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Perinatal and neonatal use of sedation and analgesia

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A B S T R A C T

Optimal obstetric and neonatal care requires the provision of adequate analgesia for painful procedures. However, anesthetic and analgesic agents have the potential to adversely impact the developing fetal/neonatal brain. In this setting, clinicians must assess the risks and benefits of pharmacologic anesthesia and analgesia for specific indications in this population. General anesthesia is required for non-obstetric surgery and cesarean section in the absence of neuraxial anesthesia for the health of the mother and fetus. Although experimental data raise concerns, human data are reassuring and future research may focus on neuroprotective adjuncts in the setting of repeated or prolonged anesthetic exposures. Opioid analgesia is standard of care for preterm infants undergoing major procedures including invasive surgery and endotracheal intubation. The use of opioids for agitation resulting from mechanical ventilation is controversial, but prevalent. Randomized and retrospective studies detect short-term toxicity with inconclusive long-term impact, suggesting the need to explore alternative therapies.

1. Introduction

The prevention and treatment of pain using anesthetics and analgesics represents an essential component of medical practice. Attention to pain control is vital in the fetal and neonatal period, given the profound long-term neurodevelopmental implications of inadequate analgesia during this period of rapid brain development. However, agents widely used for anesthesia and analgesia may also produce untoward effects in the rapidly developing brain, resulting in a unique risk–benefit calculation when considering pharmacologic pain control in this challenging population.

In rare cases, non-obstetrical surgical procedures requiring anesthesia may be necessary during pregnancy. More commonly, general anesthesia is required during emergent cesarean deliveries or those deliveries where neuraxial anesthesia is contraindicated. The importance of anesthesia to the wellbeing of the maternal–fetal dyad in these cases is not debatable. However, exposure to anesthesia during rapid fetal brain development raises significant concerns. Experimental evidence clearly suggests that anesthetic exposure may be harmful during periods of rapid synaptogenesis. However, the applicability of this evidence to human infants remains an area of active investigation. Substantially less data exists regarding exposure during fetal life.

Postpartum, infants born preterm experience frequent painful procedures during neonatal intensive care. These range in severity from heel sticks for laboratory monitoring to major surgery for complications of prematurity. Although a relatively clear approach to pain control exists for these extremes, sedation/analgesia for chronic exposures such as mechanical ventilation remains controversial. Despite large randomized controlled trials and consensus guidelines addressing this clinical scenario, wide variability exists in practice. This variability highlights the challenging balance between the provision of adequate analgesia/sedation to these fragile patients, and avoidance of the well-described (and emerging) toxicities of the agents utilized in current practice. This review summarizes available experimental and clinical data regarding the neurologic implications of anesthesia in obstetrics and analgesia/sedation in newborn medicine, highlighting the clinical and research challenges prevalent in these high-risk populations.

2. Anesthesia in pregnancy

Estimates suggest that between 0.5% and 4% of women require non-obstetric surgery at some point during their pregnancy. These procedures mostly occur early in pregnancy, with 42% occurring in the first trimester, 35% in the second trimester, and 23% in the third

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trimester. The most frequent indications for non-obstetric surgery during pregnancy are trauma, appendicitis, cholecystitis, and bowel obstruction, generally requiring prolonged anesthetic exposure. Additionally, fetal surgeries are now increasing in prevalence, requiring a therapeutic level of anesthesia in both the mother and fetus. Several anesthetic agents are widely utilized during pregnancy, including inhalational anesthetics (nitrous oxide, desflurane, isoflurane, sevoflurane), ketamine, and propofol. These agents share overlapping mechanisms of action; specifically, volatile, inhalational anesthetics are combined N-methyl-D-aspartate receptor (NMDA) antagonist/gamma-aminobutyric acid receptor ($GABA_A$) agonists, whereas propofol is a potent $GABA_A$ agonist, and nitrous oxide and ketamine are predominantly NMDA antagonists. These agents are highly lipophilic, facilitating rapid passage through the blood–brain barrier, but also the placenta. Notably, high concentrations of anesthetics are generally required for surgery during pregnancy to avoid uterine contraction and thus minimize the risk of premature labor [1].

In contrast to non-obstetric indications, exposure to general anesthesia late in pregnancy typically represents a relatively mild exposure. The utilization of general anesthesia during cesarean delivery (comprising as many as 33% of overall deliveries in developed countries) varies widely from 5% to 30% depending heavily on the urgency and setting of delivery [2]. However, in some obstetric practices, nitrous oxide is widely used for mild anxiolysis and analgesia throughout labor [3]. This often represents a more prolonged exposure in a larger proportion of obstetric patients. Multiple randomized controlled trials document the ease and short-term safety of nitrous oxide in this setting; however, studies examining the long-term implications of this and other anesthetic exposures during pregnancy are limited.

3. Anesthetic neurotoxicity

Extensive experimental studies in models ranging from rodents to non-human primates have demonstrated neurodegeneration, particularly apoptosis, and impairment of proper synapse formation after anesthetic administration during the developmental equivalent of the late second/third trimester of human gestation [4]. These perturbations result in long-term alterations in synaptic transmission and cognitive and behavioral function. Generally, studies demonstrate greater impact from multiple agents and/or longer durations of exposure. Given the pleiotropic nature of inhalational anesthetics, numerous points of developmental disruption have been identified in experimental models (Box 1) [1]. Although the pathologic (as well as therapeutic) mechanisms of anesthetics have not been completely described, NMDA antagonism and/or $GABA_A$ agonism appears to contribute significantly to these developmental disturbances. Organization of neural circuitry relies on ongoing electrochemical activity, allowing firing neurons to locate and synapse with other cells (i.e. activity-dependent network formation). Neurosuppression via NMDA antagonism/$GABA_A$ agonism suppresses electrochemical activity, curbing neurogenesis and triggering apoptotic neuronal death in the developing brain [5].

Box 1
Pathogenic mechanisms of anesthetic neurotoxicity during brain development.

- Apoptotic neurodegeneration.
- Suppression of neurogenesis.
- Impairment of proper synapse formation.
- Alteration of dendritic spine formation.
- Deformation of actin.
- Neuronal mitochondrial dysfunction.
- Dysregulation of neuronal calcium.

Adapted from Palanisamy et al. [1].

Of interest, anesthetic neurotoxicity has taken the opposite course of most pathologies examined in experimental research. Traditionally, a clinically relevant human syndrome is replicated in animals to refine understanding of the disease process and/or examine diagnostic or therapeutic approaches. By contrast, anesthetic neurotoxicity was discovered in animal models decades ago, whereas the analogous clinical syndrome in humans remains unclear. Numerous limitations prevent direct extrapolation of experimental studies to human subjects. These include, but are not limited to, discrepancies in the duration and timing of anesthetic exposure relative to gestation and/or peak neuronal proliferation in humans versus animals, differing complexities of the neuronal connectivity and function of various species, and the rudimentary measures of long-term cognition and function available in animal studies.

4. Fetal impact of anesthetic exposure

Observational clinical studies raise concerns about the potential impacts of first-trimester anesthetic exposure on the developing fetus. Specifically, population-based studies initially identified an overrepresentation of hydrocephalus and neural tube defects in pregnancies exposed to anesthesia [6]. Causality cannot be assumed, as the majority of women requiring surgery in this period are febrile, a well-described independent risk factor for neural tube defects [7]. Notably, experimental studies of anesthetic exposure during this developmental period do not replicate these observational findings [8]. In fact, subsequent observational studies have also failed to detect this association [9]. By contrast, increased risk of spontaneous abortion after first-trimester anesthetic exposure is a consistent finding in experimental and observational studies [9]. These include studies examining occupational exposure to inhalational anesthetics, which remove the confounding effects of underlying pathophysiology and surgery itself.

Second-trimester exposure to anesthesia raises different concerns. At this stage of development, embryogenesis is complete, but neuronal proliferation and migration peak. As discussed previously, this period may represent the greatest window of neurodevelopmental vulnerability to anesthetic exposure. Experimental studies of anesthetic exposure in this window demonstrate significant cognitive impairment in offspring persisting into adulthood. Unfortunately, human studies of developmental outcome after exposure during the second trimester of pregnancy do not exist.

Large, retrospective studies in humans have focused on general anesthetic exposure in the late third trimester, specifically during cesarean delivery. The largest study to date utilized a population-based cohort recruited from 1976 to 1982 in Olmsted County, Minnesota [10]. The investigators found no increased risk of learning disability among 5-year-old children born by cesarean section with anesthetic assistance compared to those born vaginally. A second study evaluated a large cohort of children with autism spectrum disorders (ASD) compared to siblings without ASD [11]. There was no difference in the rate of exposure to anesthesia during delivery between groups. Although reassuring, these studies highlight several limitations of human data regarding in-

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