REVIEW ARTICLE

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Anesthesia and women's peculiarities

Luis Antonio dos Santos Diego[1*]

Brazilian Society of Anaesthesiology

INTRODUCTION

An important issue is the establishment of concepts when the topic of discussion involves sex and gender. So, sex is a term used for the biological determinant (chromosomal), and gender is a social construct with a broad spectrum (cis, trans, etc.).

Both gender- and sex-related peculiarities may influence many aspects of anesthetic planning, although the different concepts of sex and gender are precious, as well as pregnancy status; gender and pregnancy are beyond the scope of this article.

The physiological and pharmacological aspects are extensive and, by themselves, deserve special attention. From the preoperative evaluation to the postoperative management, the anesthesiologists must know these differences and how they may influence the outcome.

However, only the main factors influencing anesthetic management and its results will be highlighted.

PHYSIOLOGICAL AND PHARMACOLOGICAL DIFFERENCES

Some physiological and pharmacological women's singularities may interfere with anesthesia management[1], and many of them result from direct or indirect actions of female sex hormones. Differences in the metabolism of drugs exist at various levels, possibly due to the genomic and nongenomic action of sex hormones. A detailed understanding of the effect of sex and its related conditions on the metabolism of drug molecules will help clinicians determine the effective therapeutic doses of drugs depending on the patient's condition and disease. As if that were not enough, female hormones vary according to ovulation. For example, vasodilatation occurs when estrogen production is high due to nitric oxide liberation[2]. Younger women, compared with men, have better diastolic function and a larger left ventricular ejection fraction, but the differences are not favorable regarding the pulmonary system. For example, women's ventilatory responses to CO_2, hypoxia, and the apneic threshold are lower[3]. No measurable effect on renal blood flow, renal vascular resistance, or filtration fraction was detected with estrogen variation; other differences include body mass index, waist circumference, body fat composition, which are usually 5–10% higher, and decreased total body water (15–20%)[4]. All these factors have implications for variances in the rate and extent of drug distribution and variations in plasma binding protein levels that can alter drug-free fractions. The free fraction is the active form of the drug.

Fluctuations in the menstrual cycle modify the volume of distribution, but few studies have examined the effect of this variability on drug volume of distribution. Nevertheless, body fat composition influences the volume of distribution of water-soluble drugs, like muscle relaxants, and consequently, less drug dosage is required for the same effect when compared to men. For lipid-soluble drugs, the opposite effect occurs and is observed with propofol and benzodiazepines.

Drug metabolism plays the most significant role in pharmacokinetic differences between the sexes[5]. The hepatic enzyme activity is crucial for the drug's hepatic clearance, and hepatic enzymes play a significant role in determining women's pharmacokinetic variability. Finnstrom et al. have demonstrated essential sex differences in some key cytochrome P450 enzymes[6], and Craft pointed to more significant analgesic effects with opioid agonists in females than in males[7].

Huhn et al. suggested that they may also influence opioid pharmacokinetics, which may produce systematic sex-based differences in opioid abuse liability[8] by modifying opioid receptor binding and density in the hypothalamus; these effects could also change opioid receptor availability, impacting how opioids are subjectively experienced. These findings may explain why men and women respond differently to pain syndrome and probably to postoperative nausea and vomiting (PONV) predisposition.

[1]Faculdade de Medicina, Universidade Federal Fluminense – Rio de Janeiro (RJ), Brazil.
*Corresponding author: luisdiego@id.uff.br
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PREOPERATIVE EVALUATION

A preoperative evaluation is essential for safe anesthesia management and should be performed before surgeries and procedures. The pre-anesthetic evaluation has several objectives: evaluating the patient's physical state, establishing anesthetic management based on exchanging information between the anesthesiologist and the patient, and obtaining the "Free and Informed Consent Form," as recommended by CFM Resolution 2174/2017[9]. Usually, anesthesiologists do not have many opportunities to meet the same patient, so the anesthesiologist should use this valuable preoperative meeting to establish mutual trust through empathic listening.

However, sex differences can interfere with disease prevalence, treatment outcomes, morbidity, and mortality[10]. As well as worldwide, cardiovascular diseases represent women's leading cause of death in Brazil[11,12], and diabetes, hypertension, obesity, sedentary life, etc. are the most common risk factors observed in clinical practice. However, oral contraceptive use is a sex-specific risk factor. Although endogenous estrogens usually protect women against cardiovascular disease, women have more microvascular dysfunction than men's large coronary artery obstruction, which may explain why they are often underdiagnosed[13]. In addition, cardiologists may not even evaluate symptoms of myocardial Ischemia as early in women as in men, underestimating risk factors, so anesthesiologists should investigate more accurately during the preoperative interview about previous suggestive symptoms. Ohkuma et al.[14]. showed by a meta-analysis that both diabetes types (1 and 2) were stronger risk factors for heart failure in women than in men[15]; consequently, the importance of a systematic sex-specific approach is necessary. In addition, women have a higher risk of venous thromboembolism during fertile years, with oral contraceptive use increasing it fourfold. Chronic obstructive pulmonary disease and asthma are more frequent in women[16].

PONV following surgery is three times more frequent in women than in men, although the rate decreases after menopause remains higher in women than in men. The incidence is higher in the follicular phase than in the luteal phase and highest during menstruation. Therefore, it may be relevant to consider scheduling elective surgery during the luteal phase of a patient's menstrual cycle when the patient has a previous history of PONV.

The female has been identified as one of the risk factors closely linked to specific sex differences and may be associated with a lower level of satisfaction. Therefore, successful preoperative anesthesia evaluation and education may improve such adverse outcomes. Nowadays, telehealth is an additional tool to attend to these objectives.

ANESTHESIA MANAGEMENT

The physiological and pharmacological peculiarities of women must be considered during the clinical anesthesia scenario. Some of the most important are the responses to hypnotics, especially the need for higher infusion rates to achieve the same anesthesia depth; this effect is observed with common lipid-soluble drugs, such as propofol and midazolam. In addition, anesthesia recovery in women is faster than in men[17].

Another drug class used in the anesthesia setting that is influenced by sex is the neuro-muscular blocking agents; their water solubility determines a lower distribution volume in women, so fewer drug doses are needed than in men for the same muscle relaxant effect[18].

Another relevant difference is the response to the analgesic and respiratory depressant effects of opioids; women are more sensitive than men[19], and the total opioid dose is approximately 30% lower in women than in men[20].

Concerning inhalational anesthetics, the sexes have no clinically relevant differences[21].

The relevance of these aspects, possible comorbidities, and the interventions to which they will be submitted are essential. So, the anesthesia choices must attend to the identifiable singularities on a case-by-case basis. In a general assessment, significant pharmacological differences are observed in the usual anesthetics most commonly utilized in care practice, such as propofol, opioids, and neuromuscular blockers. However, it should be considered that most of these agents are used by continuous infusion, including target-controlled devices. This practice allows accurate monitoring of the effects and necessary adjustments.

POSTOPERATIVE CONSIDERATIONS

The prophylaxis and treatment of postoperative pain and avoiding PONV are highly relevant and equally important goals of anesthesia, which are the subjects of recent consensus recommendations[22].

Pavlin et al., in a prospective study, examined what factors affected discharge time, including sex, and observed that, at outpatient procedures, the discharge time in women was fastest after propofol induction/maintenance and can be explained by a trend toward fewer emetic symptoms[23]. In the same way, Myles et al., comparing the overall quality of recovery from anesthesia between men (n=241) and women (n=222), observed that women emerged significantly more quickly than men, although women had a slower return to baseline health status[24].

Sex as a risk factor for chronic postsurgical pain (CPSP) was the object of a systematic review in the adult population

after any elective nonobstetric surgery[25] and confirmed a higher risk of developing CPSP in the female. Thurston et al., in a systematic review of literature considering differences in postoperative pain and postoperative pain management, racialized minorities, female sex, and individuals of lower socioeconomic status (SES), found that optimal postoperative pain relief continues to be a challenge for individuals who self-identify as racialized minorities, females, and those of lower SES[26].

CONCLUSION

Differences between men and women should be considered in the operating theatre practice. The physiological and pharmacological differences are also evident, although many studies must be conducted to clarify some aspects. In many studies, when scrutinized, confounding factors can be detected. Therefore, the anesthesiologists should make the anesthetic planning with caution and knowledge, considering the existing guidelines and the best practices.

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