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Authors
Pinyavat, Teeda
Warner, David O
Flick, Randall P
et al.

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Summary of the Update Session of Clinical Studies

Teeda Pinyavat, MD,
Department of Anesthesiology, Columbia University College of Physicians and Surgeons, New York, NY

David O. Warner, MD,
Department of Anesthesiology, Mayo Clinic College of Medicine, Rochester, MN

Randall P. Flick, MD., MPH,
Department of Anesthesiology and Department of Pediatrics, Mayo Clinic College of Medicine, Rochester, MN

Mary Ellen McCann, MD, MPH,
Department of Anesthesiology, Harvard Medical School, Boston, MA

Dean B. Andropoulos, MD, M.H.C.M.,
Department of Anesthesiology and Department of Pediatrics, Baylor College of Medicine, Houston, TX

Danquig Hu, MD,
Department of Anesthesiology, Mayo Clinic College of Medicine, Rochester, MN

Jeffrey W. Sall, MD, PhD,
Department of Anesthesiology and Perioperative Care, University of California San Francisco School of Medicine, San Francisco, CA

Marisa N. Spann, PhD, MPH, and
Department of Psychiatry, Columbia University College of Physicians and Surgeons, New York, NY

Caleb Ing, MD, MS
Department of Anesthesiology, Columbia University College of Physicians and Surgeons, New York, NY

Abstract

During the Fifth Pediatric Anesthesia Neurodevelopmental Assessment (PANDA) Symposium, experts and stakeholders met to present and discuss recent advances made in the study of neurodevelopmental outcomes following exposure to anesthetic drugs in infants and children. This article summarizes the update of five ongoing clinical studies: General Anesthesia compared to Spinal Anesthesia (GAS), Toxicity of Remifentanil and Dexmedetomidine (T-Rex), Mayo Anesthesia Safety in Kids (MASK), the UCSF (University of California San Francisco) human cohort study, and Columbia University Medical Center (CUMC) Neonatal Magnetic Resonance

Correspondence/Reprints: Teeda Pinyavat, MD, Address: 622 West 168th Street BHN4-440, New York, NY 10032, Fax: 212-305-2395, Telephone: 212-305-2413, tp2008@cumc.columbia.edu.

Imaging (MRI) study. The purpose of this summary is to discuss the contributions and limitations of these studies, how they fit into the published literature, and what questions remain to be answered.

Keywords

anesthesia; pediatric; behavior; cognition; neurodevelopment; clinical research

Introduction

While concern about the potential neurotoxic effects of anesthesia is growing, the published clinical data offer little guidance in terms of the optimal timing of anesthesia exposure for elective procedures, and whether specific anesthetic regimens should be selected to minimize risk [1]. Several observational studies have found long-term differences between children exposed and unexposed to anesthesia, but the reason for these differences remains unclear, with little data from prospective interventional studies to aid in determining if these effects are due to the actual anesthetic exposure [2–5]. In April 2016, experts in the fields of anesthesia, neuropsychology, neuroscience, surgery and epidemiology convened at the Fifth biennial PANDA symposium. An update session moderated by Drs. David O. Warner and Randall P. Flick from the Mayo Clinic College of Medicine was dedicated to outlining the progress of five ongoing clinical studies using prospective neuropsychological assessment of children exposed to anesthesia: the GAS, T-Rex, and MASK studies, a study from UCSF evaluating a cohort of children in California, and a study evaluating a cohort of neonates at CUMC. The PANDA study also performs prospective neuropsychological assessments in children, but will be described elsewhere in this supplement. (See: Proceedings of the Fifth Biennial Symposium on Anesthesia and Neurodevelopment in Children.)

Each of the five studies has a unique design and they can be divided into two overarching categories: clinical trials such as the GAS and T-Rex studies, and observational studies such as the MASK and UCSF and CUMC studies. In the clinical trials, the children are randomized to either an anesthetic strategy that is potentially neuroprotective, or a technique using a standard volatile anesthetic. The question that these studies are meant to answer is if children receiving surgical procedures develop long-term neurodevelopmental differences based on two differing anesthetic techniques. The observational studies, on the other hand, evaluate specific groups of children who have been exposed to anesthesia and surgery in the past and compare them to children who have not had anesthesia or surgery. The purpose of the observational studies is to determine if exposed children are neurodevelopmentally different from a control group of children unexposed to anesthesia or surgery.

GAS (General Anesthesia compared to Spinal Anesthesia) Trial

Dr. Mary Ellen McCann, from Boston Children’s Hospital, presented progress made in the GAS study, a prospective, open-label, international, randomized controlled equivalence trial. Premature and term infants presenting for inguinal hernia repair between 2007 and 2013 at 28 study sites were included. Exclusion criteria were any recognized risk factors for adverse neurodevelopmental outcome or previous exposure to general anesthesia. Infants presenting

for hernia repair were randomized to receive either a regional anesthetic or a sevoflurane anesthetic with or without concomitant regional anesthesia. The data presented was from the interim analysis of the 2-year follow-up with the primary outcome of the trial planned for the 5-year assessment. The aim of the study is to determine whether different types of anesthesia result in equivalent neurodevelopmental outcomes. As a secondary aim, the frequency of apnea in the postoperative period was also evaluated [6, 7].

In this update, Dr. McCann described some of the barriers to enrollment of the approximately 4,000 infants screened for eligibility including surgeon and anesthesiologist preference, lack of parental consent, and logistical barriers. Of the infants screened, ultimately over 700 infants were stratified by gestational age and randomized to receive a regional anesthetic (spinal, caudal, or both) or sevoflurane. Of the 363 randomized to regional anesthesia, 140 required additional exposure to sedation or general anesthesia, resulting in 287 receiving a pure regional anesthetic and evaluated in the per-protocol analysis. Subjects were mostly male (≈85%) with a mean chronologic age of 10 weeks (average post-menopausal age of 320 days), and mean weight of 4.2 kg at the time of surgery. Time under anesthesia ranged from 40 to 66 minutes. A subgroup analysis of the USA patients revealed an average of 0.9 MAC (minimal alveolar concentration) hours of sevoflurane (MAC $_{\text{(mean end tidal concentration \%)}}$ x anesthetic time $_{\text{(hours)}}$). Regional anesthesia resulted in less intraoperative hypotension than general anesthesia.

With respect to the evaluation of cognitive outcomes, both intention to treat and per protocol analysis were used. Both analyses showed no significant differences in neurodevelopmental outcomes at two years of age using the Bayley III and other standard neuropsychologic assessment tools. The authors concluded that an exposure to sevoflurane of less than one hour does not increase risk of adverse neurodevelopmental outcome when compared to regional anesthesia at two years of age. The primary outcome measure will take place at five years of age using the WPPSI III (Wechsler Preschool and Primary Scale of Intelligence) [6].

T-Rex (Toxicity of Remifentanil – Dexmedetomidine) Trial

As new questions concerning the safety of volatile anesthetics emerge, a feasible alternative to replace them has yet to be found. Dexmedetomidine, a sedative which acts as an alpha2-agonist, is already being widely used in the clinical setting by pediatric anesthesiologists and intensivists. While it is not yet FDA approved for use in pediatrics, its safety in this context has been well documented in the literature [8–11].

Dean Andropoulos, from Texas Children's Hospital, presented progress made in the first phase of the study – an open label single-arm pilot study to determine the feasibility of using dexmedetomidine, remifentanil, and local anesthesia via caudal catheter to provide anesthesia for lower abdominal and lower extremity surgery lasting longer than 120 minutes in infants aged 1–12 months as a potentially neuroprotective anesthetic strategy.

Funded by the SmartTots organization, under the direction of principal investigator Andrew Davidson, the pilot study design and protocol was based on a consensus of the SmartTots trial committee [12]. The primary outcome is feasibility of this anesthetic technique, as

determined by the decision of the provider not to deviate from the protocol. The secondary outcomes include the frequency of rescue treatment of light anesthesia as evidenced by movement and rescue treatment for hypotension and bradycardia, as well as measurements of intraoperative hemodynamics, time to recovery and post-operative pain. This potentially neuroprotective protocol consists of a mask induction with sevoflurane (less than 10 minutes), followed by the administration of caudal bupivacaine or ropivacaine, followed by boluses and infusions of dexmedetomidine and remifentanil.

Of the planned 50 subjects, 34 have been completed across six study sites. All except one case that met inclusion criteria were hypospadias repairs. There have been no protocol abandonments to date. Of note, in the first 17 subjects, light anesthesia (movement) was noted in 75% of participants and the committee met to revise the protocol to increase bolus and infusion doses of dexmedetomidine and remifentanil. With the new protocol, the incidence of light anesthesia has been reduced to less than 50%. In 2 of 34 subjects, a caudal catheter could not be placed and they were removed from the study. There have been no adverse events reported. The group is in the planning stages of a multicenter randomized controlled trial comparing dexmedetomidine and remifentanil plus caudal to a second arm of sevoflurane plus caudal in the same infant cohort.

Dr. Andropoulos also presented an update on a second related study evaluating dexmedetomidine in which he serves as the principal investigator. This study is a phase I study of Dexmedetomidine Bolus and Infusion in Corrective Infant Cardiac Surgery: Safety and Pharmacokinetics, and is sponsored by the Pediatric Heart Network, a clinical research network of the U.S. National Heart, Lung, and Blood Institute of the National Institutes of Health [13]. This study includes neonates and infants up to 180 days old undergoing corrective cardiac surgery with cardiopulmonary bypass for transposition of the great arteries, ventricular septal defect, and Tetralogy of Fallot. The primary aim is to demonstrate the safety of dexmedetomidine in this cohort, recording safety events such as arrhythmia, hypotension, and sedation. The secondary aim is to study the pharmacokinetics (PK) of the drug by first using a dose escalation strategy to create a dynamic pharmacokinetic model using covariates such as age, weight, bypass time, ultrafiltration volume, and temperature, and ultimately developing a dosing strategy targeting low, medium, and high blood concentrations. This dosing strategy will then be prospectively evaluated.

Enrollment of the 116 planned subjects is expected to be complete within the next six months. Among the 86 enrolled, four minor safety events have occurred including 2nd degree atrioventricular block and junctional rhythms with minimal hemodynamic change. In terms of PK, they have found a significant amount of variation amongst patients and almost no clearance of dexmedetomidine on bypass. A preliminary dosing strategy has been formulated based on these PK models including decreased doses post bypass. The ultimate goal is to perform a multicenter randomized controlled trial comparing the long-term cognitive effects of an anesthetic including dexmedetomidine to a standard sevoflurane anesthetic in infants aged 0–180 months with congenital heart disease with neurodevelopmental outcomes measured at two and five years of age.

The MASK (Mayo Anesthesia Safety in Kids) Study

The MASK study differs from the above clinical trials in that it is an observational study utilizing a population-based cohort – a birth cohort of children born to mothers residing in Olmsted County, Minnesota. Danquig Hu of the MASK team at the Department of Anesthesiology at the Mayo Clinic Children's Center presented progress made in two interrelated studies, the Prospective MASK study and Retrospective MASK study, both under the direction of principal investigators Drs. David O. Warner and Randall Flick. These observational studies utilize data gathered from birth and subsequent medical records of children in the Olmsted County birth cohort to create three propensity-stratified groups of no anesthesia exposure, single exposure before age 3 years of age, and multiple exposures before 3 years of age.

The Retrospective Mask study aims to replicate the group's previous findings from an older birth cohort from 1976 to 1982 showing an increased risk of learning disability with multiple anesthetic exposures but not a single exposure [4]. All children who were enrolled in the Rochester School District and born from 1996 to 2000 were divided into the three groups previously outlined. School and medical records were reviewed for learning and behavioral outcomes including diagnosis of learning disabilities, attention deficit hyperactivity disorder (ADHD), a need for an individualized education program, and academic achievement test scores. The records of 465 unexposed, 466 single-exposure, and 126 multiple-exposure subjects have been reviewed. Preliminary findings indicate that similarly to their prior published study, multiple anesthetic exposures, but not a single exposure, are associated with an increased frequency of learning disability and ADHD [4, 14]. This suggests that the association between early exposure to anesthesia and surgery and cognitive deficit remains despite the differences in anesthetic medications and intraoperative monitoring used in the 1970s and 1980s compared to the 1990s.

The Prospective Mask study includes children in the birth cohort born between 1994 and 2007 who currently still live in the area, now between the ages of 8 and 19 years. Subjects from the three groups mentioned above will undergo prospective testing with the Operant Test Battery, a neurodevelopmental test that can also be utilized with non-human primates, and other neuropsychologic tests for cognition, memory, language, executive function, motor and visual spatial tasks, attention, and processing speed with the goal of finding a phenotype for anesthetic neurotoxicity [15]. Projected recruitment of 1,000 subjects is expected to be completed by the end of 2016. The group has also collected data on the anesthetic agents used, in addition to intraoperative physiologic data such as maximum and minimum blood pressure and oxygen saturation and will include these parameters in their final analysis.

The UCSF (University of California San Francisco) Human Cohort Study

Translating findings from animal to human studies has been challenging. Dr. Jeffrey W. Sall, from the University of California San Francisco School of Medicine, has tried to bridge the gap in their study of the effects of a single exposure of anesthesia on recognition memory. Dr. Sall outlined the differences between the two components of recognition memory – recollection, the ability to recall specific details of an item and its context, and familiarity, the feeling that one has previously encountered an object or context. The first UCSF Human

Trial, an ambidirectional cohort study, found that 28 infants (less than one year of age) exposed to volatile anesthetic for longer than two hours exhibited a deficit in recognition memory compared to matched controls assessed between the ages of 6 and 11 years old. Specifically, a deficit in recollection but not familiarity memory was found. The effect was more prominent in males, and when exposure was of longer duration. A comparable deficit in recollection-like memory was found in rats exposed to sevoflurane at seven days of age and tested months later [16].

Dr. Sall described their progress in conducting the second UCSF Human Trial, which is another larger ambidirectional trial comparing late versus early and long versus short exposure to general anesthesia with a volatile agent as the primary anesthetic. Four groups will be created with a target of 46 subjects in each group: early-short (<2 years and <30 minutes), early-long (<2 years and >120 minutes), late-long (4–7 years and >120 minutes), and a control group consisting of either siblings and friends of exposed patients or age- and gender-matched anesthesia naïve subjects from the Center for Mind and Brain at UC Davis. The battery of neuropsychologic testing includes the Child Behavioral Check List filled out by parents, measure of recognition memory using the dual process signal detection model, overall IQ using the Wechsler Abbreviated Scale of Intelligence (WASI) 2nd edition, and digit span [17, 18]. A brief listening comprehension test (for 8–11 year olds) was added as some studies are pointing to language as a potential target for neurotoxicity [19].

Across three sites, UCSF, Oakland, and UC Davis, of 107 subjects eligible and able to participate, 81 have completed testing, of which roughly 60% are male. Of note, non-English speaking households are included in the study to aid with recruitment and broaden the applicability of the results. However, non-English speaking children tested so far have shown lower verbal scores in a subset of the WASI-II so the study team plans to adjust and match for this variable in all groups to be studied.

CUMC (Columbia University Medical Center) Neonatal MRI Study

As 60% of deliveries in the United States include a regional anesthetic, the question arises as to whether fetal exposure to local anesthetics and narcotics play a role in long-term neurodevelopment [20]. Dr. Marisa N. Spann, from CUMC, studies prenatal factors and their effect on brain structure and cognitive function using developmental neuroimaging.

Dr. Spann presented her published study “The Effects of Regional Anesthesia During Labor and Delivery on the Neonatal Brain,” which is a secondary analysis of a larger NIH-funded study investigating the impact of in utero exposure to drugs. In this study, pregnant women between the ages of 18 and 45 with normal pregnancies were recruited from CUMC between 2005 and 2010. They were excluded if other toxic exposures such as tobacco, alcohol, or recreational drugs were present. A non-sedated anatomic MRI was performed on 37 babies in their first 6 weeks of life. Infants exposed to maternal regional anesthesia had greater brain volumes in bilateral frontal and right occipital lobes than infants who had no maternal exposure. A dose effect was seen in the occipital cortex for the epidural group when measured by the duration of the maternal anesthetic exposure [21]. Future plans include measurement of MRI images at different time points of development as well as correlation with neuropsychological and behavioral testing. Dr. Spann also pointed out that the message

of the study is not to deny women pain relief for labor. She quoted the American College of Obstetrics and Gynecology and American Society of Anesthesiologists: “There is not other circumstances where it is considered acceptable for an individual to experience untreated severe pain” [22]. If these MRI findings can be correlated with neuropsychological or behavioral findings, decisions may need to be made regarding the risks and benefits of regional anesthesia and alternatives found during labor.

Discussion

The GAS, T-Rex, MASK, UCSF cohort, and CUMC neonatal MRI studies when completed, will all contribute valuable information to the discussion of anesthetic neurotoxicity. However, it is important to recognize the differences between these five prospective studies and the published studies on anesthetic neurotoxicity. The vast majority of the published studies including those involving the Raine cohort from Perth, the Mayo Clinic cohort from Rochester, the Medicaid study from New York State, and the Danish birth cohort are observational population-based birth cohort studies [2–4, 19, 23]. They compare children exposed to surgery and anesthesia with other children not exposed to surgery or anesthesia within a given population. Some of these studies found that children exposed to surgery and anesthesia had an increased risk of cognitive deficit, particularly in the neuropsychological domains of language and cognition [3, 24], while others found no effect [5, 23]. This may be due to the use of academic achievement scores, which may not be sensitive enough to measure differences in children exposed to anesthesia, or perhaps there may be differences in the children or anesthetics themselves. For example, many of the negative studies evaluate children from Europe [19, 25]. While directly assessed neuropsychological testing outcomes are likely to be the most sensitive in measuring cognitive differences in children, these outcomes are rarely available in large population studies, with the exception of the Raine cohort. However, a limitation of the Raine cohort is that these children had surgery in the early 1990s and some received anesthetics no longer commonly used (e.g. halothane).

In order to study cohorts of children in the modern era with directly assessed neuropsychological testing, ambidirectional observational studies such as the PANDA, MASK, and UCSF studies have retrospectively identified children exposed to anesthesia and evaluated them with prospective cognitive testing – a more efficient method of identifying exposed children than a population-based observational design. However, the limitation of this design is possible selection bias for households with higher socioeconomic status. Households of higher socioeconomic status are those with more geographic stability and are more commonly able to be contacted many years after exposure to anesthesia. It has been proposed that a more enriched learning environment potentially present in these households could negate some potential ill effects of anesthetics as neurotoxins [26].

At this time, the GAS study is the only clinical trial with published data. While the 2-year follow-up may be unable to adequately assess language and other higher order brain functions, the 5-year follow-up will help to assess whether a short exposure to only sevoflurane for hernia repair results in differences in cognitive outcomes compared to regional anesthesia alone, an anesthetic technique presumed to be non-neurotoxic.

Even as we learn the results of the above five studies that were presented, important questions may still remain. While the GAS and PANDA studies evaluate the safety of single short exposure for hernia repair, preclinical data suggests that longer exposures are more likely to cause toxicity, particularly when a combination of agents are used. While the MASK study attempts to further shed light on whether a detrimental neurodevelopmental effect may only be measured in multiple and longer exposures as opposed to single short exposures. The concern with MASK as well as all other observational studies is whether there are unmeasured and unaccounted for clinical differences between the exposed and unexposed children. For ambidirectional cohort studies, the self-selection of parents who desire for their child to undergo extensive testing may not be representative of the general population. The UCSF human cohort study is similar to the MASK study, but answers the question of dose response from a slightly different perspective, looking at the duration of exposure instead of the total number of exposures, while also looking to see if outcomes after exposure at younger ages differed from exposures at older ages. This work, when complete, may offer some additional guidance as to the correct group of children to assess in a clinical trial. The T-Rex study is already working to lay the groundwork for the next iteration of clinical trials, evaluating an anesthetic technique and potential mitigation strategy that can be used for longer procedures. The utility of the T-Rex study however, is contingent on the confirmation of a neurotoxic anesthetic exposure that needs to be mitigated. Also, both the GAS and T-Rex protocols employ a regional anesthesia technique and therefore may only be applicable in children undergoing surgery below the level of the abdomen.

The CUMC neonatal cohort study offers some preliminary data questioning whether neuraxial blocks in mothers have any effect on the unborn child. This could potentially point to toxicity from the local anesthetic, hemodynamic variation in the mother, or conversely that pain due to a lack of labor analgesia may have a detrimental effect. Currently while differences in MRI findings have been appreciated, until these MRI findings can be linked with cognitive outcomes, it is difficult to interpret the implications of these findings.

In conclusion, even after the completion of the studies presented at this session, there will likely still be significant gaps in clinical knowledge in terms of the long-term neurocognitive effects of anesthetic drugs in infants and young children, specifically in the dose, frequency, duration, and combination of anesthetic drugs resulting in toxicity in children, as well as the existence of any vulnerable populations and age of vulnerability. As these and other studies begin to use more sensitive outcomes to evaluate specific groups of children with specific anesthetic exposures, there will no doubt be important advances in the understanding of anesthetic neurotoxicity in children.

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References

1. Rappaport BA, et al. Anesthetic Neurotoxicity - Clinical Implications of Animal Models. N Engl J Med. 2015; 372(9):796–797. [PubMed: 25714157]
2. DiMaggio C, et al. A retrospective cohort study of the association of anesthesia and hernia repair surgery with behavioral and developmental disorders in young children. J Neurosurg Anesthesiol. 2009; 21(4):286–91. [PubMed: 19955889]
3. Flick RP, et al. Cognitive and behavioral outcomes after early exposure to anesthesia and surgery. Pediatrics. 2011; 128(5):e1053–61. [PubMed: 21969289]
4. Wilder RT, et al. Early exposure to anesthesia and learning disabilities in a population-based birth cohort. Anesthesiology. 2009; 110(4):796–804. [PubMed: 19293700]
5. Bartels M, Althoff RR, Boomsma DI. Anesthesia and cognitive performance in children: no evidence for a causal relationship. Twin Res Hum Genet. 2009; 12(3):246–53. [PubMed: 19456216]
6. Davidson AJ, et al. Neurodevelopmental outcome at 2 years of age after general anaesthesia and awake-regional anaesthesia in infancy (GAS): an international multicentre, randomised controlled trial. The Lancet. 2016; 387(10015):239–250.
7. Davidson AJ, et al. Apnea after Awake Regional and General Anesthesia in Infants: The General Anesthesia Compared to Spinal Anesthesia Study-Comparing Apnea and Neurodevelopmental Outcomes, A Randomized Controlled Trial. Anesthesiology. 2015
8. Hauber J, et al. Dexmedetomidine as a Rapid Bolus for Treatment and Prophylactic Prevention of Emergence Agitation in Anesthetized Children. Anesth Analg. 2015; 121(5):1308–1315. [PubMed: 26332857]
9. Koroglu A, et al. A comparison of the sedative, hemodynamic, and respiratory effects of dexmedetomidine and propofol in children undergoing magnetic resonance imaging. Anesth Analg. 2006; 103(1):63-7. table of contents. [PubMed: 16790627]
10. Wu J, et al. Comparison of propofol and dexmedetomedine techniques in children undergoing magnetic resonance imaging. Pediatric Anesthesia. 2014; 24(8):813–818. [PubMed: 24814202]
11. Chrysostomou C, et al. A phase II/III, multicenter, safety, efficacy, and pharmacokinetic study of dexmedetomidine in preterm and term neonates. J Pediatr. 2014; 164(2):276–82.e1–3. [PubMed: 24238862]
12. Ramsay JG, Roizen M, Davidson A. SmartTots: a public-private partnership between the United States Food and Drug Administration (FDA) and the International Anesthesia Research Society (IARS). Paediatr Anaesth. 2012; 22(10):969–72. [PubMed: 22967154]
13. Mahony L, et al. The Pediatric Heart Network: A Primer for the Conduct of Multicenter Studies in Children with Congenital and Acquired Heart Disease. Pediatric Cardiology. 2005; 27(2):191–198.
14. Sprung J, et al. Attention-deficit/hyperactivity disorder after early exposure to procedures requiring general anesthesia. Mayo Clin Proc. 2012; 87(2):120–9. [PubMed: 22305025]
15. Paule MG, et al. Operant Test Battery Performance in Children: Correlation with IQ. Neurotoxicology and Teratology. 1999; 21(3):223–230. [PubMed: 10386825]
16. Stratmann G, et al. Effect of general anesthesia in infancy on long-term recognition memory in humans and rats. Neuropsychopharmacology. 2014; 39(10):2275–87. [PubMed: 24910347]
17. Weschler, D. Wechsler Abbreviated Scale of Intelligence - Second Edition (WASI-II). San Antonio, TX: NCS Pearson; 2011.
18. Achenbach TM, Ruffle TM. The Child Behavior Checklist and related forms for assessing behavioral/emotional problems and competencies. Pediatr Rev. 2000; 21(8):265–71. [PubMed: 10922023]
19. Ing C, et al. Long-term Differences in Language and Cognitive Function After Childhood Exposure to Anesthesia. Pediatrics. 2012; 130(3):e476–85. [PubMed: 22908104]
20. Osterman MJ, Martin JA. Epidural and spinal anesthesia use during labor: 27-state reporting area, 2008. Natl Vital Stat Rep. 2011; 59(5):1–13. 16.
21. Spann MN, et al. Morphological features of the neonatal brain following exposure to regional anesthesia during labor and delivery. Magn Reson Imaging. 2015; 33(2):213–21. [PubMed: 25179140]

22. American College of Obstetricians and Gynecologists. Pain relief during labor. ACOG Committee Opinion No. 295. Obstet Gynecol. 2004; 104:213. [PubMed: 15229040]

23. Hansen TG, et al. Academic performance in adolescence after inguinal hernia repair in infancy: a nationwide cohort study. Anesthesiology. 2011; 114(5):1076–85. [PubMed: 21368654]

24. Ing CH, et al. Neurodevelopmental outcomes after initial childhood anesthetic exposure between ages 3 and 10 years. J Neurosurg Anesthesiol. 2014; 26(4):377–86. [PubMed: 25144506]

25. Ing CH, et al. Comparative analysis of outcome measures used in examining neurodevelopmental effects of early childhood anesthesia exposure. Anesthesiology. 2014; 120(6):1319–32. [PubMed: 24694922]

26. Shih J, et al. Delayed environmental enrichment reverses sevoflurane-induced memory impairment in rats. Anesthesiology. 2012; 116(3):586–602. [PubMed: 22354242]