mandated, regardless of personal affinities, prior experiences, personal beliefs, and emotional differences. Diverse teams perform better and are associated with improved outcomes, as they bring different attitudes and perspectives to the care team, distinctive tactics, and unique solutions to solving problems and promote innovation [77]. However, team leading roles in the operative theatre and perioperative period have, traditionally, been male, assuming stereotypical leading styles [78]. Recently, more inclusive leading styles have been proposed, regardless of team composition, in order to increase patient safety through better communication between team members, which is one of the main causes of medical errors [79,80].

Improved outcomes were reported when female providers lead the care team in acute settings, probably because women are more likely to adhere to clinical guidelines and evidence-based medicine and have a more patient-centered practice [77,81]. Gender concordance between physicians and patients was also associated with improved outcome [18]. However, both men and women prefer female anesthesiologists to care for a family member, being ranked more confident [82].

In medicine, in general, and anesthesiology, in particular, there have been historical differences in access to positions of prominence, be it academic or clinical. Despite representing the majority of the health workforce (more than 70%), women are less in chief-executive positions or elected in boards of medical societies and professional organizations [83]. Academic women are less published, invited to speak to congresses, to guidelines panels and editorial boards, awarded grants, or recognition [84]. Although the number of women in academic anesthesiology is increasing, the percentage of female full professors is still significantly smaller than that of males [84].

These disparities have been attributed to many causes such as unconscious biases against women, male dominance in selection committees, more family duties for women but also to a “pipeline” issue, suggesting women are less willing to take leadership roles. Interestingly, a survey performed by the European Society of Anaesthesiology and Intensive Care looking for reasons to pursuing and barriers to career advancement found that women are as eager as men to take a leadership role [85]. Both men and women reported similar barriers to career advancement, although more women experienced these barriers, which included lack of research and leadership training, woman role models, mentorship programs, and opportunities that enable a better ‘work-life integration’. These results suggest several strategies, such as mentoring and leadership training and flexible work opportunities, for reducing barriers to career development and improving gender equity in anesthesiology [85].

Conclusions

Although it is clear that sex and gender play a role in physiology, pharmacology, and a variety of illnesses, which may influence the management of anesthesia, it is difficult to make a compelling case that sex/gender of the patient influence perioperative outcome. Sex/gender of the anesthesiologist may also contribute to the differences in perioperative outcome. Further studies are needed to explore the impact of sex/gender of both patients and providers in anesthesiology and move toward more individualized care.

Practice points

- Anesthesiologists are optimally positioned to improve perioperative patient safety through preoperative evaluation and optimization and individualized anesthetic technique and postoperative care.
- Knowledge of preoperative sex and gender differences in clinical phenotypes of chronic illnesses help to better address individual risk factors of patients.
- Women need higher infusion rates of common hypnotics to achieve the same plasma concentration and depth of anesthesia, have higher risk of awareness, and recover faster after general anesthesia.
- Women are more sensitive to both the analgesic and respiratory depressant effects of opioid analgesics.
- Women are more susceptible to PONV and report worse patient-related outcomes related to satisfaction, health-related quality of life, and pain levels.
- Women are at greater risk of adverse outcomes postoperatively in non-cardiac, cardiac, and transplantation surgery.
- Transgender patients have anatomical particularities and drug interferences relevant to the anesthesia care.
- Female anesthesiologists improve team performance and are preferred by both female and male patients.

Research agenda

- We need evidence that sex- and gender-tailored interventions impact perioperative outcomes.
- We need evidence that scheduling surgeries for female patients during the luteal phase of the menstrual cycle decreases postoperative pain and improves patient-reported outcomes.
- Further work is needed to assess the role of female anesthesiologists in improving perioperative outcomes.

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Declaration of competing interest

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References

*[1] Shannon G, Jansen M, Williams K, et al. Gender equality in science, medicine, and global health: where are we at and why does it matter? Lancet 2019;393(10171):560–9.
*[2] Tollinche LE, Van Rooyen C, Afonso A, et al. Considerations for transgender patients perioperatively. Anesthesiol Clin 2020;38(2):311–26.
*[3] Mauvais-Jarvis F, Bairey Merz N, Barnes PJ, et al. Sex and gender: modifiers of health, disease, and medicine. Lancet 2020 Aug;396(10250):565–82.
[4] Gender and health. Available from: https://www.who.int/health-topics/gender#tab=tab_1. [Accessed September 2020].

[5] Tadiri CP, Gisinger T, Kautzy-Willer A, et al. The influence of sex and gender domains on COVID-19 cases and mortality. Can Med Assoc J 2020;192(36):E1041–5.
[6] Leslie K, Edgley C, Lee AC-Y, et al. Reporting of sex and gender in human studies published in anaesthesia journals. Br J Anaesth 2018;120(5):1128–30.
[7] Mellin-Olsen J, Staender S, Whitaker DK, et al. The Helsinki declaration on patient safety in anaesthesiology. Eur J Anaesthesiol 2010;27(7):592–7.
*[8] Swisher J, Blitz J, Sweitzer B. Special considerations related to race, sex, gender, and socioeconomic status in the preoperative evaluation. Anesthesiol Clin 2020;38(2):263–78.
[9] Douglas P, Poppas A. Overview of cardiovascular risk factors in women. Available from: https://www.uptodate.com/contents/overview-of-cardiovascular-risk-factors-in-women. [Accessed September 2020].
[10] Millett ERC, Peters SAE, Woodward M. Sex differences in risk factors for myocardial infarction: cohort study of UK Biobank participants. BMJ 2018;363:k4247.
[11] Honigberg MC, Zekavat SM, Aragam K, et al. Association of premature natural and surgical menopause with incident cardiovascular disease. JAMA 2019;322(24):2411.
[12] Matyal R. Newly appreciated pathophysiology of ischemic heart disease in women mandates changes in perioperative management: a core review. Anesth Analg 2008;107(1):37–50.
[13] Mehta PK, Bess C, Elias-Smale S, et al. Gender in cardiovascular medicine: chest pain and coronary artery disease. Eur Heart J 2019;47(11):3819–26.
[14] Bairey Merz CN, Pepine CJ, Walsh MN, et al. Ischemia and no obstructive coronary artery disease (INOCA): developing evidence-based therapies and research rgenda for the next decade. Circulation 2017;135(11):1075–92.
[15] Vallabhajosyula S, Ya'Qoub L, Singh M, et al. Sex disparities in the management and outcomes of cardiogenic shock complicating acute myocardial infarction in the young. Circ Heart Fail 2020;13(10).
[16] Douglas P, Pagidipati N. Management of coronary heart disease in women. Available from: https://www.uptodate.com/contents/management-of-coronary-heart-disease-in-women#H3136765. [Accessed September 2020].
[17] Pelletier R, Khan NA, Cox J, et al. Sex versus gender-related characteristics. J Am Coll Cardiol 2016;67(2):127–35.
[18] Greenwood BN, Carnahan S, Huang L. Patient–physician gender concordance and increased mortality among female heart attack patients. Proc Natl Acad Sci 2018;115(34):8569–74.
[19] Caso V, Santalucia P, Acciarresi M, et al. Antiplatelet treatment in primary and secondary stroke prevention in women. Eur J Intern Med 2012;23(7):580–5.
[20] Ohkuma T, Komorita Y, Peters SAE, et al. Diabetes as a risk factor for heart failure in women and men: a systematic review and meta-analysis of 47 cohorts including 12 million individuals. Diabetologia 2019;62(9):1550–60.
[21] Dennis JM, Henley WE, Weedon MN, et al. Sex and BMI alter the benefits and risks of sulfonylureas and thiazolidinediones in type 2 diabetes: a framework for evaluating stratification using routine clinical and individual trial data. Diabetes Care 2018;41(9):1844–53.
[22] DeMeo D, Ramagopalan S, Kavati A, et al. Women manifest more severe COPD symptoms across the life course. Int J Chronic Obstr Pulm Dis 2018;13(11):3021–9.
[23] Zein JG, Denson JL, Wechsler ME. Asthma over the adult life course. Clin Chest Med 2019;40(1):149–61.
[24] Markell M, Brar A, Stefanov DG, et al. Gender disparity in fistula use at initiation of hemodialysis varies markedly across ESRD networks-Analysis of USRDS data: geographic disparities in arteriovenous fistula rate. Hemodial Int 2018;22(2):168–75.
[25] Mawhinney LJ, Mabourakh D, Lewis MC. Gender-specific differences in the central nervous system's response to anesthesia. Transl Stroke Res 2013;4(4):462–75.
[26] de Bastos M, Stegeman BH, Rosendaal FR, et al. Combined oral contraceptives: venous thrombosis. Cochrane Fertility Regulation group. Cochrane Database Syst Rev 2014;3(3).
[27] Tagalakis V, Patenaude V, Kahn SR, et al. Incidence of and mortality from venous thromboembolism in a real-world population: the Q-VTE Study Cohort. Am J Med 2013;126(9):832.e13–21.
[28] Muluk V, Cohn S, Whinney C. Perioperative medication management. Available from: https://www.uptodate.com/contents/perioperative-medication-management. [Accessed September 2020].
*[29] Gordon EH, Peel NM, Samanta M, et al. Sex differences in frailty: a systematic review and meta-analysis. Exp Gerontol 2017;89:30–40.
[30] Gordon EH, Peel NM, Hubbard RE. The male-female health-survival paradox in hospitalised older adults. Maturitas 2018;107:13–8.
[31] Global health 50/50 report power, privilege & priorities [Internet]. [cited 2020 Nov 1]. Available from: https://globalhealth5050.org/2020report/; 2020.
[32] Buchanan FF, Myles PS, Cicuttini F. Patient sex and its influence on general anaesthesia. Anaesth Intensive Care 2009;37(2):207–18.
[33] Kurdi MS, Ramaswamy AH. Does the phase of the menstrual cycle really matter to anaesthesia? Indian J Anaesth 2018;62(5):330–6.
[34] Campesi I, Fois M, Franconi F. Sex and gender aspects in anesthetics and pain medication. In: Regitz-Zagrosek V, editor. Sex and gender differences in pharmacology. Handbook of Experimental Pharmacology. 214. Berlin Heidelberg: Springer-Verlag; 2012. p. 265–78.
*[35] Pleym H, Spigset O, Kharasch ED, et al. Gender differences in drug effects: implications for anesthesiologists. Acta Anaesthesiol Scand 2003;47(3):241–59.
[36] Moller DH, Glass PSA. Should a patient's gender alter the anesthetic plan? Curr Opin Anaesthesiol 2003;16(4):379–83.
[37] Buchanan FF, Myles PS, Leslie K, et al. Gender and recovery after general anesthesia combined with neuromuscular blocking drugs. Anesth Analg 2006;102(1):291–7.
*[38] Buchanan FF, Myles PS, Cicuttini F. Effect of patient sex on general anaesthesia and recovery. Br J Anaesth 2011;106(6):832–9.
[39] Pandit JJ, Andrade J, Bogod DG, et al. 5th National Audit Project (NAP5) on accidental awareness during general anaesthesia: summary of main findings and risk factors. Br J Anaesth 2014;113(4):549–59.

[40] Liu Y-W, Zuo W, Ye J-H. Propofol stimulates noradrenalin-inhibited neurons in the ventrolateral preoptic nucleus by reducing GABAergic inhibition. Anesth Analg 2013 Aug;117(2):358–63.
[41] Fu F, Chen X, Feng Y, et al. Propofol EC 50 for inducing loss of consciousness is lower in the luteal phase of the menstrual cycle. Br J Anaesth 2014;112(3):506–13.
[42] Xiong M, Zheng Z-X, Hu Z-R, et al. Propofol-sparing effect of different concentrations of dexmedetomidine: comparison of gender differences. Anaesthesist 2019;68(1):15–21.
*[43] Niesters M, Dahan A, Kest B, et al. Do sex differences exist in opioid analgesia? A systematic review and meta-analysis of human experimental and clinical studies. Pain 2010;151(1):61–8.
[44] Chia Y-Y, Chow L-H, Hung C-C, et al. Gender and pain upon movement are associated with the requirements for post-operative patient- controlled iv analgesia: a prospective survey of 2,298 Chinese patients. Can J Anesth Can Anesth 2002; 49(3):249–55.
[45] Lee SY, Jeong YY, Lee BH, et al. Sex-related differences in effect-site concentration of remifentanil for preventing anes-thetic emergence cough in elderly patients. Clin Interv Aging 2018;13:81–9.
[46] Ferner R, Aronson J. Susceptibility to adverse drug reactions. Br J Clin Pharmacol 2019;85(10):2205–12.
[47] Jee D, Moon H-L. Gender may affect the hemodynamic response to induction and intubation in young adults. J Clin Anesth 2004;16(8):563–7.
[48] Butala B, Brandom B. Muscular body build and male sex are independently associated with malignant hyperthermia susceptibility. Can J Anesth Can Anesth 2007;64(4):396–401.
[49] Benhamou D. Sex-based differences in local anaesthetic-induced motor block. Eur J Anaesthesiol 2011;28(4):235–6.
[50] Pei Q, Yang Y, Liu Q, et al. Lack of sex difference in minimum local analgesic concentration of ropivacaine for ultrasound-guided supraclavicular brachial plexus block. Med Sci Monit 2015;21:3459–66.
[51] Pereira MP, Pogatzki-Zahn E. Gender aspects in postoperative pain. Curr Opin Anaesthesiol 2015;28(5):546–58.
[52] Tighe PJ, Riley JL, Fillingim RB. Sex differences in the incidence of severe pain events following surgery: a review of 333,000 pain scores. Pain Med 2014;15(8):1390–404.
[53] Kwon AH, Flood P. Genetics and gender in acute pain and perioperative opioid analgesia. Anesthesiol Clin 2020;38(2): 341–55.
*[54] Popescu A, LeResche L, Truelove EL, et al. Gender differences in pain modulation by diffuse noxious inhxibitory controls: a systematic review. Pain 2010;150(2):309–18.
[55] Riley JL, Cruz-Almeida Y, Staud R, et al. Age does not affect sex effect of conditioned pain modulation of pressure and thermal pain across 2 conditioning stimuli. Pain Rep 2019;5:e796.
[56] Melchior M, Poisbeau P, Gaumond I, et al. Insights into the mechanisms and the emergence of sex-differences in pain. Neuroscience 2016;338:63–80.
[57] Periasamy S. Influences of gender on postoperative morphine consumption. J Clin Diagn Res 2014;8(12):GC04–7.
*[58] Elvir-Lazo OL, White PF, Yumul R, et al. Management strategies for the treatment and prevention of postoperative/ postdischarge nausea and vomiting: an updated review. F1000Research 2020;9:983.
[59] Patel AP, Gronbeck C, Chambers M, et al. Gender and total joint arthroplasty: variable outcomes by procedure type. Arthroplasty Today 2020;6(3):517–20.
[60] Bechtel AJ, Huffmyer JL. Gender differences in postoperative outcomes after cardiac surgery. Anesthesiol Clin 2020;38(2): 403–15.
[61] Kozlov N, Benzon HT. Role of gender and race in patient-reported outcomes and satisfaction. Anesthesiol Clin 2020;38(2): 417–31.
[62] Chou EL, Sgroi MD, Chen SL, et al. Influence of gender and use of regional anesthesia on carotid endarterectomy out-comes. J Vasc Surg 2016;64(1):9–14.
[63] Nicolini F, Vezzani A, Corradi F, et al. Gender differences in outcomes after aortic aneurysm surgery should foster further research to improve screening and prevention programmes. Eur J Prev Cardiol 2018;25(1_suppl):32–41.
[64] Basques BA, Bell JA, Fillingham YA, et al. Gender differences for hip and knee arthroplasty: complications and healthcare utilization. J Arthroplasty 2019;34(8):1593–1597.e1.
[65] Robinson J, Shin JI, Dowdell JE, et al. Impact of gender on 30-day complications after primary total joint arthroplasty. J Arthroplasty 2017;32(8):2370–4.
[66] Johnston A, Mesana TG, Lee DS, et al. Sex differences in long-term survival after major cardiac surgery: a population-based cohort study. J Am Heart Assoc 2019;8(17):e013260.
[67] Dalén M, Nielsen S, Ivert T, et al. Coronary artery bypass grafting in women 50 years or younger. J Am Heart Assoc 2019; 8(18):e013211.
[68] Enger TB, Pleym H, Stenseth R, et al. Reduced long-term relative survival in females and younger adults undergoing cardiac surgery: a prospective cohort studyParolari A, editor. PloS One 2016;11(9):e0163754.
[69] Park H, Ahn J-M, Yoon Y-H, et al. Effect of age and sex on outcomes after stenting or bypass surgery in left main coronary artery disease. Am J Cardiol 2019;124(5):678–87.
[70] Wong SC, Yeo I, Bergman G, et al. The influence of gender on in-hospital clinical outcome following isolated mitral or aortic heart valve surgery. Cardiovasc Revascularization Med 2019;20(6):468–74.
[71] Chaker Z, Badhwar V, Alqahtani F, et al. Sex differences in the utilization and outcomes of surgical aortic valve replacement for severe aortic stenosis. J Am Heart Assoc 2017;6(9):e006370.
[72] Caponcello MG, Banderas LM, Ferrero C, et al. Gender differences in aortic valve replacement: is surgical aortic valve replacement riskier and transcatheter aortic valve replacement safer in women than in men? J Thorac Dis 2020;12(7): 3737–46.
[73] Walters SM, Richter EW, Lutzker T, et al. Perioperative considerations regarding sex in solid organ transplantation. Anesthesiol Clin 2020;38(2):297–310.
[74] Melk A, Babitsch B, Borchert-Mörlins B, et al. Equally interchangeable? How sex and gender affect transplantation. Transplantation 2019;103(6):1094–110.
[75] Tollinche LE, Walters CB, Radix A, et al. The perioperative care of the transgender patient. Anesth Analg 2018;127(2): 359–66.

[76] Lennie Y, Leareng K, Evered L. Perioperative considerations for transgender women undergoing routine surgery: a narrative review. Br J Anaesth 2020;124(6):702–11.
[77] Hilton EJ, Lunardi N, Sreedharan R, et al. Two sides of the same coin. Anesthesiol Clin 2020;38(2):369–77.
[78] Minehart RD, Foldy EG, Long JA, et al. Challenging gender stereotypes and advancing inclusive leadership in the operating theatre. Br J Anaesth 2020;124(3):e148–54.
*[79] Minehart RD, Foldy EG. Effects of gender and race/ethnicity on perioperative team performance. Anesthesiol Clin 2020; 38(2):433–47.
[80] Preckel B, Staender S, Arnal D, et al. Ten years of the Helsinki Declaration on patient safety in anaesthesiology: an expert opinion on peri-operative safety aspects. Eur J Anaesthesiol 2020;37(7):521–610.
[81] Meier A, Yang J, Liu J, et al. Female physician leadership during cardiopulmonary resuscitation is associated with improved patient outcomes. Crit Care Med 2019;47(1):e8–13.
[82] Forkin KT, Dunn LK, Kotha NC, et al. Anesthesiologist age and sex influence patient perceptions of physician competence. Anesthesiology 2021 Jan 1;134(1):103–10.
[83] Haylock-Loor C, Onajin-Obembe B, Filipescu D, et al. The gender gap. In: Duval Neta GF, editor. Occupational well-being in anesthesiologists. Update. Rio de Janeiro: Brazilian Society of Anesthesiologists; 2018. p. 309–34.
[84] Toledo P, Lewis CR, Lange EMS. Women and underrepresented minorities in academic anesthesiology. Anesthesiol Clin 2020;38(2):449–57.
*[85] Matot I, De Hert S, Cohen B, et al. Women anaesthesiologists' attitudes and reported barriers to career advancement in anaesthesia: a survey of the European Society of Anaesthesiology. Br J Anaesth 2020;124(3):e171–7.