Effects of Anesthetics on Neurodevelopment of Fetus

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Objectives: Upon completion of this presentation, participants will be able to:

1. Identify the pertinent literature on the effects of anesthesia on the fetal and neonatal CNS.
2. Discuss the relevance of these preclinical findings to the care of obstetrical and pediatric patients.

Summary: Millions of newborn and infants receive anesthetic, sedative and analgesic drugs for surgery and painful procedures on a daily basis. Recent laboratory reports clearly demonstrate that anesthetic and sedative drugs induced both neuroapoptosis and neurocognitive deficits in laboratory models. This issue is of paramount interest to obstetrical and pediatric anesthesiologists and intensivists because it questions the safety of anesthetics used for fetal and neonatal anesthesia. In an attempt to summarize the rapidly expanding laboratory-based literature on anesthetic-induced developmental neurotoxicity (AIDN), this review will examine published reports on the characterization and clinical extrapolation of this phenomenon in the care of obstetrical and pediatric patients.

N-methyl-D-aspartate antagonists (ketamine and nitrous oxide) and γ-aminobutyric acid agonists (isoflurane, sevoflurane, desflurane, propofol and midazolam) clearly induce neurodegenerative changes in neonatal animals. There are two distinct historical changes associated with animal models of AIDN; neuroapoptosis and altered dendritic growth. AIDN leads to neuroapoptosis in neonatal and adult neurocognitive deficits in rats, mice and rhesus monkeys. Altered dendritic growth has also been demonstrated in vitro and in juvenile mice. Susceptibility to AIDM is not limited to the postnatal period, but to the fetus as well. Significant neuroapoptosis and neurocognitive decline has been reported in the offspring of pregnant rats and rhesus monkeys exposed to anesthetic drugs for a prolonged period. Taken together, three factors appear to induce AIDN: 1. period of peak synaptogenesis, 2. high dose of the anesthetic and 3. long duration of exposure.

The extrapolation of these laboratory findings to clinical practice is vexing. No human phenotype of AIDN has been identified. Epidemiological studies suggest that multiple anesthetic exposures during childhood are associated with learning disabilities. However, neuraxial anesthesia for cesarean delivery had a lower incidence of subsequent learning disabilities compared with vaginal delivery. The incidence of learning disability was the same for the vaginal delivery with and without labor epidurals and caesarian sections under general anesthesia. The Anesthesia and Life-Support Advisory Committee of the Food and Drug Administration convened an open public hearings on the Neurotoxic Potential of Anesthetics on Neurodevelopment of Fetus March 27, 2007 and March 10, 2011. The first meeting concluded with the statement, “well-understood risks of anesthesia (respiratory and hemodynamic morbidity) continue to be the overwhelming considerations in designing an anesthetic, and the understood risks of delaying surgery are the primary reasons to determine the timing.”

Key Points:

1. Preclinical reports clearly demonstrate that anesthetic drugs induce neuroapoptosis during developmentally susceptible periods in a dose- and duration-dependent manner.
2. Epidemiological reports have not identified a clear manifestation of AIDN in humans and extensive clinical investigations are underway.
3. Anesthesiologists should be aware of the rapid developments in this arena and be able to effectively communicate the significance of these findings to their patients.

Key References: