In late April, FDA announced approval of revised labels for general anesthetic and sedation medications to include new information highlighting the risks of administering these agents to pregnant women and pediatric patients younger than 3 years of age. Specifically, the new warning will state that administration of these agents over an extended period of time—longer than 3 hours—or over multiple surgeries or procedures may affect brain development in young children. For a list of agents affected by this label change, see the sidebar.

Overview of the data
Both animal and human studies have shown that administration of general anesthetic and sedation medications may affect brain development. In animals, early exposure of anesthetic agents resulted in adverse neurotoxic effects in a variety of species. FDA noted that in juvenile animal studies, use of anesthetic and sedation drugs that block N-methyl-D-aspartate receptors and/or potentiate gamma-aminobutyric acid activity for longer than 3 hours have demonstrated an increase in neuronal apoptosis in the brain resulting in long-term cognitive deficits. In addition, in pregnant primates, prolonged exposure to ketamine, isoflurane, or propofol during late gestational periods increased neuronal cell loss in the fetus.

In humans, the data are controversial, with some observational studies suggesting an increased risk of adverse neurodevelopment outcomes and others not finding an increased risk. More recently, data from the GAS (General Anesthesia Compared to Spinal Anesthesia) and PANDA (Pediatric Anesthesia NeuroDevelopment Assessment) studies showed that short-term use of select anesthetic agents did not result in adverse neurodevelopment outcomes. In GAS, use of awake-regional anesthesia was compared with sevoflurane-based general anesthesia (median duration of 54 min) in children younger than 60 weeks of age who required inguinal hernia repair. Results from the interim analysis of this trial showed that use of sevoflurane-based general anesthesia for less than 1 hour did not appear to increase the risk of adverse neurodevelopment outcomes at 2 years of age compared with awake-regional anesthesia.

Similar findings were observed in the PANDA trial, a sibling-matched observational cohort study that assessed a single anesthesia exposure (median duration of 84 min) in healthy children younger than 3 years of age. The results of this trial showed that mean impaired global cognitive function scores were not significantly different between the exposed and unexposed siblings later on in childhood (i.e., at ages 8–15 y).

Counseling pearls
FDA noted that no specific anesthetic or sedation agent is safer than any other in effects on the brain. In addition, the window of vulnerability seems to correlate with exposures in the third trimester of pregnancy through the first year of life but may extend to the first 3 years of life.

Clinicians are encouraged to consider the risks and benefits of administering these agents to pregnant women and young children. They should inform pregnant women and parents and caregivers of young children of the potential adverse effects on brain development if anesthetic or sedation agents are given for an extended period of time or for multiple procedures. In addition, clinicians should consider delaying procedures that are not critical until after the woman has given birth or until the child is older.

FDA encourages all adverse events to be reported to its MedWatch program, as increased reporting will result in a better ability to capture the occurrence of these events.

References
2. www.fda.gov/Drugs/DrugSafety/ucm532356.htm
4. JAMA. 2016;315:2312–20

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