



Anesthetic neurotoxicity in the developing brain: an update on the insights and implications for fetal surgery

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This review describes an in-depth analysis of the neurotoxicity associated with the anesthetic agents used during fetal surgery, intending to highlight the importance of understanding the effects of general anesthetics on the developing brain, particularly in the context of open fetal surgery, where high doses are applied to facilitate surgical access and augment uterine relaxation. We examined evidence from preclinical studies in rodents and primates, along with studies in human subjects, with the results collectively suggesting that general anesthetics can disrupt brain development and lead to long-lasting neurological deficits. Our review underscores the clinical implications of these findings, indicating an association between extensive anesthetic exposure in early life and subsequent cognitive deficits. The current standard of anesthetic care for fetal surgical procedures was scrutinized, and recommendations have been proposed to mitigate the risk of anesthetic neurotoxicity. These recommendations emphasize the need for careful selection of anesthetic techniques to minimize fetal exposure to potentially harmful agents. In conclusion, while the benefits of fetal surgery in addressing immediate risks often outweigh the potential neurotoxic effects of anesthesia, the long-term developmental impacts nevertheless warrant consideration. Our analysis suggests that the use of general anesthetics in fetal surgery, especially at high doses, poses a significant risk of developmental neurotoxicity. As such, it is imperative to explore safer alternatives, such as employing different methods of uterine relaxation and minimizing the use of general anesthetics, to achieve the necessary surgical conditions. Further research, particularly in clinical settings, is essential to fully understand the risks and benefits of anesthetic techniques in fetal surgery.

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ANESTHETIC NEUROTOXICITY IN THE DEVELOPING BRAIN

One of the principal goals of anesthesia is to ensure the patient returns to the physiological state they were in before administering the anesthetic; thus, anesthetic drugs have been selected for use in practice based on the presumption that they do not cause lasting changes in any organ system. However, over the last two decades, anesthesia research has raised concerns that commonly used anesthetics may have lasting effects on the brain when administered to patients in vulnerable states. Data have suggested that anesthetic exposure that occurs in childhood, old age, and injured states can have lasting harmful consequences on brain function [1-5]. This finding may have serious implications for anesthetic management in fetal surgery, as current practice often involves high-dose and potentially lengthy exposure to general anesthesia.

The US Food and Drug Administration has cautioned that repeated or prolonged exposure to anesthetic and sedative medications in young children may potentially harm brain development [6,7]. This advisory was based on clinical and preclinical studies of cognitive outcomes following early postnatal anesthetic exposure. Investigations in rodents in the 1980s initially suggested that chronic environmental exposure to anesthetic agents might disrupt brain development [5]; however, the first clear demonstration of the harmful effects of anesthetics on brain development designed to model clinical exposure during surgery was sourced from a landmark study by Todorovic et al. [6] in 2003. In this study, the authors demonstrated that rat pups exposed to a mixture of isoflurane, nitrous oxide, and midazolam in the early postnatal period exhibited reduced performance in behavioral tests of learning and memory several months later. Since then, numerous studies have assessed the toxic effects of early developmental anesthesia. Several large retrospective epidemiologic studies have reported correlations between worsened cognitive outcomes in patients exposed to general anesthetic agents (GAs) at a young age compared to those in controls. Numerous rodent model investigations conducted by independent laboratories have incontrovertibly demonstrated that GAs can disrupt many aspects of brain development in lower animals, including investigations in nonhuman primates that have demonstrated cognitive and behavioral deficits resulting from early developmental GA exposure [3,8-17]. However, there have been only two extant clinical trials designed to assess whether short

anesthesia exposures in healthy children, which constitute the majority of pediatric anesthetics, were safe [16,18,19]. Both trials have provided reassurance that brief anesthetic exposures at normal doses do not exert adverse effects on intelligence, the primary outcome that was assessed [16,18,19]; however, both studies did find any evidence of behavioral abnormalities as secondary outcomes, which will require further investigation [8,20,21]. Thus, there is no clear understanding of which doses of GA exposure in children may cause neurodevelopmental effects, and the phenotype of human anesthetic neurotoxicity remains incompletely understood; however, the preponderance of evidence provides no basis to dismiss the concerns that GAs are neurotoxic in early development.

Although numerous studies investigating the effects of postnatal anesthesia exposure have been published, the effects of intrauterine anesthesia exposure have not been investigated in depth. One of the only two extant epidemiologic studies indicated that brief fetal exposure to anesthetics does not increase the risk of learning disabilities [22], which is unsurprising, as single, brief exposures in a healthy organism seem to be benign in all contexts. However, another report derived from an observational cohort study of 2,024 children who underwent full neuropsychological testing reported that maternal exposure to general anesthesia increased the externalizing behavior score in the child behavioral checklist assay [23]. Surgery and comorbid diseases were confounders in this study, and there were no significant findings in other elements of the neuropsychological testing; however, this finding raises a concern that is analogous to those that are associated with postnatal anesthetic exposure.

Relatively few studies have modeled fetal exposure to general anesthetic agents in animals, but the existing literature is not reassuring, particularly for rodent models. In an early study conducted by Kong et al. [24], rat fetuses exposed to isoflurane in utero showed worse performance on a commonly used behavioral learning test. These animals have been found to undergo frontal cortical neuronal apoptosis and notable disruption of synaptic ultrastructure [24]. These deficits were observed one month after birth and indicate clear evidence of the potential for fetal exposure to isoflurane to impair subsequent brain function. The exposure occurred at 14 gestational days, which represents the late mid-gestation in rodents; however, given the differences in the timing of brain development, it is not entirely clear how well these findings would translate to humans. Another

study in rodents demonstrated that gestational exposure to sevoflurane resulted in abnormal social interaction behavior, thus demonstrating that deficits in rodents may not be limited to the cognitive domain [25,26]. A study of esketamine, a long-lasting derivative of the general anesthetic agent ketamine, conducted in mid-gestational rodents, showed disrupted neuronal and neural stem cell development, attenuated long-term potentiation, and worsened performance in behavioral tests of cognitive function [27]. Given that esketamine and N-methyl-D-aspartate (NMDA) receptor antagonists act via a mechanism distinct from that of isoflurane and sevoflurane, which are Gamma-Aminobutyric Acid (GABA) receptor agonists, this raises the possibility that different anesthetics might be neurotoxic when administered during gestation. The mechanisms underlying the observed deficits in cognitive function in rodents caused by gestational exposure to general anesthetics are likely multifactorial. One study suggested an inflammatory mechanism of injury mediated by the activation of microglia and the Nucleotide-binding Oligomerization Domain (NOD), Leucine-Rich Repeat (LRR), and pyrin domain-containing protein 3 inflammasome as key contributors to sevoflurane general anesthesia-induced gestational brain injury [28]. Another study using a similar model provided evidence of disruptions in neural stem cell differentiation attributed to changes in activity in the Sonic Hedgehog glioma-associated oncogene homolog 1 signaling pathway [29], a result that was corroborated by a similar investigation showing the actions of sevoflurane on radial glia that are critical for neural stem cell development [30]. While it appears to be clear that intrauterine exposure to general anesthetics has long-lasting effects on brain development and subsequent function, further studies are needed to elucidate the underlying mechanisms. Moreover, it is not necessarily clear which effects might be translatable to human patients.

The concept of gestational anesthetic exposure toxicity has been explored in large animal models, but to a much lesser extent than that in rodent models. Sheep exposed to isoflurane at a mid-gestational time point exhibited decreased neuronal density when examined near the end of gestation [31]. This finding is interesting, as it shows that this phenomenon is not unique to rodents; however, it is difficult to reach any conclusion beyond the obvious inference that isoflurane can be toxic to developing neurons in many contexts. Not all exposures in the large animal model cause detectable injury—a different study using sevoflurane exposure in the sheep fetus model did not find any significant differ-

ences in histological or neurobehavioral outcomes [32], which does not disprove the findings of the earlier study noted but merely shows that different exposures and assays may produce different results. Large animal studies would be conducted in a nonhuman primate model, focusing on chronic outcomes at adolescent time points or beyond, and would incorporate cognitive assessment to demonstrate functional significance. However, this type of study has not yet been conducted and may not be in the future due to the substantial resources required. Nevertheless, existing animal data raises serious concerns that intrauterine anesthetic exposure may harm the developing brain. Furthermore, studies that have been conducted on intrauterine exposure to anesthetics have been designed to model non-obstetric surgery in pregnant patients rather than exposures associated with fetal surgery, which may be far more substantial in terms of dose and thus have the potential for substantially greater harm.

A review paper on anesthesia for fetal surgery examined the evidence suggesting that general anesthesia during fetal surgery could constitute toxic exposure with potential negative neurocognitive effects. Here, we reviewed the standard of care for common fetal surgical procedures and discussed strategies to minimize the risk of anesthetic neurotoxicity. This topic is crucial because of the existing concerns regarding the impact of anesthesia on brain development, particularly in vulnerable states such as fetal surgery, where high doses and lengthy exposure to general anesthesia are common.

Fig. 1 provides a visual representation of the current knowledge regarding anesthetic neurotoxicity in the developing brain. To provide a structured overview of the diverse literature informing this review, we have compiled “Table 1: Fetal Surgery and Anesthetic Neurotoxicity: A Curated Reference Table,” which categorizes the key references to elucidate the multifaceted aspects of fetal surgery and the implications of anesthetic neurotoxicity.

FETAL SURGERY: HISTORY, DEVELOPMENT, AND CURRENT USES

The first human fetal surgery was performed to treat erythroblastosis fetalis with fetal blood transfusion by William Liley [33] in 1963 (Auckland, New Zealand). More invasive fetal procedures have since been developed based on the results of extensive animal studies conducted in the 1980s. These procedures involved midline laparotomy and open hysterotomy, usually performed under general anes-

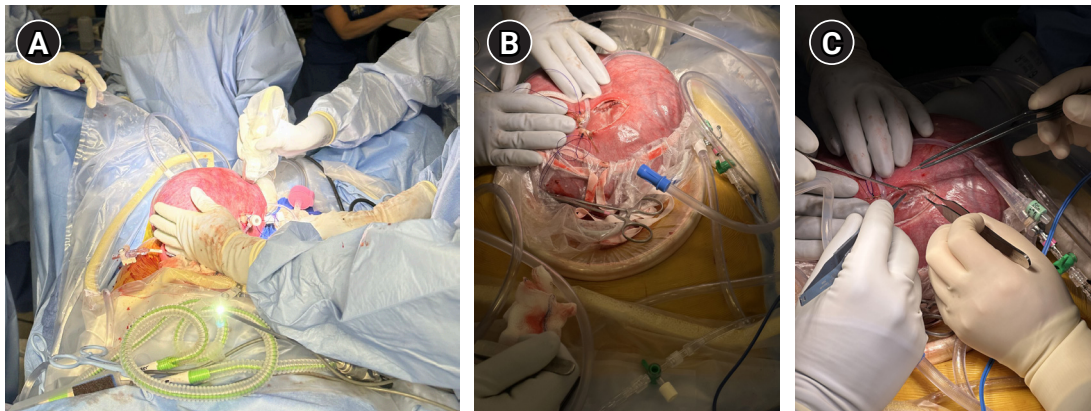
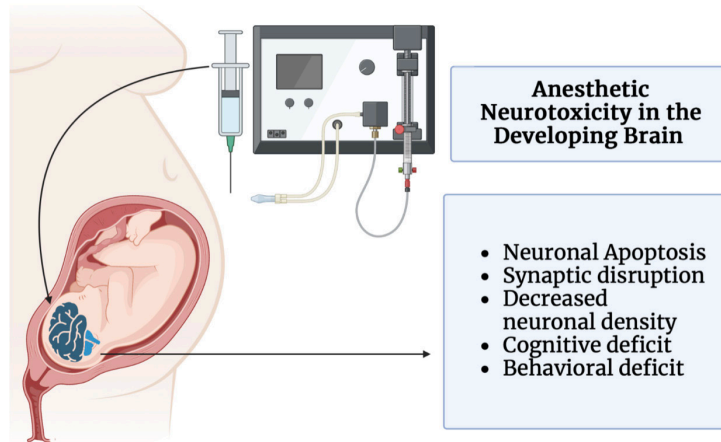


Fig. 1. A visual illustration of the impact of anesthetic neurotoxicity on the developing brain, highlighting its diverse effects on brain structure and function. (A) Fetoscopic myelomeningocele repair. A photograph illustrating the fetoscopic approach to myelomeningocele repair. The key features include exteriorization of the uterus and the presence of two ports in the right posterior segment. Throughout the procedure, fetal monitoring is conducted using ultrasound to ensure precision and safety. (B) Outcome of open myelomeningocele repair. Image showing the completion of the Open Myelomeningocele Repair procedure. Notable aspects include an exteriorized uterus with an open incision and the strategic placement of an amnioinfusion catheter around the dorsal region of the fetus connected to a rapid infuser. This configuration is critical for a successful repair. (C) Open fetal surgery by pediatric neurosurgeons and fetal surgeons. Image capturing a pivotal moment in open fetal surgery for myelomeningocele defect closure. The procedure involves an incision in the uterus, the placement of an irrigation catheter around the back of the fetus, and continuous fetal heart rate monitoring using ultrasound. Administration of a drug cocktail comprising atropine, rocuronium, and fentanyl via fetal intramuscular injection is a critical component of this surgery as it facilitates operative efficacy and fetal safety.

thetia, to conduct surgery on the fetus [33].

In more recent years, the techniques and planning of fetal surgery have vastly improved with the advent of real-time ultrasonography. The use of ultrasonography in obstetrics and prenatal care has revolutionized the ability of physicians to diagnose fetal abnormalities and to perform minimally invasive techniques to treat many of these abnormalities. These conditions initially included hydrocephalus, fatal neoplasms, and congenital diaphragmatic hernia and have now expanded to include lower urinary tract obstruction, twin-twin transfusion syndrome, thoracoamniotic shunting, myelomeningocele, and congenital high airway obstruction

[33]. The scope of fetal therapy procedures has been examined in relation to maternal, fetal, and neonatal risk levels and graded into three levels of care complexity, defining the care levels for fetal therapy centers [34].

CLOSED OR MINIMALLY INVASIVE FETAL SURGICAL THERAPIES: ANESTHETIC PLAN AND CURRENT IMPLICATIONS

Percutaneous procedures are the most frequent fetal interventions and can be performed at any gestational age. However, they are most commonly performed in the late second

Table 1. Fetal Surgery and Anesthetic Neurotoxicity: A Curated Reference Table

Category	Author (yr)	Key field of investigation
Preclinical Studies on Anesthetic Neurotoxicity	Levin et al. [5], 1991	Neurobehavioral toxicology of halothane in rats
	Todorovic et al. [6], 2003	Impact of anesthetic exposure on rat brain development
	Kong et al. [24], 2012	Fetal exposure to high isoflurane concentration induces deficits in rats
Clinical Studies on Anesthetic Neurotoxicity	Yu and Liu [1], 2013	Developmental anesthetic neurotoxicity: from animals to humans?
	De Tina and Palanisamy [2], 2017	General Anesthesia During the Third Trimester: Any Link to Neurocognitive Outcomes?
	Andropoulos [3], 2017	Effect of Anesthesia on the Developing Brain: Infant and Fetus
Fetal Surgery Techniques and Procedures	Kitagawa and Pringle [33], 2017	Fetal surgery: a critical review
	Baschat et al. [34], 2022	Care Levels for Fetal Therapy Centers
Anesthetic Management in Fetal Surgery	Hoagland and Chatterjee [35], 2017	Anesthesia for fetal surgery
	Massa et al. [36], 2012	Effects of Morphine on the Differentiation and Survival of Developing Pyramidal Neurons During the Brain Growth Spurt
Outcomes and Implications of Fetal Surgery	Massa et al. [36], 2012	Effects of Morphine on Developing Neurons
	Bajic et al. [37], 2013	Morphine-enhanced apoptosis in neonatal rats
Recommendations and Guidelines	Zakowski and Geller [42], 2014	The Placenta: Anatomy, Physiology, and Transfer of Drugs
	Hoagland et al. [43], 2022	Avoiding the Use of Halogenated Anesthetic Agents for Uterine Relaxation
Case Studies and Reports	Sprung et al. [22], 2009	Anesthesia for Cesarean Delivery and Learning Disabilities
	Ing et al. [23], 2021	Prenatal Exposure to General Anesthesia and Childhood Behavioral Deficit
Historical Perspectives and Developments	Kitagawa and Pringle [33], 2017	Fetal surgery: history, development, and current uses

or early third trimester. In these cases, small trocar sheaths and percutaneous needles were used to access the uterine cavity [35]. Ultrasound, or a fetoscope inserted through a trocar, is used for intraoperative imaging of the fetus.

The anesthetic plan for minimally invasive fetal surgeries is extremely variable, ranging from local anesthesia or mild sedation to neuraxial or general endotracheal anesthesia. Laser ablation of vessels for twin-to-twin transfusion syndrome, for example, can generally be performed with local anesthesia and minimal maternal IV sedation only. Sedation regimens may include the use of propofol, opioids, and/or benzodiazepines to treat maternal pain and anxiety and decrease the fetal stress response and fetal movement [35]. However, fetal cardiac procedures require the insertion of needles into the fetal heart and/or great vessels and require complete paralysis and general anesthesia of both the mother and fetus. In cases where fetal anesthesia is required in addition to maternal anesthesia, it may be administered directly via fetal intramuscular injection or injection into the umbilical vein, or it may be passively transferred to the fetus from the placenta after maternal administration of IV anesthetic agents [33].

Data from both animal and human studies of developmental anesthetic neurotoxicity suggest a dose-dependent

phenomenon that occurs in the upper ranges of clinically used anesthetic concentrations and durations of exposure. In minimally invasive cases where general anesthesia is used, relatively low doses of volatile anesthetics are often sufficient, as uterine relaxation is not a requirement for these procedures, and pregnant patients have a lower anesthetic requirement than that in non-pregnant patients of the same age and weight. The risks associated with the direct delivery of anesthetics to the fetus are more difficult to assess, and no definitive evidence exists to date regarding the specific benefits or risks of this approach. Agents used to achieve direct fetal anesthesia include opiates and non-depolarizing muscle relaxants, none of which have been shown to exert any lasting negative neurocognitive effects on the developing fetus. Massa et al. [36] reported a lack of discrete neurotoxic effects when morphine was administered to rats during a brain growth spurt. In addition, Bajic et al. [37] observed increased supraspinal apoptosis in the sensory cortex and amygdala of neonatal rats following repeated morphine administration; however, they did not identify any effects of this regimen on learning or other areas of the brain. Although these data are reassuring, further studies are needed to directly assess the potential toxicities associated with direct fetal anesthesia. Fig. 1A describes an intricate depiction

of fetoscopic myelomeningocele repair, showcasing the advanced surgical technique employed in utero to correct this form of spinal defect, highlighting both the complexity and precision of the procedure.

OPEN FETAL SURGICAL THERAPIES: ANESTHETIC PLAN AND CURRENT IMPLICATIONS

Open fetal procedures are commonly employed at the end of the second trimester or the beginning of the third trimester to correct myelomeningoceles, bladder outlet obstruction, sacrococcygeal teratomas, and resection of lung or upper airway lesions, which can cause mass effects [33]. In these cases, a maternal laparotomy is performed, followed by imaging of the placental edges using intraoperative ultrasound [33]. A hysterotomy is then performed at a location that avoids interference with the placenta. Upon completion of the fetal surgical procedure, the externalized portion of the fetus is returned to the uterus, and the hysterotomy is closed with sutures.

These procedures require the induction of maternal general anesthesia and the placement of a lumbar epidural catheter for postoperative analgesia. Complete uterine relaxation is necessary to allow fetal manipulation and prevent the initiation of preterm labor. This is typically achieved using an anesthetic technique employing three to four times the concentration of the volatile anesthetic required to induce maternal anesthesia [38]. Alternatively, some providers choose to employ a combination technique involving volatile anesthetics at a concentration approximately double that required for maternal anesthesia, along with an intravenous anesthetic infusion and a high dose of short-acting opiate [39,40]. In either case, if adequate uterine relaxation is not achieved using these techniques, nitroglycerin boluses or infusions may be added. Direct fetal anesthesia can further be achieved with an intramuscular injection of opiate along with a paralytic agent as an adjunct [35]. Anesthetic concentrations are typically reduced during closure if uterine relaxation is not required.

Under these conditions, substantial fetal exposure to high doses of general anesthetic agents, which far exceed those that have been studied in the pediatric anesthetic literature, is unavoidable. These anesthetic doses greatly exceed those used in primate studies of anesthetic neurotoxicity and, in many cases, are higher than the high-dose ranges used in rodent studies. Thus, as is currently practiced, anesthetic

management for open fetal surgery may carry a significant risk of developmental anesthetic neurotoxicity. Fig. 1B shows the outcome of open myelomeningocele repair, showing the post-procedure surgical site. Fig. 1C shows a collaborative effort between pediatric neurosurgeons and fetal surgeons performing open fetal surgery, a testament to the intricate and advanced surgical techniques currently used in prenatal care.

EX-UTERO INTRAPARTUM TREATMENT PROCEDURES: ANESTHETIC PLAN AND CURRENT IMPLICATIONS

Ex-utero intrapartum treatment (EXIT) procedures are modified cesarean sections that are usually performed in cases of potential airway compromise, such as fetuses with congenital high airway obstruction, anomalies or masses of the neck, mediastinum, or lung that may cause tracheal or mediastinal compression, and congenital diaphragmatic hernia with the placement of a tracheal clip or balloon [33,35,41]. These procedures are similar to open procedures in that they involve a maternal laparotomy followed by a carefully planned hysterotomy; however, they differ in that they occur immediately before delivery. In EXIT, the baby is partially or completely delivered while maintaining placental perfusion. The duration of the procedure ranges greatly, from as short as a few minutes in the case of fetal intubation to several hours for more complex airway procedures or mass resections. Upon completing fetal surgery, delivery occurs, thereby concluding the anesthetic exposure of the fetus.

Two anesthetic plans are possible for the EXIT procedure. The first is a high-dose maternal general anesthetic identical to that described above for open fetal surgery. The second option, which is increasingly popular largely due to concerns related to anesthetic neurotoxicity, is a neuraxial technique to provide maternal anesthesia supplemented with a nitroglycerin infusion to facilitate uterine relaxation. Typically, in this procedure, the fetus receives intramuscular or umbilical vein opioids and muscle relaxants. Currently, no evidence exists of adverse cognitive outcomes in the fetus stemming from maternal neuraxial anesthesia or the direct fetal administration of opioids and muscle relaxants; thus, this approach is widely preferred due to concerns regarding developmental anesthetic neurotoxicity.

CONCLUSION

Most reviews addressing the potentially toxic effects of anesthetics during development have concluded that there is no evidence to support any change in practice. Certainly, there is no direct evidence from any clinical study proving that anesthetic exposure during fetal surgery has adverse consequences for brain development or subsequent cognitive function. However, it is unlikely that a study testing this hypothesis clearly and unambiguously could be conducted owing to both practical and ethical limitations. Thus, the available guidelines must be based on the interpretation of studies conducted on animal models. The results of existing studies in both rodents and large animals suggest that general anesthetic agents have the potential to injure the developing brain and impair cognitive function. However, these studies have clear limitations, particularly when considering the differences in placental function between species and the potential impact of both maternal and fetal medical comorbidities, neither of which can be easily modeled in animals. Thus, clinical studies, including observational studies, in human patients are essential for understanding the risks and benefits of different approaches.

Therefore, with a wide variety of anesthetic techniques available to fetal therapists, ranging from local anesthesia to deep general anesthesia, the technique chosen for each procedure should be carefully considered to minimize fetal exposure to general anesthetics. Most fetal therapies are instituted for conditions with immediate fetal or postdelivery risks, and the benefits to the fetus of performing the procedure outweigh the potential adverse effects of both the procedure and the administration of anesthetic agents in the majority of cases. Accordingly, long-term developmental impacts in the context of fetal treatment are frequently not considered in pre-procedure counseling and assessment, as these conditions have such high immediate morbidity and mortality. Nevertheless, the risks associated with different anesthetic techniques should be considered when assessing potential anesthetic management strategies for these procedures.

Similar conclusions regarding the potential for neurotoxicity have been drawn from animal models examining early postnatal anesthesia exposure; however, a key distinction in the context of fetal surgery is the common practice of employing very high doses of volatile anesthetics. These doses are not primarily intended to achieve the desired sedative/hypnotic effect but rather to facilitate uterine relaxation.

Many anesthetic agents readily cross the placenta, resulting in passive administration to the fetus, with the dose of the drug administered being directly proportional to the placental blood flow [42]. Common drugs with a high rate of placental transfer include atropine, nitroglycerin, local anesthetics, opioids, benzodiazepines, sedative-hypnotic intravenous agents, and inhalation agents [42]. Given that general anesthetics carry the potential to harm the developing brain, we propose that it may be safer to employ other means to achieve the necessary degree of uterine relaxation. Several such viable alternatives exist to achieve rapid and profound uterine relaxation, including nitroglycerin, terbutaline, atosiban, and magnesium. Atosiban is highly effective but is not available in the US. The atosiban approach was safely accomplished in a two-patient case report [43]. Further, many newer, less invasive procedures, such as laser ablation and ultrasound-guided procedures, may be viable means to avoid the need for general anesthesia and thus have potential fetal benefits. While further studies in this area are warranted, in the interim, until there is evidence suggesting that the current practice is safe, we recommend that anesthesiologists and fetal surgeons attempt to limit general anesthetic exposure in favor of other means to achieve uterine relaxation.

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CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

DATA AVAILABILITY STATEMENT

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