General Anesthesia During the Third Trimester

Any Link to Neurocognitive Outcomes?

Annemaria De Tina, MD, FRCPC[a], Arvind Palanisamy, MD, FRCA[b,*]

KEYWORDS

- Fetal neurodevelopment • Fetal surgery
- Developmental neurotoxicity of anesthetics • Maternal anesthesia
- Prenatal exposure • Third trimester anesthesia

KEY POINTS

- Most anesthetic agents have been shown to cause neurotoxicity in the developing rodent and nonhuman primate brain by increasing neuronal apoptosis and inducing long-term behavioral deficits.
- Developmental neurotoxicity of anesthetic agents is well-studied in postnatal rodents, but emerging evidence indicates that this phenomenon also occurs in utero during maternal anesthetic administration in rodents.
- Animal data for third trimester exposure are conflicting although evidence supports the overall notion that prolonged administration of anesthetic agents is detrimental to the fetal brain.
- Emerging evidence suggests that dexmedetomidine does not cause neuroapoptosis, at least in primate models.
- Human studies are sparse and the evidence is conflicting and weak to draw meaningful conclusions or influence current practice.

In the past decade, elegant work from animal studies has conclusively shown that anesthetic agents, both inhalational and intravenous, cause widespread apoptotic neurodegeneration and behavioral abnormalities when administered during critical periods of brain development.[1–4] The most widely evaluated period is the phase of synaptogenesis, which, in humans, extends from late second trimester to the first few years of life.[5,6] Therefore, these preclinical studies have caused a lot of concern

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[a] Obstetric Anesthesiology, Department of Anesthesiology, Perioperative and Pain Medicine, Brigham and Women's Hospital, 75 Francis Street – CWN L1, Boston, MA 02115, USA; [b] Department of Anesthesiology, Perioperative and Pain Medicine, Brigham and Women's Hospital, Harvard Medical School, 75 Francis Street – CWN L1, Boston, MA 02115, USA
* Corresponding author.
E-mail address: APALANISAMY@BWH.HARVARD.EDU

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among clinical anesthesiologists.[7] The aim of this review is to elaborate on current preclinical evidence for developmental neurotoxicity of anesthetic agents in animal models and discuss its relevance to humans. Only studies involving anesthesia exposure during mid to late pregnancy are included.

USE OF GENERAL ANESTHESIA DURING THE THIRD TRIMESTER

More than 80,000 parturients undergo nonobstetric surgery in the United States every year.[8] Despite the popularity of neuraxial techniques in obstetric anesthesia, many pregnant women continue to require general anesthesia for either pregnancy-related or nonobstetric surgical procedures during the third trimester.[8–11] These include emergency cesarean deliveries, trauma surgery, surgery for acute surgical conditions such as appendicitis and cholecystitis, and fetal interventions. Although the use of general anesthesia during the third trimester has not been determined precisely, the incidence can be as high as 5% to 44% for cesarean delivery in some European countries.[12,13] Although such high rate of general anesthesia is uncommon in the United States, it is clear that a significant number of pregnant women receive and will continue to receive general anesthesia during the third trimester for a variety of indications in addition to cesarean delivery. Until recently, the neurodevelopmental consequences for the fetus of maternal anesthesia were largely unstudied, despite a solid line of evidence that pharmacologic or environmental influences at this stage of life can cause defective cortical structure and abnormal behavior in adulthood.[14–17] This topic merits further scrutiny for a variety of important reasons. First, most general anesthetic agents are lipophilic, cross the placenta easily, and influence the fetal brain. This is supported by work from Li and colleagues,[18] who confirmed that the fetal brain isoflurane concentration after 6 hours of 1.3% isoflurane administration was comparable to the concentration in the maternal brain (0.40 vs 0.42 μmol/g, respectively). Similarly, propofol crosses the placenta readily,[19] but the overall maternal/fetal ratio of mean plasma propofol concentration was high (5.4 vs 0.35 μg/mL; maternal/fetal ratio of approximately 15),[20] which suggests a more complex pharmacokinetic model. Second, some of the surgical procedures required by pregnant patients may necessitate general anesthesia because of the increased complexity and prolonged duration of surgery. Apart from emergent cesarean deliveries, in most cases, the fetus is a bystander. Third, high concentrations of anesthetic (approximately 1.5 minimal anesthetic concentration) are sometimes required to achieve adequate uterine relaxation and minimize the risk of preterm labor. Thus, clinical necessity may inadvertently increase fetal exposure to general anesthetic agents.

NEURODEVELOPMENTAL EVENTS DURING THE THIRD TRIMESTER

To better understand the impact of neurodevelopmental perturbations during the third trimester, it is essential to sequence the key neurodevelopmental events that unfold during this time period. All neurodevelopmental processes are propelled by a preordained genetic program, which is readily modified by environmental and pharmacologic influences. Neural proliferation and differentiation are essentially complete by late second trimester, and the third trimester is characterized by burgeoning brain connectivity and a 5-fold increase in cerebral cortical volume.[21] Specifically, synapse formation accelerates during this critical period at a rate of 4% every week (approximately 40,000 synapses every minute) and continues at least into the first 2 to 3 years of life. Extensive dendritic arborization, cortical lamination, and myelination overlap with this phase of synaptogenesis. The main drivers of these processes include an array of neurotransmitters, of which γ-amino butyric acid (GABA) and glutamate are