Fetal Anesthesia and Brain Development

PRECLINICAL studies in neonatal mice, rats, piglets, and primates have shown that exposure to a variety of clinically used general anesthetic and sedative drugs causes widespread age-dependent neurodegeneration that is associated with learning deficits. These findings have created enormous anxiety among anesthesiologists, parents, and other practitioners about the safety of general anesthesia for young children. Little is known about the long-term effects of general anesthesia on the fetus. In this issue of Anesthesiology, Palanisamy and colleagues show that exposure of fetal rats in utero to 4 h of isoflurane at gestational age 14 days (roughly equivalent to second trimester in humans) leads to impaired spatial memory acquisition and perhaps greater impulsivity in young adulthood.1

Epidemiologic studies have not provided a clear picture as to whether toxicity seen after anesthetizing young mammals is relevant to human development.2,3 Further studies are being designed and conducted using epidemiologic and case-control methodologies to determine whether a signal for harm can be detected in humans. Previous investigators have questioned whether the relatively long duration of anesthesia in animals studies are relevant to the human gestation; the same issues potentially apply to this study. In this study, the authors treated dams with isoflurane for 4 h. Four hours of isoflurane anesthesia accounts for a much larger portion of the gestation than a 4-h anesthetic administered to a human mother–fetus pair. Whereas frank neuronal apoptosis appears to take hours to develop in animal models, exposure of neonatal rodents to volatile anesthetics causes increases in dendritic spine density in as little as 30 min, that persist for up to 4 weeks.4 It is not known whether these increases in spine density are translated into temporary or permanent behavioral deficits, but there is need for further study.

Rats have relatively brief focused brain development, and it is hard to superimpose changes induced by a single anesthetic onto the long, more gradual development of the human brain. However, a previous study in guinea pigs,5 an animal with more gradual brain development, has shown that a 4-h exposure to isoflurane at the period of peak synaptogenesis induces neuroapoptosis. Behavior was not evaluated in that study, and histopathology was not done in the current study. Studies that incorporate parallel measures of histopathology and behavior are particularly informative in this respect.

These findings should concern but not alarm the obstetrical anesthesia community. The current study1 and the previous study in guinea pigs5 both used isoflurane as a test agent. However, this presumably is a class effect related to potentiation of γ-aminobutyric acid receptor activity, because all volatile anesthetics, propofol, and midazolam have been shown to be neurotoxic in studies on infant mammals. However, it is not clear which anesthetic technique might be least toxic, nor has any general anesthetic agent been convincingly shown to be more toxic. Elective surgery is not conducted during pregnancy. Most women who undergo general anesthesia during pregnancy do so to address a medical issue critical to their well-being or that of their fetus. Regional anesthesia has always been preferred during pregnancy predominantly because of concerns about the maternal airway and with the very theoretical consideration of exposing the fetus to fewer medications. Of course, it is not feasible to conduct some types of necessary surgery under regional anesthesia.

Concern about anesthesia exposure at delivery is at least reduced by recent epidemiologic studies of mothers exposed to regional and general anesthesia during vaginal and cesarean delivery whose children did not show an increased incidence of learning disabilities compared with those unexposed.2,6,7 However, the risk in nonhuman mammals is timing and exposure dependent. The possibility remains that longer exposures at different gestational ages might be more, or less, toxic. This question will be tricky to answer with epidemiologic studies, because it would not be surprising if fetuses that require surgery are at higher risk for learning disabilities than the general population or if severe maternal illness that requires surgery is a risk factor in development. Surgery itself causes inflammation that can induce changes in the central nervous system. These questions can not be ethically addressed with a randomized controlled trial. As we await clarity, certainly nonurgent surgery should continue to be postponed until after pregnancy. These concerns should be added to the other risks and benefits in determining anesthetic technique used in a pregnant woman. Consideration should be made to using regional anesthesia when possible.

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