Translational research updates in female health anesthesiology: a narrative review

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Background and Objective: Females represent 49.6% of the global population and constitute a significant proportion of surgical patients and hospital admissions. Little is known about the bi-directional effects of sex and anesthetics or the impact of anesthetic interventions on long-term female health outcomes. Sex differences in pain pathways can influence pain experience and treatment effectiveness. The impact of anesthetic management on the recurrence of breast cancer is poorly understood, as are the long-term consequences of cardiovascular disease and safe and effective treatments in pregnancy. This review aims to outline recent advances in translational science in female health anesthesiology research and highlight critical research opportunities in pain, cancer outcomes, and cardiovascular disorders.

Methods: We searched PubMed and summarized relevant articles published in English between December 2021 and June 2022.

Key Content and Findings: Studies reveal sex differences in pain pathways and highlight the importance of sex as a biological variable in experimental designs and translational medicine. Sex differences have also been observed in side effects attributed to opioid analgesics. We summarize some of the neural circuits that might underlie these differences. In the perioperative setting, specific anesthetics are implicated in metastatic seeding potential and acute and chronic pain outcomes, suggesting the importance of anesthetic selection in comprehensive care during oncologic surgery. In the peridelivery setting, preeclampsia, a cardiovascular disorder of pregnancy, affects maternal outcomes; however, biomarkers can risk-stratify females at risk for preeclampsia and hold promise for identifying the risk of adverse neurological and other health outcomes.

Conclusions: Research that builds diagnostic and predictive tools in pain and cardiovascular disease will help anesthesiologists minimize sex-related risks and side effects associated with anesthetics and peri-hospital treatments. Sex-specific anesthesia care will improve outcomes, as will the provision of practical information to patients and clinicians about the effectiveness of therapies and behavioral interventions. However, more research studies and specific analytic plans are needed to continue addressing sex-based outcomes in anesthesiology.

Keywords: Sex differences; opioids; breast cancer; cardiovascular; review

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Introduction

Anesthesiologists routinely evaluate, monitor, and supervise patient care before, during, and after perioperative and peripartum procedures. In the United States, more than 3 million females are hospitalized for childbirth every year, and females are expected to experience an average of seven surgical procedures during their lifetime (1). Millions of these individuals receive anesthesia care annually, to treat complex conditions or pain related to invasive surgical procedures. Acknowledging differences between females and males relevant to anesthetic management is paramount to optimize peri-hospital outcomes and improve human health.

Research in anesthesiology has evolved to focus on addressing knowledge gaps on sex-differences in pain, perioperative considerations for breast cancer surgery, and cardiovascular disease in pregnancy. Historically, pain research was not specifically designed to elucidate sex-differences, but rather evaluated these differences using post-hoc analyses (2). Data suggests that only 33.3% of females are represented in published research studies versus 61.7% males, highlighting a lack of evidence specific to female health, and subsequent lag in evidence generalizability for females (3). A growing body of evidence suggests that there are sex differences associated with pain, and that long-term consequences of diseases such as breast cancer primarily affect females (4-6). Perioperative and peripartum procedures that affect primarily females (e.g., mastectomies for breast cancer, neuraxial anesthesia during labor and delivery) require customized pain management plans. These sex differences extend to female-predominant cardiovascular disorders, such as those related to placentation (preeclampsia) or are manifested in pregnancy (peripartum cardiomyopathy) that can potentially result in long-term cardiovascular and neurological sequelae.

The purpose of this review is to provide an overview of female health in translational anesthesiology research (*Figure 1*). This review will focus on the complexity of anesthesia and analgesia in females, and anesthesia advances in females with breast cancer, preeclampsia, and cardiovascular disorders during and after labor and delivery. In this article, the term female refers to the sex of human participants or other sex-related biological or physiological factors (7), and sex refers to biological differences between females and males, including chromosomes, sex organs, and endogenous hormonal profiles (8). We present this article in accordance with the Narrative Review reporting checklist (available at: https://atm.amegroups.com/article/view/10.21037/atm-22-3547/rc).

Methods

We searched PubMed to identify relevant articles published in English from December 2021 to June 2022. Relevant articles were abstracted, and information that included perioperative and peridelivery implications for females was summarized. Results were reviewed by all authors (*Table 1* and Table S1).

Discussion

Basic science research reveals complexity in how females experience pain

Pain differences between sexes

Although several animal studies suggest that pain processing can differ between sexes due to genetic factors, neuronal circuitry, or molecular and cellular mechanisms, most findings are skewed toward male-prevalent diseases (6). This lack of research on females negatively impacts how therapeutics are developed and raises concerns about the number of drugs that may have been overlooked to treat pain in females. To address this challenge, the National Institutes of Health has introduced policies and guidelines for basic researchers to justify the exclusion of females in studies and consider sex as a biological variable in experimental designs (9). These policies have helped expand our knowledge of the safety, efficacy, and effectiveness of anesthetics and analgesics in females.

A study demonstrated that morphine has a 50% effective dose (ED_{50}) that is about two-fold greater in female rats than in male rats (10). Therefore, morphine provides better somatic (11) and visceral pain (12) relief in male rats than in female rats. These sex differences in the effect of morphine are also observed in humans (13,14). Nevertheless, the basis by which sex determines responses to pain and analgesic medications are likely multi-factorial (e.g., hormonal, environmental, and genetic factors).

A study on rats revealed that males express higher levels of mu-opioid receptors (MORs) in the periaqueductal gray (PAG), and this higher expression might depend on the estrous cycle of female rats (15). In the same study, ablation of the MOR-positive neurons altered the ED_{50} in males, and after that, the ED_{50} resembled that of females (15). A separate study found that acute pain is reduced in male mice

Table 1 Search strategy summary

Items	Specification
Date of search	December 2021 to June 2022
Databases and other sources searched	PubMed
Search terms used	See Table S1 for details
Time frame	1998–2022
Inclusion and criteria	Full-text articles relevant to anesthesia implications for women
Selection process	All authors extracted relevant information including differences in pain pathways by sex, pain management related to breast cancer, pregnancy-associated cardiovascular conditions, preeclampsia biomarkers

Figure 1 Schematic depicting interlinked factors that affect anesthesia in females. Sex-related differences influencing female anesthesia and analgesics can be caused by genetic factors, cancers, hypertension, chemical exposures, age, or hormonal changes during and after pregnancy.

after stimulation of dopamine neurons in the PAG, but activation of the same PAG neurons in female mice does not diminish pain (16). Instead, activating these same neurons in female rodents facilitated locomotor activity (16).

To complicate sex differences in pain pathways, studies suggest that the immune system may also play a role. Thus, a possible explanation for the sex differences in the anti-nociceptive effects of morphine may be due to more significant activity of microglia in the PAG in female rats than male rats (17). In an animal model of fibromyalgia, minocycline (a microglia inhibitor) only blocked allodynia in male mice but not female mice (18). Similarly, animal studies conducted in models of chemotherapy-induced neuropathic pain show that peripheral macrophages modulate allodynia only in male mice (19). Although the reason for differences in the pain pathways between males

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and females is still unclear, this work emphasizes the role of sexually dimorphic neuroimmune signaling pathways, such as those arising from the PAG, in modulating behavioral responses to pain.

Genetic factors involved in pain with anesthetic implications

Data collected from a genome-wide-association study conducted on 209,093 females and 178,556 males revealed 31 genes in males and 37 genes in females linked to chronic pain; surprisingly, males and females shared only one common gene that could be associated with chronic pain (20). It is important to note that pain-specific genetic associations in humans can be difficult to replicate due to differences in method(s) of measurement and reporting among studies (21,22). Thus, powerful genetic tools applied to animal pain models are often used to evaluate the associations between genetic effects on analgesia and the development of chronic pain. A study by Mogil *et al.* showed that melanocortin 1 receptor null (MC1R$^{-/-}$) mice have an increased pain threshold that resembles the pain reported by patients with the red hair phenotype (23). Mogil *et al.* also showed that MC1R only mediates kappa-opioid analgesia in female mice (24). The same study revealed that females with a variation of the MC1R allele had increased analgesic sensitivity to kappa-opioid pentazocine (24). Therefore, in the future, clinicians may have to consider and factor in genetic determinants when administering anesthetics or analgesics to females.

The role of gene-environment and epigenetics in females

Epigenetic mechanisms such as chromatin remodeling, DNA methylation, or histone modifications are believed to occur after environmental exposures and can be maintained through cell division (25). Epigenetic processes mediate genomic imprinting and X chromosome inactivation (25). Genomic imprinting is crucial for differences in brain structure between males and females (26,27) and general physical development (28). Epigenetic changes involving the X chromosome in females may be involved in autoimmune diseases such as rheumatoid arthritis (29) and systemic lupus (30). Studies conducted in humans and rodents with pain revealed that gene function might be altered due to environmental factors (31-33). Studies in rats demonstrated that exposure to bladder inflammation early in life could alter nociceptors during adulthood (34,35). In a mouse nerve injury model, epigenetic silencing of

the promoter regions of OPRM1 and Kcna2 (encodes the potassium-voltage gated Kv1.2 gene family) takes place in the dorsal root ganglia due to DNA methylation caused by DNA methyltransferase 3a (DNMT3a) and DNMT1, respectively (36,37). Although these studies demonstrate that chronic pain can elicit epigenetic changes, it is not clear how epigenetic mechanisms contribute to the transition of pain from acute to chronic in human males and females.

However, evidence suggests that epigenetic processes are involved in pain conditions, mainly affecting females. For example, in interstitial cystitis/bladder pain syndrome, DNA extracted from voided urine specimens revealed that genes in the mitogen-activated protein kinase pathway were predominantly methylated (38). In a female rat model of neonatal cystitis, miRNA-mediated epigenetic downregulation of GABA Aα1 receptors in the spinal cord was linked to visceral hyperalgesia (39). Moreover, epigenetic mechanisms can mediate estrogen output and the immune system; thus, it is theorized that changes to the epigenome drive the pathogenesis of endometriosis (40,41). These findings suggest that studies are needed to elucidate the exact epigenetic mechanisms that affect patients who receive anesthetics or analgesics.

Sex differences in response to the side effects of opioid medications: possible mechanisms

In addition to the aforementioned sex-dependent responses to the analgesic effects of opioid medications, there are also sex differences in responses to opioid side effects (13,42). For example, a common side effect experienced by female patients is opioid-induced pruritus (43) (*Figure 2*). Neuraxial opioid-induced pruritus has an incidence of 30–100%, is highly common in obstetric settings, and thus disproportionately affects females (43). When neuraxial opioids are used in same-day procedures (settings that should affect males and females equally) such as orthopedic and laparoscopic surgeries, pruritus has been reported to be higher among female patients (43), indicating a further challenge in achieving optimal pain control for females.

Although sex as a variable has not been studied in detail at the mechanistic level, it has recently been shown that neuraxial opioid-induced itch may occur through spinal disinhibition (44-47), likely through spinal neurons that make dynorphin. As dynorphin is the endogenous peptide for the kappa-opioid receptor, and females have been shown to have increased sensitivity to kappa-agonist medications (24,48), it is possible that modulation of dynorphin release by opioid medications could explain how females more
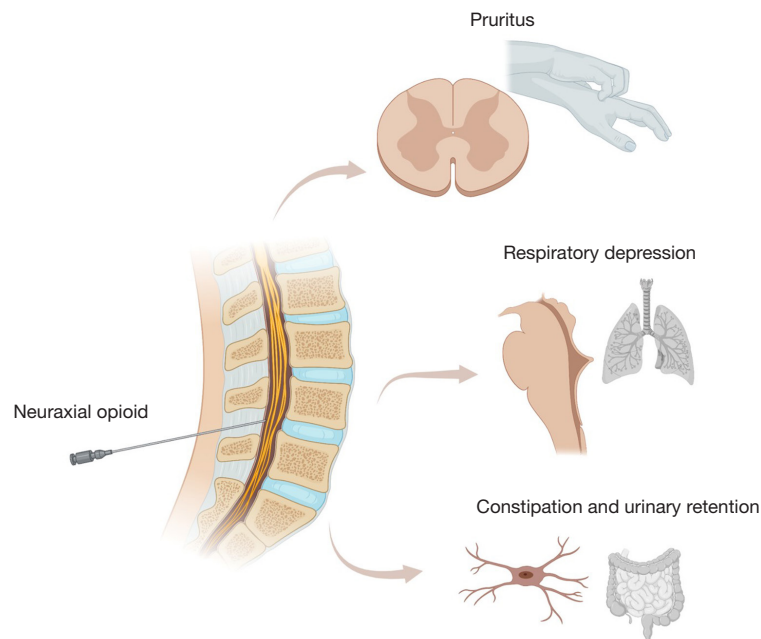
Figure 2 Mechanisms underlying opioid side effects. These are the common side effects of opioids administered neuraxially. The cells, molecules, and circuits involved in mediating these side effects have recently been delineated. Pruritus is thought to originate at the spinal level, respiratory depression is thought to originate in the brainstem, and the hypokinetic effects of opioids are thought to originate through primary afferent neurons.

often experience opioid-induced pruritus than males.

Another common side effect of opioids is opioid-induced respiratory depression (OIRD) (49). Female sex has been considered a risk factor for OIRD (50). Until recently, it has been challenging to identify the specific region of the brainstem that could be responsible for mediating OIRD (51). Excitatory neurons in the parabrachial nucleus (PBN) containing the MOR are both necessary and sufficient for OIRD (52). Although the intraperitoneal administration of morphine more robustly produces OIRD, it is likely that neuraxial morphine also induces OIRD through the cephalad spread of morphine to neurons in the PBN. The PBN is often considered a homeostatic hub for coordinating responses to external and internal threats (53). As such, the PBN exhibits extensive connectivity with sensory, autonomic, and limbic structures such as the bed nucleus of the stria terminalis. It is interesting to speculate that these structures could modulate the differences in OIRD between males and females.

Side effects of parenteral opioids, such as opioid-induced urinary retention and constipation, have not yet been investigated using similar gain-of-function or loss-of-function approaches. The effect of opioids on gut motility is likely to be mediated by mu-expressing sensory fibers within the enteric nervous system (54). The neurons involved in opioid-induced urinary retention are not well-characterized. Nevertheless, nalbuphine, a mixed mu-antagonist, and kappa-agonist have been proposed to improve urinary output (55), suggesting a potential typical role for kappa agonism in both opioid-induced pruritus and urinary retention.

Despite the unwanted side effects of opioids, particularly for neuraxial analgesia, they remain the safest, most feasible, and most accessible options. A robust mechanistic understanding of how they influence the nervous system, particularly in the context of sex differences, will guide the development of therapies that can improve and augment their roles in clinical practice. Although the mechanisms by which opioids affect neurophysiology in males and females have only begun to be examined, the expansion of technical tools in preclinical research represents a novel opportunity to define the molecules, cells, and circuits upon which anesthetics work.

The future of alternative non-opioid therapeutics in female predominant surgery

In response to the 21st-century opioid epidemic in the

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US, clinicians are often recommended to prescribe non-opioid pain medication (e.g., non-steroidal anti-inflammatory drugs) before prescribing opioids for pain control (56). Therefore, it is critical to investigate whether pain processing differs by sex during non-opioid therapy. A recent study comparing postoperative care between patients prescribed opioid versus non-opioid medications showed no significant differences in clinical or patient-reported outcomes in females (total n=13,269) or males (total n=9,076) (56). As a result, non-opioid pain management options such as lidocaine, diclofenac, capsaicin, or ketoprofen patches are becoming popular alternatives to treat pain (57-59). Clinicians should consider using non-opioid multimodal analgesics to prolong the duration of non-opioid therapies, thereby helping to reduce the use of opioids. Interestingly, clinical studies show that performing an erector spinae plane block (ESPB), a regional anesthetic technique, and non-opioid drugs can improve the quality of anesthesia in patients (60-63). A study that compared paravertebral block (PVB) with ESPB in females undergoing breast surgery showed that postoperative morphine consumption was significantly reduced in patients who received ESPB (62). To safely implement multimodal analgesic therapies in females, further studies are needed to address the efficacy and effectiveness of several non-opioid analgesics based on (I) delivery route(s), (II) side effects on anesthetics or opioids, and (III) population heterogeneity (e.g., sex differences).

Perioperative considerations for breast cancer surgery

Breast cancer is the most frequently diagnosed female cancer and has consistently remained a leading cause of malignancy-associated female deaths. Breast cancer is 100-fold more prevalent in females than males; male breast cancer's molecular and genetic composition generally mimics that of female disease (64). Patients with breast cancer require careful perioperative anesthetic and analgesic care, including acute and chronic outpatient pain management after a primary presentation and advanced recurrence.

Risk of metastatic disease associated with anesthesia type

Breast cancer surgery includes mastectomies and breast-conserving surgical approaches. Choice of anesthetic technique and pharmacological approach in surgical oncology have long been investigated for potential associations between anesthetic choice and patient survival and cancer recurrence outcomes (65,66). The effects of anesthesia on direct and indirect immune suppression mechanisms, inflammation, chemoresistance, and tumor-promoting effects are still controversial. These mechanistic interactions inform translational and clinical research on anesthetic interventions to minimize metastatic seeding and distant recurrence (67). PVB alongside propofol total intravenous anesthesia (TIVA) has been reported to reduce postoperative inflammatory marker levels (68) (*Figure 3*), although recent reviews have identified no recurrence-free survival associations with a select intravenous or inhaled anesthetic (65,67,69). The ongoing Volatile Anesthesia and Perioperative Outcomes Related to Cancer clinical trial evaluates the effect of disease-free survival, comparing propofol and sevoflurane in colonic, rectal, and non-small cell lung cancers (NCT04316013) (70). A recent study examining patients undergoing breast-conserving surgery found a reduction in locoregional recurrence when provided dual PVB and propofol TIVA induction compared to sevoflurane (71). One study explored the effect of propofol/remifentanil-based TIVA compared to sevoflurane to investigate the possibility of a chosen anesthetic promoting the tumor microenvironment. Propofol was found to reduce vascular endothelial growth factor, a marker for angiogenesis, during breast surgery; however, no significant short-term effect on breast cancer recurrence was observed (72) (*Figure 3*). In a parallel approach, lignocaine administered in the surgical field of a modified radical mastectomy led to decreased angiogenesis markers and better postoperative analgesia (73). Although anesthesia's causality of metastatic spread has been thoroughly studied, there remains a lack of conclusive evidence that anesthetic choice and route contribute to cancer progression.

Breast cancer surgery management and the impact of acute postsurgical pain

Reduction in undue postoperative acute and chronic pain can be attributed to both surgical and anesthetic interventions. In the perioperative setting, the surgical complexity level helps predict pain and guide anesthetic involvement. A meta-analysis by Wang *et al.* found that including axillary lymph node dissection in breast surgery resulted in a 21% increased risk of persistent pain, while type of breast surgery and previous therapeutic regimes had no association (74). Propofol induction during breast cancer surgery has previously been associated with a lower incidence of postoperative chronic pain compared to sevoflurane with
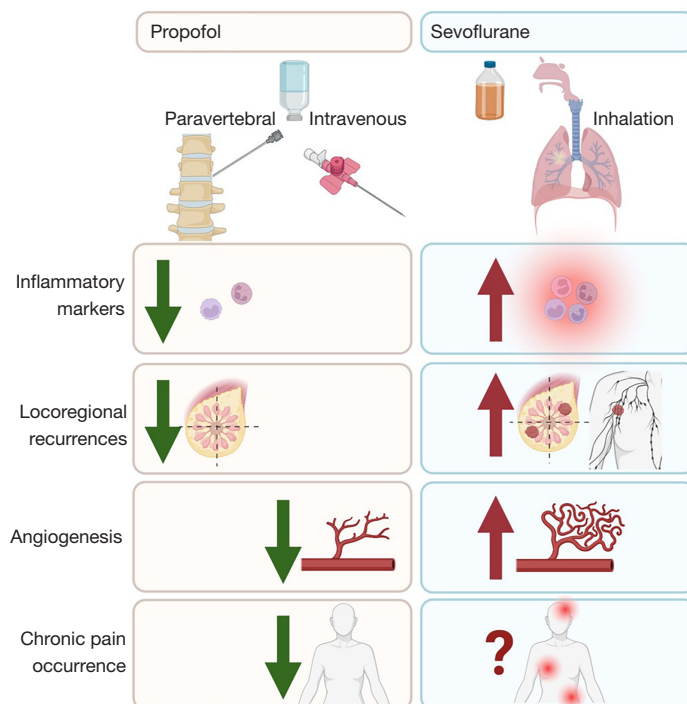
Figure 3 Benefits of non-inhalation propofol anesthetic in breast cancer patients. In patients undergoing breast cancer procedures, a literature review shows a reduction in inflammatory markers, locoregional breast malignancy recurrences, and angiogenesis in patients anesthetized by paravertebral propofol blocks rather than sevoflurane inhalation anesthetic. Chronic pain is reduced in patients who receive intravenous propofol.

no effect on the severity or duration of pain (75) (*Figure 3*). Another study did not find significant benefits with regional or volatile anesthesia in the prevalence of breast pain (69). Nevertheless, regional anesthesia with peripheral nerve blocks may confer several potential benefits breast during cancer surgery (66). In one study, preoperative ESPBs or PVBs in patients undergoing unilateral breast surgery resulted in fewer in-hospital postoperative intravenous analgesia requirements (62). In addition, thoracic PVB in conjunction with general anesthesia led to better quality-of-life measures and less chronic pain (persistent pain beyond three months due to surgical tissue healing) compared to general anesthesia with inhalational agents alone (76). Although PVBs did not decrease the incidence of chronic pain post-surgically up to 12 months, acute pain was more adequately controlled in the postoperative setting (77). A COVID-19 study found that using PVBs instead of general anesthesia for breast surgery led to shorter recoveries (78). In addition, PVBs resulted in less intensive care hospitalization and reduced postoperative nausea and vomiting compared to the pre-COVID-19 era when general

anesthesia was more predominant (78). Thoracic PBV, including ketamine in the block, reduced postoperative pain and neuropathic pain symptoms one month postsurgically (79). Similar studies assessing pectoral type-2 blocks found equivalent postoperative analgesic efficiency to PVBs, with both superior to systemic analgesia (80). The importance of regional anesthesia cannot be understated in the acute care period following breast cancer surgery, and the long-term effects of chronic pain management may yet be uncovered.

Anesthetic considerations for persistent postmastectomy and chronic pain

Persistent pain after breast cancer treatment affects 21–30% of breast cancer survivors (81). In a 1-year study, postsurgical pain was present in 60% of all breast surgery cases one week postoperatively, with chronic pain persisting beyond the typical healing time reported in approximately 40% of cases (82,83). The underlying pathophysiology of pain in breast cancer patients is likely influenced by multiple factors like direct surgical injury, postsurgical inflammation,

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lymphedema, radiation, pharmacologic adverse effects, or indirect local damage from surgical inflammation.

Chronic pain has been reported in up to 57% of postmastectomy patients alone (84), some of whom are at risk for developing postmastectomy pain syndrome (PMPS) (5). PMPS is still poorly defined and encompasses neuropathic chronic postmastectomy pain and neuropathic pain following other breast surgeries (5). This syndrome is localized to the axilla, upper medial arm, and anterior thorax, with pain persisting beyond three to 6 months (5). In addition, lymphatic pain has been reported to be prevalent in 33% of breast cancer survivors (85). Neuropathic pain disorders include those induced by chemotherapy or radiation and injury caused to peripheral nerves during surgery (86).

Aromatase inhibitors are a mainstay treatment in hormone receptor-positive breast cancer; however, over one-third of postmenopausal patients receiving this therapy will develop aromatase inhibitor-induced associated musculoskeletal syndrome (AIMSS) (87). AIMSS is characterized by arthralgia, myalgia, and arthritis, which cause 25% of early breast cancer patients to discontinue treatment (87). The current pharmacological interventions proposed to relieve chronic pain in PMPS and AIMSS include opioids, tricyclic antidepressants, serotonin-norepinephrine reuptake inhibitors, and gabapentinoids (88). A recent study evaluated the effect of an intraoperative 0.5 mg/kg bolus of ketamine with an infusion of low-dose 0.12 mg/kg/h ketamine in persistent postsurgical pain; no significant decrease in chronic pain was appreciated beyond three months (89). However, a meta-analysis found a small but significant outcome in PMPS in patients who had received intraoperative ketamine infusions (90). Similarly, a bolus of 2 mg/kg lidocaine with subsequent 2 mg/kg/h infusions intraoperatively resulted in decreased chronic pain at three months (91).

Nefopam, a non-opioid medication available in Europe (but not yet FDA-approved in the US), has been investigated as a preemptive analgesic prior to lumpectomy with axillary lymph node dissection or sentinel lymph node biopsy. Patients receiving 20mg nefopam intravenously over 15 minutes perioperatively had significantly reduced acute pain up to 24 hours and less persistent pain at three months (36.6% *vs.* 59.5%, P=0.04) (92). A study using preoperative ultrasound-guided multilevel PVBs with 25 ml of ropivacaine 0.5% showed a significant decrease in persistent pain at three months (93). A study published in 2017 reported that a 3-day continuous 5 mL/hour ropivacaine 0.4% infusion with a PVB significantly reduced pain-induced dysfunction (94). Even without conclusive anesthetic-associated metastatic spread, regional anesthesia and analgesia intervention have significantly impacted both acute and chronic pain. Minimal pain prevention for patients diagnosed with breast cancer can drastically affect their quality of life.

Oncology teams traditionally drive postsurgical management, hormonal treatment, and pain therapy; however, a multidisciplinary approach that includes anesthesia pain specialists is necessary. Complications resulting from surgery or medication adverse events need to be acutely managed to ensure patient quality-of-life is upheld and acknowledged, even in light of poor disease prognoses.

Cardiovascular disease in pregnancy: *peridelivery considerations*

Preeclampsia: new diagnostic tools and adverse neurologic outcomes

In recent years, the field of cardio-obstetrics has surged due to increased rates of cardiovascular disease (e.g., hypertension) in pregnancy, requiring a multidisciplinary team that includes anesthesiologists. Preeclampsia is a hypertensive multisystem disorder of pregnancy and a leading cause of maternal morbidity and mortality in the US (95). Many mechanisms have been postulated to explain the etiology of preeclampsia; however, the most well-studied potential mechanism is uteroplacental ischemia, which eventually causes the release of angiogenic factors, resulting in widespread, multi-organ endothelial dysfunction (96). As a result, multiple organ systems, including the brain, are affected by preeclampsia, causing adverse short-and long-term neurological complications. Therefore, predicting females at the highest risk for preeclampsia and those who will develop adverse outcomes remains a healthcare priority, as cardiovascular disease remains the leading cause of maternal morbidity and mortality (91,97).

Predicting preeclampsia using biomarkers

Timely identification of those at risk for preeclampsia before the onset of labor can improve outcomes. Although the pathogenesis of preeclampsia starts early in the first trimester, typical clinical presentation varies and can complicate anesthetic management. Therefore, diagnosis remains challenging. Preeclampsia diagnosis is based on clinical features such as hypertension or proteinuria at or

after 20 weeks of gestation. Clinical risk factors and risk scores can stratify patients with a high risk of early onset preeclampsia but have limited sensitivity (41%) (74). To identify who can benefit from early screening or prophylactic measures such as low-dose aspirin treatment to prevent preterm deliveries, circulating angiogenic factors/biomarkers have been suggested as a diagnostic tool.

Upregulation of soluble fms-like tyrosine kinase-1 (sFlt-1) and downregulation of placental growth factor (PlGF) are seen in suspected cases of preeclampsia (98). When including PIGF levels with clinical measurements of mean arterial blood pressure and maternal uterine artery resistance, the ability to detect early preeclampsia achieved a sensitivity of 82% (99). Among patients with suspected preeclampsia and less than 35 weeks of gestation, a PIGF level of less than 100 pg/mL alone is a highly predictive biomarker with a 96% sensitivity for the disease and the need to deliver within a two-week diagnostic period (100). An sFlt-1/PlGF ratio of less than 38 has been shown to have a negative predictive value (99.3%) for preeclampsia in the ensuing weeks among females with <37 weeks of gestation, but at >38 weeks of gestation, it offered only a modest predictive value of 36.7% with a sensitivity of 66.2% (101). Significant work has been done to predict early-onset preeclampsia; however, successful prediction of term preeclampsia with biomarkers remains an area of promising and active research. Developing "point of care" biomarkers in the immediate clinical setting can potentially guide early aspirin treatment and customize therapeutics to prevent adverse maternal outcomes in early- and late-onset preeclampsia.

Biomarkers associated with preeclampsia prognosis

Biomarkers have also been used to prognosticate preeclampsia outcomes, particularly for the risk of preterm delivery. The rate of change of sFlt-1/PlGF ratios can indicate the progression and severity of the disease (102). For instance, differences in the absolute change per day in the sFlt-1/PlGF ratio was seen among preeclamptic patients who developed adverse outcomes (e.g., pulmonary edema) versus those without these outcomes (15.1 *vs.* 2.7; P<0.004 respectively) (103). On the contrary, a low repeated measured ratio has been associated with improved patient outcomes, including longer latency to delivery (104). When the sFlt-1/PlGF ratios are used concomitantly with gestational age and natriuretic peptide (NT-proBNP) levels, the preterm delivery prediction improves compared to the model without NT-proBNP levels (areas under the curve:

0.845 and 0.786, respectively), suggesting that the latter may be a short-term prediction marker (105).

Predicting preeclampsia-associated cerebrovascular events using biomarkers

The definitive treatment of preeclampsia is the delivery of the placenta. Several lines of evidence suggest that preeclampsia has lifelong effects on female health. Patients with preeclampsia are at higher risk for developing cerebrovascular disease later in life, including stroke and dementia (106). White matter lesions in the frontal, parietal, insular, and temporal regions of the brain were seen in former preeclamptic/eclamptic patients, similar to those found in elderly patients diagnosed with dementia (107). Compared to normotensive patients, those with a history of preeclampsia had a trend toward higher rates of mild cognitive impairment (20% *vs.* 8%; P=0.10), with significant deficits in Trail Making Test B (executive domain) scores (101.0 *vs.* 59.5 time/sec; P=0.018), suggesting potential impairment of the frontal subcortical brain areas (108). Although there is radiographic evidence of signs of dementia in former preeclamptic patients, there remains a paucity of objective cerebral biomarkers for complications associated with preeclampsia.

One potential framework to assess cerebral biomarkers is the neurovascular bed (NVU) concept. NVU highlights the relationship between brain cells and the cerebral blood vessels and can be defined as a complex of endothelial cells, smooth muscle cells, pericytes, astrocytes, neurons, and extracellular matrix proteins, thus harboring multiple specialized functions (109). The integrity of these elements is essential to maintain the blood-brain barrier (BBB). Because of the BBB's imperative role in preventing harmful molecules from the systemic circulation from entering the brain parenchyma, its disruption in the setting of preeclampsia can increase permeability and result in elevated levels of cerebral biomarkers.

Using the NVU framework, studies have postulated promising cerebral biomarkers such as neurofilament light (NfL), tau, neuron-specific enolase (NSE), and S100B that could be associated with BBB integrity and have been reported in different neurological pathologies. In the preeclampsia setting, high S100b and NSE concentrations were linked to neurological symptoms such as visual disturbances (110,111). A report recently demonstrated that NfL, tau, GFAP, and axonal and glial proteins are elevated in patients with preeclampsia and neurological complications such as eclampsia, cortical blindness, and

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stroke (112). Other proteins such as alpha-1-microglobulin and alpha-1-microglobulin/bikunin precursor were more abundant in preeclamptic patients, suggesting an altered BBB permeability (112,113). Preeclamptic patients also had higher concentrations of FSTL3, IL-1ß, α-SNAP, and activin A, which are implicated in vascular remodeling, neuronal growth, and inflammation (114). These cerebral biomarkers can be useful as diagnostic tools and can serve as predictors for the degree of neurologic involvement after preeclampsia.

Lifelong neurological complications of preeclampsia are challenging to predict but measuring circulating cerebral biomarkers alone or in combination with clinical data could potentially identify patients at the highest risk for developing these complications. This can further help develop treatments that include more aggressive hypertensive control, neuroprotective agent (MgSO$_4$) administration, or delivery timing.

Advances and opportunities in cardiopulmonary peripartum anesthesia care

Although hypertensive disorders of pregnancy (HDPs) contribute an additional 7–12% of maternal deaths in the US annually (115), complex cardiovascular conditions such as heart failure also raise maternal mortality rates. Over half of cardiovascular-related maternal deaths are preventable with improved prenatal counseling, intrapartum and postpartum surveillance, and multidisciplinary team planning (116).

Three risk stratification models exist for pregnant patients with cardiac disease: CARPREG II, mWHO, and ZAHARA. According to the 2018 European Society of Cardiology (ESC) guidelines for managing cardiovascular disease during pregnancy, mWHO is the most accurate of the models (117). The ESC identified pulmonary hypertension as the most significant risk factor for an adverse event in pregnant patients. Valvular heart disease, HDPs, and the increasing age of repaired congenital heart lesions are among the highest risk factors for adverse events in pregnant patients, with the highest risks around delivery, immediately after delivery, and the first year after delivery (117).

Patients with mWHO class III and IV cardiac lesions have better outcomes if they deliver in specialized centers; therefore, it is recommended that these patients have a care team with maternal-fetal medicine, obstetric, and cardiac anesthesiology experts and receive care at centers with cardiothoracic surgery and advanced heart failure care

capabilities (118). Even with improved management, new data suggests maternal cardiac risk does not entirely normalize after delivery. Whether cardiac disease exists before or during pregnancy, patients who suffer cardiovascular complications face elevated lifelong risk (119). Within five years of delivery, HDPs were associated with all-cause mortality [hazard ratio (HR) 2.21; 95% confidence interval (CI): 1.61–3.03], coronary disease (HR 3.79; 95% CI: 3.09–4.65), and stroke (HR 3.10; 95% CI: 2.09–4.6) (120).

Risk stratification models aid in identifying and managing pregnant patients with cardiac diseases and associated complications; however, little evidence is available to predict the risk for new-onset cardiovascular disease in pregnancy. Since data suggests these patients are at elevated lifelong risk, further research to understand these disease processes and interventions is vital.

Pregnancy may unmask cardiac disease in females with underlying pathology. Therefore, identifying early biomarkers is an ongoing area of interest. Recent clinical studies suggest that an imbalance in prostacyclin and thromboxane A2 is involved in the pathogenesis of preeclampsia, and recent guidelines, therefore, recommend low-dose aspirin to reduce the incidence of preeclampsia in at-risk patients (121). Statins may also show therapeutic promise as placental angiogenesis is better understood (115).

With the incidence of cardiac complications rising, it is crucial to understand the adaptations of the heart during normal pregnancy. Only recently have echocardiographic and other imaging measures of myocardial function been examined. Pregnancy increases preload, stroke volume, augments heart rate, and decreases systemic vascular resistance (122). Pregnancy promotes reversible eccentric hypertrophy with more spherically shaped chambers with increased volumes. A study measuring strain in normal pregnancy using deformation rate found increased myocardial contractility in the first trimester, but strain decreased significantly between the second and third trimesters despite increasing stroke work and normal ejection fraction (122). This period of decreased contractility but increased demand suggests a vulnerable state with potentially increased risk. Since echocardiography can identify these changes earlier than other monitoring modalities, it will likely have an expanding role for future anesthesiologists in identifying cardiovascular insult and optimizing care.

Peripartum cardiomyopathy (PPCM) is a diagnosis of exclusion and a leading cause of maternal mortality (115,116). The pathogenesis of PPCM is poorly

understood. However, recent studies suggest various possible cell signaling pathway etiologies (115) including prolactin induced PPCM. More recently, a prospective randomized clinical trial in patients with PPCM compared bromocriptine (a prolactin inhibitor) to heart failure standard therapy and showed heart function improvement with fewer adverse outcomes (123).

Despite the improved understanding of cardiac disease in pregnancy, much progress must be made to prevent the disease. Until then, obstetric and cardiac anesthesiologists will need to become increasingly familiar with resuscitating and managing pregnant patients with cardiovascular disease. Risk stratification and guidelines are helpful for multidisciplinary team planning, and in most cases, neuraxial labor analgesia is favorable as it decreases sympathetic drive and myocardial demand. However, Valsalva maneuver safety, hemorrhage risk, invasive monitoring, echocardiography, general anesthesia need, and mechanical cardiovascular support should be considered in advance to improve outcomes.

Conclusions

This review highlighted preclinical studies that reveal the complexity of peripheral and central mechanisms that drive sex-dependent differences in pain processing. Despite advances in breast cancer research in the past decade, knowledge gaps remain regarding cancer dormancy and immunity invasion. The mechanisms of the tumor microenvironment and dormant tumor remain to be elucidated.

We also discussed recent human and rodent genetic discoveries that will allow future studies to uncover critical environmental factors and epigenetic mechanisms that mediate pain sex differences and responses to anesthetics. Because anesthesiologists play vital roles in surgical and oncologic teams, understanding recent discoveries related to pain sex differences and gaps in the field will help improve awareness of sex biases related to pain control options, peri-surgical care, or administration of perioperative analgesics. Providing adequate anesthesia during surgical tumor extraction and postoperatively can improve outcomes.

The anesthesiologist's role in female healthcare extends beyond perioperative and peridelivery settings. Personalized clinical care for complex cardiac conditions in pregnancy highlights the critical role of anesthesiologists in the multidisciplinary team. Early biomarker identification of females at the highest risk for developing preeclampsia

and its long-term cerebrovascular effects hold promise for optimizing future anesthetic and perioperative clinical practice.

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