Clinical update regarding general anesthesia-associated neurotoxicity in infants and children

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Purpose of review
The U.S. Federal Drug Administration (FDA) recently released a warning stating that ‘repeated or lengthy use of general anesthetic and sedation drugs during surgeries or procedures in children younger than 3 years or in pregnant women during their third trimester may affect the development of children’s brains’ (www.fda.gov/ucm582356.htm). The goal of this article is to review the most recent clinical studies which provide evidence that these concerns may be overstated for the majority of healthy young children who require surgery and anesthesia.

Recent findings
Three large retrospective matched cohort studies published within the past year provide data on a total of 59,814 children exposed to general anesthesia before age 4 (including 30,021 <2 years and 9,814 multiple exposure). All three studies independently conclude that neither exposure to anesthesia in children under 2 years of age nor multiple exposures are associated with adverse neurodevelopmental consequences in the patient populations studied. Biological, environmental, and social factors were found to be of far greater import.

Summary
These findings suggest that anesthetic neurotoxicity is not a major contributory pathway for adverse neurodevelopmental outcomes in the majority of healthy children who require surgery before 3 years of age. Future work should focus on the particular vulnerabilities of the fetus, premature infant, and children with developmental disabilities, major congenital, cardiac or neurological abnormalities not specifically addressed by these studies.

Keywords
anesthesia, cognition, neurodevelopment, neurotoxicity, pediatric

INTRODUCTION
Since the seminal demonstration of widespread neuroapoptosis and subsequent behavioral abnormalities in rat pups exposed to a cocktail of N₂O, midazolam, and isoflurane [1], clarification of the potential risk that anesthetic agents pose to human neurodevelopment has been of paramount concern to medical practitioners, parents, and regulatory bodies alike. After more than 15 years of intense animal study, the evidence is irrefutable: exposure to a sufficient dose and duration of general anesthesia during a species-specific period of rapid brain growth is toxic to the immature animal brain. Research now extends beyond anesthesia induced apoptosis to include effects on neurogenesis, synaptogenesis, glycogenosis, and neural network formation, in multiple species including nonhuman primates. Walters and Paule [2*], Disma et al. [3], Jevtovic-Todorovic [4], and Creeley [5] provide excellent reviews. A compilation of preclinical mechanistic studies suggests that anesthetics are developmental stage-specific modulators of neuronal plasticity [6]. As brain maturation follows similar trajectories across all mammalian species [7] and all species fall on a similar growth curve, using dimensionless scaling for mass and time [8], the argument that similar effects could be present in humans is both biologically plausible and compelling. However, after a decade of intense clinical study, using diverse outcome measures and populations, translation of these concerns to children remains unconfirmed. Despite this, a recent review of the...
General anesthetics have been shown to have negative effects at every stage of neurodevelopment with long-lasting neurocognitive consequences in immature animal models, if administered with a sufficient dose and duration during the period of rapid brain growth.

Translation of the potential risk to humans remains unclear, but was of sufficient concern for the FDA to release a warning regarding potential harm to fetuses and children less than 3 years requiring either longer (>3 h) or multiple anesthetic exposures.

The recent GAS and PANDA trials provide robust evidence that a single brief general anesthetic is unlikely to be harmful in children. More recent large retrospective matched cohort studies extend these findings to multiple surgical procedures and anesthetic exposures. Minimal neurocognitive deficits were limited to children older than 2 years at the time of anesthetic exposure with no evidence that risk increased with multiple exposures, suggesting that anesthetic neurotoxicity may be of minimal consequence to neurocognitive outcomes in the children assumed to be at greatest risk, whereas environmental, social, and biological factors are of far greater import.

The impetus to examine anesthetic neurotoxicity is unlikely to result in clinically relevant neurodevelopmental abnormalities. The following review will address the rationale behind preclinical animal modeling, its applicability to clinical anesthesia, and the most recent retrospective and prospective human studies which provide more reassuring evidence that for the majority of young children exposure to anesthetic agents is unlikely to result in clinically relevant neurodevelopmental abnormalities.

RATIONAL

The impetus to examine anesthetic neurotoxicity in animals was based on an understanding of the cumulative body of evidence evinced enough concern for the U.S. Food and Drug Administration (FDA) to release a warning in late 2016 that ‘repeated or lengthy use of general anesthetic and sedation drugs during surgeries or procedures in children younger than 3 years or in pregnant women during their third trimester may affect the development of children’s brains’. In response, editorials and medical associations argued that patients and parents may be dissuaded from undergoing medically indicated procedures, where the potential adverse consequences of delaying or avoiding surgery could far outweigh any theoretical risk to brain development [9]. The FDA revised the statement in April 2017 to incorporate these amendments, but all stakeholders require more definitive answers to these ongoing concerns.

The following review will address the rationale behind preclinical animal modeling, its applicability to clinical anesthesia, and the most recent retrospective and prospective human studies which provide more reassuring evidence that for the majority of young children exposure to anesthetic agents is unlikely to result in clinically relevant neurodevelopmental abnormalities.

PERIOD OF VULNERABILITY

Neural development follows an orderly sequence that is similar across species, but is highly variable in timing for different brain areas and for different species relative to birth. Although the window of exposure chosen for animal studies is not predicated on direct translatability to humans but driven by the ability to observe a quantifiable signal [12], maximal vulnerability is consistently demonstrated during the period of vigorous synaptogenesis and rapidly tapers off outside this time window [13]. In the human, the period of rapid neuronal growth extends from late gestation up to 3–4 years of life, but peak synaptogenesis occurs from late gestation to approximately 12–24 months [4,14]. Consistent with this hypothesis, the developmental switch in function of the GABA receptor from immature excitatory to mature inhibitory occurs at approximately 1 year of age in humans [15]. As such, although human susceptibility could conceivably extend prenatally into the fourth year of life, neonates and infants should be at greatest risk for neurocognitive effects.

DOSE/CUMULATIVE DOSE

Preclinical studies provide clear evidence for a cumulative dose–toxicity relationship [3]. Correspondingly, previous observational studies that suggest that a single anesthetic exposure is unlikely to be harmful [16–19] are bolstered by the interim report of the General Anesthesia Compared to Spinal Anesthesia (GAS) trial [20*]. This is the first prospective randomized controlled study to compare regional to general anesthesia for hernia repair.
in healthy infants. No difference in individual cognitive testing at age 2 years was found between children with a brief (<80 min) exposure to sevoflurane compared to children undergoing surgery under spinal anesthesia. The Pediatric Anesthesia NeuroDevelopment Assessment (PANDA) study [21*], a multicenter ambidirectional sibling cohort study, corroborates these results in otherwise healthy children having a single sevoflurane anesthetic for hernia repair at less than 3 years compared to an unexposed sibling. Individual IQ testing in later childhood was not different between groups. Although reassuring, these were not designed to address potential toxicity associated with increasing anesthetic dose/duration.

The Mayo Anesthesia Safety in Kids (MASK) trial is an ongoing population-based propensity matched study to prospectively compare cognitive outcomes in children exposed to single and multiple general anesthetics before age 3 years. Results are expected this year [22]. In the interim, retrospective observational studies attempt to address the question of dose/duration using multiple exposures as a surrogate for increased dose. Although some earlier studies suggest increased risk with increased number of anesthetic exposures [16,17,23], they are limited by the inability to account for unknown or residual confounding and a lack of statistical power because of small numbers. Wang and Miao [24] reported a combined hazards ratio of 1.7 [95% confidence interval (CI), 1.32–2.33] for multiple general anesthetic exposure in children less than 4 years, based on a meta regression of seven previous observational trials, only three of which contribute data on multiple exposures, with less than 100 children per study.

More recent observational studies include a much larger cohort of children, using domain-specific outcome measures and increased modeling for known confounders, including health, social, and demographic covariates. Three large retrospective matched cohort studies, published within the past year, now provide data on a combined total of 59 814 children exposed to general anesthesia before age 4, of which 30 021 were exposed before age 2, including 9814 patients with multiple general anesthetic exposures [25*,26*,27*]. All three studies independently conclude that neither age less than 2 years (i.e. the period of maximal synaptogenesis) nor multiple anesthetic exposures are associated with adverse neurodevelopmental consequences in the patient populations studied.

**REVIEW OF RECENT CLINICAL STUDIES**

Two Canadian studies examined the association between anesthesia exposure in children less than 4 years and later academic performance, assessed by the Early Development Index (EDI), a validated and predictive test for school readiness, which encompasses five developmental domains: physical health, social competence, emotional health, language/cognitive development, and communication skills/general knowledge – an assessment administered in kindergarten. O’Leary et al. [25*] determined the association between early anesthetic exposure and developmental vulnerability, defined as test results below the 10th percentile for any EDI domain, in 28 366 Ontario children exposed to general anesthesia matched by gestational age at birth, maternal age, rurality, and year and quarter of birth to 55,910 unexposed controls. Children with a preexisting propensity for developmental disability were excluded. The cohort included 22,812 children exposed to a single general anesthetic, 4167 with two general anesthetics, 1008 with three general anesthetics, and 378 with at least four general anesthetics. In this very large matched cohort, the authors determined an exceedingly small but significant increase in the proportion of children demonstrating early vulnerability in the exposed group overall (25.6 vs. 25.0%) (P = 0.047). The adjusted odds ratio (OR) was 1.05 (95% CI, 1.01–1.08). In subgroup analysis however, this small but significant difference was only evident in children more than 2 years at the time of exposure. Children who underwent surgery and anesthesia before age 2, those presumed to be at greatest risk, did not demonstrate increased developmental vulnerability in any EDI domain. Furthermore, with a multiply exposed cohort of more than 5500 children, this study could not confirm increased risk with increasing anesthetic exposures. The OR for any developmental vulnerability was 1.04 (95% CI, 1.00–1.08, P = 0.03) with one general anesthetic, and 1.06 (P = 0.2–0.7) for two, three, or at least four general anesthetics.

The second large Canadian trial compared 4480 Manitoba children exposed to surgery and general anesthesia before age 4, matched by sex, year of birth, mother’s age, income quintile, and urban versus rural residence [26*] to 12 000 unexposed children. Health status in the year prior to general anesthetic exposure and the year prior to EDI testing, and important sociodemographic parameters and birth characteristics were included as covariates in the models. Analyzed as a single cohort, these authors also report a small but significant negative association between any general anesthetic exposure and the estimates for most EDI domains (maximum score = 10), most relevant for communication/general knowledge (−0.35; 95% CI, −0.45 to −0.26) and language/cognition domains (−0.23, 95% CI, −0.3 to −0.16). However,
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as in the O’Leary study, when analyzed by age, these small deficits were entirely accounted for by children more than 2 years at the time of exposure, with no evidence of a dose response. Including more than 600 children in the multiple exposure group, there was no significant difference in EDI estimates between single versus multiple exposures for the group as a whole or when analyzed by multiple exposures restricted to age 0–2 years or 2–4 years.

In the largest cohort study to date, Glatz et al. [27] report on academic achievement at age 16 and IQ scores in males at military entry in 33 514 Swedish children exposed to a single general anesthetic and 3640 exposed to multiple general anesthetic before age 4, matched for sex, maternal education level, and year and month of birth to a control group of 159 619 unexposed children. To reduce confounding, they excluded surgical procedures associated with serious comorbidities and children with hospitalizations between the general anesthetic exposure and academic testing. They found a minimal effect of anesthesia and surgery on academic achievement at age 16 years [academic grades 0.41% lower (95% CI, 0.7 to –0.12%) and 0.97% lower IQ test scores in males at military entry that was remarkable again for significance only in children aged 3–4 years at the time of general anesthetic exposure. The magnitude of the difference in test results was similar with multiple exposures, corroborating the Canadian studies.

Consistent with these findings, Kermany et al. [28] performed cognitive evaluations on a retrospective cohort of 115 otherwise healthy children with a history of glaucoma. Within this group, 47 children had no general anesthetic exposure, 22 had one general anesthetic and 46 children underwent 2–20 general anesthetics before age 3 years. With this small, but controlled cohort, they were unable to demonstrate any discernible detrimental effect of either single or multiple anesthetic exposures before age 3 on the specific cognitive domains of attention, working memory, executive function and verbal ability, determined between age 6 and 15 years.

The limitation of all observational studies is the inability to infer causality when significant associations are discovered. However, three large independent studies now provide convincing evidence for a lack of association between anesthetic exposure and measurable deficits in neurocognition in the children for whom neurotoxicity should be most manifest and no association with multiple anesthetic exposures. The increased power that attends large data sets provides greater confidence that the small negative effects observed in the older children are unlikely to be causally related to anesthetic exposure and more likely related to residual confounding. In this regard, Glatz et al. [27] report a modest increase in deficits with ear, nose, and throat (ENT) surgery (–1.22%) or eye surgery (–1.37%) compared to hernia repair (–0.31%). Graham et al. [26], stratifying surgical procedures by age, report that children less than 2 years were more likely to undergo simple general surgical and ENT procedures (hernia repair, myringotomy, and insertion of inflation tubes) whereas children more than 2 years were more likely to undergo dental rehabilitation and ENT procedures such as tonsillectomy and adenoidectomy. These findings support the assertion that the combination of biopsychosocial and genetic factors that predispose the older children to the need for surgery and anesthesia may also account for the subsequent decrements in neurodevelopmental testing reported [29]. Possibilities include nutritional deficiencies in socially disadvantaged children requiring dental rehabilitation and the consequences of sleep disordered breathing in children requiring tonsillectomy.

OTHER FACTORS

Comparing the relative effect of general anesthesia to other covariates in the analysis, Graham et al. [26] report that social factors – either social assistance or involvement with the child welfare system and health status in the year prior to EDI testing are associated with effects on EDI estimates that are two to three times greater than that of general anesthetic exposure. Likewise, Glatz et al. [27] report that the difference in academic testing associated with general anesthetic exposure (–0.41%) is trivial compared to that associated with male sex (–9.88%), maternal education (–9.89%), or month of birth (–5.34%).

The initial impetus to examine potential anesthesia-related neurotoxicity arose from the known effects of alcohol on prenatal brain development [30]. Even with this recognized toxin, however, the threshold dose and duration of exposure that results in the defined spectrum of alcohol-related abnormalities is poorly delineated and significant alcohol consumption during pregnancy may be mitigated by social, nutritional, genetic, and environmental factors that remain poorly understood [31]. These same factors may play a role in modifying the putative negative effects of anesthesia on the developing brain.

As such, although further preclinical study is ongoing and larger prospective trials comparing anesthetics of longer duration and multiple exposures are required to confirm these retrospective findings, significant focus must equally be afforded to the important social, genetic and environmental
Anesthesia-associated neurotoxicity in children

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REFERENCES AND RECOMMENDED READING

Papers of particular interest, published within the annual period of review, have been highlighted as:

■ of special interest

■■ of outstanding interest


Most recent comprehensive review of preclinical rodent and nonhuman primate studies of anesthesia associated neurotoxicity including newer work involving microPET studies and potential biomarkers of injury.


To date, this remains the only multicentre prospective randomised controlled trial comparing a brief sevoflurane general anesthetic to regional anesthesia for hernia repair in healthy infants. Interim neurocognitive testing at 2 years was not different between groups.


22. Prospective neurocognitive assessment of a retrospectively obtained cohort of children who underwent hernia repair at less than 3 years compared to a sibling, showing no differences in individualized testing.


Determinants of health in specific populations of children who may be at particular risk. Additional study must also address the particular vulnerabilities of the fetus, premature infant, and children with developmental disabilities, major congenital, cardiac or neurological abnormalities not specifically addressed in these recent studies.

In this regard, two recent publications [32,33] report postoperative gray and white matter MRI abnormalities in preterm infants requiring surgery in the neonatal period. Although concerning, neither study provides preoperative imaging for comparison such that the relevance of these findings to anesthesia remains unknown. Weiss et al. [34*] stress that, due to the exquisite sensitivity of the neonatal brain to ischemic insult, the conduct of anesthesia, which include better delineation of well tolerated physiological parameters such as blood pressure and CO2 control, may be more important than the anesthetic per se, in this vulnerable population.

CONCLUSION

Notwithstanding the inherent limitations of retrospective study design, these current results, reproduced in three large independent studies which demonstrate no association between anesthetic exposure and cognitive outcomes in healthy children less than 2 years, even with multiple anesthetic exposures, cannot be dismissed. Together these findings suggest that for the majority of otherwise healthy infants and children, the long term neurodevelopmental risk attributable to anesthesia is either nonexistent, or minimal. By comparison, biological, environmental, and social determinants of cognitive development are much more important. While further study should focus on specific populations and procedures that may place the immature brain at greater risk, these findings should be reassuring to both caregivers and parents when discussing the risks and benefits of surgery that may be required for the children in their care.

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Conflicts of interest

There are no conflicts of interest.

Overview of the Genetic Basis and Epigenetic Mechanisms that Contribute to FASD Pathobiology Top of Form.
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The first of the recent very large population based retrospective cohort studies which shows very small effects of anesthetic exposure in domain specific tests of school readiness in children exposed to anesthesia before age 4 years, but only in children more than 2 years at time of exposure. There was no evidence for increased risk with multiple exposure.


The second recent large population based retrospective cohort matched study corroborating the results of O’Leary et al. In addition, these authors provide evidence that social factors and health status in the year prior to cognitive testing are of much greater relevance than anesthetic exposure to subsequent neurocognition.


The largest population based retrospective cohort matched study to date, also demonstrating small effects on subsequent educational and IQ testing, attributable to anesthetic exposure but limited to children 3–4 years at the time of exposure. As in the Graham et al. study, biological and social factors were found to be of much greater relevance to outcomes of subsequent neurocognitive testing.


Important article placing anesthetic toxicity in the context of other factors relevant to the safe conduct of anesthesia for the neonate and infant. Emphasis is placed in the need for studies to better define safe blood pressure and CO$_2$ parameters to ensure adequate cerebral perfusion for immature brains at risk for cerebral ischemia.