General Anesthesia During the Third Trimester
Any Link to Neurocognitive Outcomes?

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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.\(^1\text{-}^4\) 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.\(^5\text{-}^6\) Therefore, these preclinical studies have caused a lot of concern...
among clinical anesthesiologists.7 The aim of this review is to elaborate on current pre-clinical 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
critically important. Abnormal or unphysiologic stimulation or inhibition of these neurotransmitter systems during this period of early brain circuitry formation, as would occur in the setting of maternal general anesthesia, can have long-standing functional consequences. Fetal exposure to anesthetic agents, which act by modulating GABA and NMDA-subtype of glutamate receptors, therefore, has the potential to disrupt these processes, alter developmental trajectories, and induce circuit malfunction.

PRECLINICAL EVIDENCE FOR GENERAL ANESTHETIC NEUROTOXICITY

Most of our understanding of the developmental neurotoxicity of anesthetic agents derives from preclinical studies in rodents and nonhuman primates. This review focuses specifically on evidence generated from pregnant animal models and applies that knowledge to the framework of clinical obstetric anesthesia to determine the possible implications, if any. All studies are summarized in Table 1 for easy reference.

Rodent Studies

Historically, the phenomenon of developmental neurotoxicity of anesthetic agents was first reported in neonatal rodents. Ontogenically, the stage of brain development in neonatal rodents (postnatal days 0–7) can be considered equivalent to the human third trimester, and, therefore, the results could be directly applicable to humans. However, this extrapolation ignores the hormonal milieu of pregnancy. Estradiol, progesterone, and oxytocin have all been shown to influence early brain development during pregnancy, and particularly during labor and delivery. Considering that this hormonal environment is absent in neonates, it is essential to evaluate only studies in pregnant rodents to draw meaningful conclusions.

Inhalational agents

In one of the earliest studies of its kind, Li and colleagues administered 1.3% isoflurane for 6 hours to rats at embryonic day 21 (E21), a time point that reflects late third trimester. Contrary to findings in neonatal rodents, this well-designed study actually showed a reduction in physiologic apoptosis in the hippocampal CA1 region, without any impairment of either juvenile or adult spatial reference memory and learning in the Morris water maze. Interestingly, when the investigators repeated the experiment with a higher concentration of isoflurane (3% in 100% oxygen for 1 hour), there was evidence of increased apoptosis in the CA1 region of the hippocampus and the retrosplenial cortex, accompanied by an increase in plasma levels of S100beta, an astrocytic protein that is released during early brain injury. Neither control treatment (100% oxygen) nor 1.3% isoflurane for 1 hour were associated with neuroapoptosis. Learning and memory, however, were not evaluated in this study. Consistent with previous findings in rats, a similarly designed study in pregnant guinea pigs failed to show increased neuroapoptosis after administration of an anesthetic “cocktail” of 0.55% isoflurane + 75% N2O + midazolam 1 mg/kg during the third trimester (gestational day >50, total duration of gestation 59–72 days), although the fetal brains in earlier stages of pregnancy showed remarkable vulnerability to anesthetic-induced damage. When these rodent studies are extended to the late or mid second trimester, there is considerable evidence for the detrimental effects of anesthetic exposure. A single exposure to 1.4% isoflurane (1 minimal anesthetic concentration) for 4 hours during the second trimester (E14) caused long-lasting impairment of spatial working memory and reduced anxiety in the rat offspring. Mechanisms were not explored in this study, but subsequent work has established that mid gestational exposure to inhalational agents such as isoflurane or sevoflurane upregulates the proapoptotic protein caspase-12, downregulates neuroplasticity-associated protein GAP-43,
decreases overall synapse numbers in the fetal hippocampus, induces fetal brain inflammation, and increases caspase-3 activation. Thus, collectively, it seems that the fetal brain is more vulnerable to the adverse effects of inhalational anesthetic agents during the second rather than the third trimester. This counteracts the prevailing dogma that the best time to perform urgent nonobstetric surgery in pregnancy is during the second trimester, when organogenesis is complete and the risk of preterm labor is low. However, this dogma has never been validated scientifically, and with current evidence that anesthetic agents could be detrimental to early neurodevelopment, it is essential to revisit and challenge this precept.

Intravenous agents
Neurotoxicity data for intravenous anesthetic use during third trimester are not as robust as those for inhalational agents. Intravenous administration of a sedative dose of ketamine for 2 hours in mid pregnancy (E14) caused neuronal loss in the fetal brain, decreased cell proliferation in the hippocampus, induced depression and anxietylike behaviors, and impaired memory during adolescence. These findings were partly related to an imbalance in the expression of NMDA-subtype of glutamate receptors in the hippocampus. Furthermore, even a clinically relevant dose of 2 mg/kg ketamine administered to pregnant rats at E17 (early third trimester) decreased cell proliferation in the subventricular zone of the fetal rat cortex, suggesting that neurogenesis could be impaired. Administration of a 2-hour intravenous infusion of propofol (0.4 mg/kg/min) to rats at E18 (third trimester) induced cleaved caspase-3 activation in the fetal brain at 6 hours, and decreased subsequent hippocampal neuronal density at postnatal days 10 and 28. In addition, propofol-exposed offspring demonstrated less exploratory activity in the open field test and impaired spatial working memory in the radial arm maze task. In a separate experiment, the same group also showed that fetal exposure to 2 hours of propofol during the third trimester was associated with poor development of neurologic reflexes in the neonatal period. Collectively, it seems that ketamine and propofol, unlike inhalational agents, consistently cause adverse neurodevelopmental effects when administered during the third trimester. The reasons for this discrepancy, thus far, remain unknown.

Nonhuman Primate Studies
Inhalational and intravenous agents
Ketamine is among the most extensively studied anesthetic agents in nonhuman primate studies. The first study to specifically address the question of fetal neurotoxicity of anesthetic agents was by Slikker and colleagues. Here, the investigators administered a 24 hours infusion of ketamine to pregnant macaques during late second trimester (gestational day 122, duration of gestation approximately 165 days) and reported that such exposure was associated with a significant increase in apoptotic neuronal death in the fetal brain compared with control treatment. Although a 24-hour duration of anesthesia is uncommon, if not unlikely, in routine anesthetic practice, these findings have also been reported after a 5 hours anesthetic exposure in utero. Most of the work in this regard comes from Brambrink and colleagues. In a series of experiments in pregnant macaques, Brambrink’s work has revealed unique patterns of fetal brain neurodegeneration for commonly administered anesthetic agents. In an experimental paradigm similar to that of Brambrink and colleagues, investigators administered a 10 mg/kg bolus of ketamine followed by an infusion to 10 to 85 mg/kg/h to maintain moderate anesthetic depth for 5 hours in pregnant macaques at gestational day 120 (comparable with the human third trimester). The control group received intravenous saline. The animals were monitored extensively; physiologic monitoring...
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<tr>
<td>Brambrink et al,40</td>
<td>Ketamine</td>
<td>5 h IV INF</td>
<td>Macaque</td>
<td>E120</td>
<td>Late second</td>
<td>AC3</td>
<td>Multiple brain regions including forebrain, midbrain, cerebellum, and brain stem</td>
<td>None</td>
<td>5-fold increase in apoptosis</td>
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<tr>
<td>Chien et al,45</td>
<td>GA for CD</td>
<td>NA</td>
<td>Human</td>
<td>E20–42 wk</td>
<td>Second and third</td>
<td>NA</td>
<td>NA</td>
<td>Autism</td>
<td>Neonates delivered via CD with GA had 52% higher risk of autism compared with vaginal delivery. No significant risk if CD with regional.</td>
</tr>
<tr>
<td>Creagh et al,46</td>
<td>GA in utero or first 2 y of life</td>
<td>NA</td>
<td>Human</td>
<td>E0 - 2 y</td>
<td>All</td>
<td>NA</td>
<td>NA</td>
<td>Autism</td>
<td>No evidence for association</td>
</tr>
<tr>
<td>Creeley et al,42</td>
<td>Propofol</td>
<td>5 h IV INF</td>
<td>Macaque</td>
<td>E120</td>
<td>Late second</td>
<td>AC3, silver, fractin, MBP, GFAP, Iba1, PDGFRα, NeuN, DAPI</td>
<td>Multiple brain regions including forebrain, midbrain, cerebellum, and brain stem</td>
<td>None</td>
<td>2.5-fold increase in both apoptotic neurons and oligodendrocytes in the fetal brain.</td>
</tr>
<tr>
<td>Creeley et al,41</td>
<td>Isoflurane</td>
<td>5 h</td>
<td>Macaque</td>
<td>E120</td>
<td>Late second</td>
<td>AC3, silver, fractin, MBP, GFAP, Iba1, PDGFRα, CC-1, NeuN, DAPI</td>
<td>Multiple brain regions including forebrain, midbrain, cerebellum, and brain stem</td>
<td>None</td>
<td>4-fold increase in neuronal cell death. Oligoapoptosis more severe than neuronal apoptosis.</td>
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<tr>
<td>Dong et al,36,2016</td>
<td>Ketamine</td>
<td>Single IP dose</td>
<td>Rat</td>
<td>E17</td>
<td>Third</td>
<td>BrdU and DAPI</td>
<td>Cortex (ventricular zone and subventricular zone)</td>
<td>None</td>
<td>Doses of ketamine 20 mg/kg or greater demonstrated an inhibition of neural cell proliferation in a dose-dependent manner</td>
</tr>
<tr>
<td>Kong et al,32,2012</td>
<td>1.3% isoflurane</td>
<td>4 h</td>
<td>Rat</td>
<td>E14 - term</td>
<td>Second to third trimester</td>
<td>CHOP, C12a, synapse structure change</td>
<td>Hippocampus</td>
<td>Postnatal spatial memory and learning impairments</td>
<td>Neuronal apoptosis, change in synapse structure.</td>
</tr>
<tr>
<td>Kong et al,31,2011</td>
<td>1.3% or 3% isoflurane in 30% O₂</td>
<td>1 h</td>
<td>Rat</td>
<td>E14</td>
<td>Second</td>
<td>AC3</td>
<td>Hippocampus - C1 region</td>
<td>Postnatal spatial memory and learning impairments in 3% group</td>
<td>3% isoflurane had more neurodegeneration compared with controls and 1.3% isoflurane</td>
</tr>
<tr>
<td>Koo et al,43,2014</td>
<td>Dexmedetomidine, ketamine</td>
<td>12 h INF</td>
<td>Cynomolgus</td>
<td>E120</td>
<td>Late second</td>
<td>AC3, TUNEL, silver, HE</td>
<td>Frontal cortex, midbrain, cerebellum, medulla and brainstem</td>
<td>None</td>
<td>Dexmedetomidine at low and high doses did not induce apoptosis. Ketamine caused apoptosis and degeneration</td>
</tr>
<tr>
<td>Li et al,38,2014</td>
<td>Propofol, intralipid</td>
<td>1 vs 2 h vs intralipid 2 vs saline 2 h</td>
<td>Rat</td>
<td>E18</td>
<td>Third</td>
<td>None</td>
<td>None</td>
<td>Slower eye maturation, slower and delayed reflexes</td>
<td>Brain and body weights in 2H propofol group on P10 were lower (no different at P0 or P28).</td>
</tr>
<tr>
<td>Li et al,31,2007</td>
<td>1.3% isoflurane</td>
<td>6 h</td>
<td>Rat</td>
<td>E21</td>
<td>Third</td>
<td>AC3, TUNEL</td>
<td>Hippocampus, cortex</td>
<td>No memory/learning impairment</td>
<td>Apoptosis decreased at 2 h, but not at 18 h, or postnatal day 5</td>
</tr>
<tr>
<td>Palanisamy et al,30,2011</td>
<td>1.4% isoflurane</td>
<td>4 h</td>
<td>Rat</td>
<td>E14</td>
<td>Second</td>
<td>None</td>
<td>None</td>
<td>Impaired spatial memory acquisition and reduced anxiety</td>
<td>Deficits in spatial memory after in utero isoflurane exposure</td>
</tr>
<tr>
<td>Rizzi et al., 2008</td>
<td>Isoflurane + N20 + 4 h midazolam</td>
<td>Guinea pig</td>
<td>E50+</td>
<td>Third</td>
<td>AC3, C9, NeuN and Nissl</td>
<td>Retrosplenial, parietal, cingulate, occipital and piriform cortical regions; amygdala, subiculum, hippocampus and anterior thalamus</td>
<td>None</td>
<td>No significant increase in neuroapoptosis in fetus’ exposed to anesthesia in the third trimester, but fetal brains in earlier stages of pregnancy showed remarkable vulnerability to anesthetic-induced damage</td>
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<td>Slikker et al., 2007</td>
<td>Ketamine</td>
<td>24 h INF</td>
<td>Macaque</td>
<td>E122</td>
<td>Late second</td>
<td>AC3, Fluoro-Jade C, silver, TUNEL, in situ hybridization and autoradiographs, EM</td>
<td>Whole brain</td>
<td>None</td>
<td>Increase in apoptosis. EM findings indicate ketamine cell death is apoptotic and necrotic in nature</td>
</tr>
<tr>
<td>Sprung et al., 2009</td>
<td>GA during CD</td>
<td>—</td>
<td>Human</td>
<td>CD</td>
<td>Third</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>Risk similar in SVD and CD, but reduced in children getting RA + CD then SVD</td>
</tr>
<tr>
<td>Wang et al., 2009</td>
<td>1.3 or 3% isoflurane</td>
<td>1 h</td>
<td>Rat</td>
<td>E21</td>
<td>Third</td>
<td>AC3, S100 B in fetal blood</td>
<td>CA1 region of hippocampus and retrosplenial cortex</td>
<td>None</td>
<td>Neurodegeneration in hippocampal and retrosplenial cortex after 1 h of 3%, not 1.3%</td>
</tr>
<tr>
<td>Xiong et al., 2014</td>
<td>Propofol, intralipid</td>
<td>2 h</td>
<td>Rat</td>
<td>E18</td>
<td>Third</td>
<td>AC3, synaptophysin, Nissl, NeuN</td>
<td>Hippocampus CA1 and CA3 regions</td>
<td>Exploratory and learning behaviors reduced in propofol group</td>
<td>Increased levels of AC3, neuronal density reduced, synaptophysin levels reduced</td>
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<tr>
<td>Zhao et al,34</td>
<td>Ketamine</td>
<td>2 h</td>
<td>Rat</td>
<td>E14</td>
<td>Second</td>
<td>Nissl, BrdU, Golgi-Cox, BDNF, PSD-95, NR1, NR2A, NR2B</td>
<td>Dorsal hippocampus CA1 and CA3 regions</td>
<td>Depression and anxiety like behaviors and impaired memory</td>
<td>Fetal brain exposed to ketamine exhibited neuronal loss, pyramidal neuron abnormalities, and reduced cell proliferation in the hippocampus.</td>
</tr>
<tr>
<td>Zhao et al,35</td>
<td>Ketamine</td>
<td>2 h</td>
<td>Rat</td>
<td>E14</td>
<td>Second</td>
<td>PSD-95, synaptophysin, NR2A, NR2B, TUNEL, AC3, Nissl, Golgi-Cox</td>
<td>Prefrontal cortex</td>
<td>None</td>
<td>Fetal ketamine exposure caused neuroapoptosis, cell loss, and impaired neuronal development of the prefrontal cortex</td>
</tr>
<tr>
<td>Zheng et al,33</td>
<td>2.5% sevoflurane for 2 h or 4.1% sevoflurane for 6 h</td>
<td>2 or 6 h</td>
<td>Mice</td>
<td>E14</td>
<td>Second</td>
<td>Interleukin-6, PSD-95, synaptophysin, AC3, B-actin</td>
<td>Entire cerebral hemisphere</td>
<td>Impaired learning and memory</td>
<td>Induced apoptosis, increased IL-6 levels, and reduced postsynaptic density and synaptophysin levels</td>
</tr>
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**Abbreviations:** AC3, activated caspase-3, a marker for apoptosis; BDNF, brain-derived neurotrophic factor; BrdU, bromodeoxyuridine, marker for cells in the S-phase; C12a, caspase-12 antibody; C9, caspase-9, a marker for apoptosis; CC-1, marker for mature oligodendrocytes; CD, cesarean delivery; CHOP, C/EBP homologous transcription factor protein; DAPI, 4', 6-diamidino-2-phenylindole (detects abnormal changes in nuclear chromatin pattern indicative of apoptotic cell death); E, embryonic day; EM, electron microscopy; fractin, breakdown product by caspase mediated proteolysis of actin; GA, general anesthesia; GFAP, glial fibrillary acidic protein, a marker for astrocytes; Golgi-Cox, dendritic length and branch number; HE, hematoxylin and eosin staining; Iba1, ionized calcium-binding adaptor molecule 1, a marker for microglia and macrophages; INF, infusion; IP, intraperitoneal; IV, intravenous; MBP, myelin basic protein, identifies young premyelinating and myelinating differentiated oligodendrocytes; NA, not applicable; NeuN, neuronal nuclei antigen, marker for mature neurons; Nissl, neuronal cell body staining; NR1, NR2A, NR2B, N-methyl-D-aspartate (NMDA) receptor subunits; PDGFRα, platelet-derived growth factor receptor alpha, a marker for OL progenitors; PSD-95, postsynaptic density protein 95; silver, DeOlmos cupric silver method; RA, regional anesthesia; SVD, spontaneous vaginal delivery; TUNEL, terminal deoxynucleotidyl transferase dUTP nick end labeling.
and perianesthetic care was comparable with operating room standards. Neuronal death in the fetal brain was assessed 3 hours after cessation of treatment using activated caspase-3, a marker for apoptosis. Ketamine administration was associated with an approximately 5-fold increase in apoptosis in the fetal brain compared with control treatment. The most affected regions of the brain included the cerebellum, caudate nucleus, putamen and nucleus accumbens, a pattern of neurodegeneration that is unique in that the hippocampus, the focus of most rodent studies, was relatively spared.

These studies have since been extended to the more clinically relevant inhalational and intravenous anesthetics. Creeley and colleagues\(^4\) administered 1% to 1.5% isoflurane to maintain moderate surgical plane of anesthesia in late second trimester pregnant macaques (control group animals were handled similarly but did not receive any anesthetic). Similar to ketamine, in utero exposure to isoflurane caused a 4-fold increase in neuronal cell death in the fetal brain compared with control treatment. An interesting aspect of this study was that the investigators also quantified oligodendrocytic cell death after in utero isoflurane exposure, and confirmed that oligoapoptosis was more severe than neuronal apoptosis (59% vs 41% of all apoptotic profiles, respectively). Finally, in a similar study, pregnant rhesus macaques were exposed to 5 hours of either propofol anesthesia or control treatment ("no anesthesia").\(^4\) Animals that received propofol underwent a stable, well-monitored, clinically realistic, and uneventful anesthesia. Three hours later, there was an approximately 2.5-fold increase in both apoptotic neurons and oligodendrocytes in the fetal brains of propofol-treated macaques. Of note, the brain regions most affected by propofol were similar to those affected by isoflurane. Finally, promising recent data suggest that even a 12 hours infusion of high-dose dexmedetomidine in gestational day 120 (second trimester) cynomolgus monkeys had no effect on neuroapoptosis in the frontal cortical layers of the fetal brain.\(^4\) This is not surprising, considering that most adverse neurodevelopmental events have been attributed to modulation of either glutamate or GABA-ergic pathways and not adrenoceptor mechanisms.

With this robust line of evidence from nonhuman primate models, it is clear that the fetal brain is susceptible to maternally administered anesthetic agents in the third trimester, especially when administered for a prolonged period (≥5 h). However, it is not known if a shorter duration of anesthetic administration, which is most often the case in clinical practice, induces similar adverse neuropathologic effects. Furthermore, the 2.5- to 5-fold increase in neuronal apoptosis is modest when compared with rodent studies, but we do not know if such neurodegeneration induces any long-term learning and memory dysfunction. This critical question will only be addressed when shorter durations of anesthetic administration are investigated specifically, along with comprehensive assessment of learning and memory in nonhuman primates.

**Population Studies**

The relatively robust animal data, however, are not supported by a wealth of human studies. In the only well-designed population-based birth cohort study (Olmsted County, Minnesota),\(^4\) the authors asked the question if exposure to general or regional anesthesia during cesarean delivery increased the risk of learning disabilities in the offspring. Using educational and medical records of all children born between the years 1976 and 1982 in Olmsted County, Minnesota, the authors directly compared the rates of learning disability in offspring who underwent cesarean birth under either general (n = 193) or regional anesthesia (n = 304) and uncomplicated vaginal delivery. The rates of learning disability were no different between the general
anesthesia group for cesarean delivery and vaginal birth, but were significantly reduced for babies born after regional anesthesia for cesarean delivery. It is reassuring that even the children whose mothers required emergency general anesthesia (presumably secondary to presumed fetal compromise) did not have an higher incidence of learning disability. However, learning disability is only 1 component of altered brain function and it remains to be seen if other domains of human function are affected. Recent studies have explored the association between general anesthesia during the third trimester and autism spectrum disorders in the offspring, but the results are conflicting. Using a propensity score–matched technique to adjust for underlying risk factors, Chien and colleagues evaluated the link between general anesthesia during cesarean delivery and autism risk in a population-based data set derived from national registries in Taiwan. General anesthesia for cesarean delivery, but not regional anesthesia, was associated with a 52% higher risk for developing autism than vaginal delivery in this study. By contrast, a population-based sibling cohort study from Puerto Rico found no evidence for an association though this study included anesthesia exposures during both pregnancy and during the first 2 years of life. Future studies are required to determine the impact of anesthesia for nonobstetric surgeries and neonatal neurodevelopmental outcomes.

SUMMARY

The third trimester fetal brain seems vulnerable to both inhalational and intravenous anesthetics administered during the third trimester in rodents and nonhuman primates especially when administered for prolonged periods. Most intravenous anesthetic agents investigated, with the exception of dexmedetomidine, consistently produce adverse neurodevelopmental consequences, but the evidence is mixed for inhalational agents. Human studies are unequivocal; general anesthesia during emergent cesarean delivery is not associated with learning disability, but shows a possible association with an increased risk of autism diagnosis. The prevalence of numerous confounding variables, including factors that drive the need for general anesthesia, precludes making a robust determination.

REFERENCES