FDA Warning on Anesthesia and Brain Development: Implications for Obstetric and Fetal Surgery

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Implications for Obstetric and Fetal Surgery

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Short Version of Article Title: Detrimental effect of anesthesia on fetal brain development.
Abstract- There has been growing concern about the detrimental effects of certain anesthetic agents on the developing brain. Preclinical studies in small animal models as well as non-human primates, have suggested loss or death of brain cells and consequent impaired neurocognitive function following anesthetic exposure in neonates and late gestation fetuses. Human studies in this area are limited and currently inconclusive. On December 14, 2016, the United States Food and Drug administration (FDA) issued a warning regarding impaired brain development in children following exposure to certain anesthetic agents used for general anesthesia, namely the inhalational anesthetics isoflurane, sevoflurane, desflurane, and the intravenous agents, Propofol and midazolam, in the third trimester of pregnancy. Furthermore, this warning recommends that Health care professionals should balance the benefits of appropriate anesthesia in young children and pregnant women against the potential risks, especially for procedures that may last longer than 3 hours or if multiple procedures are required in children under 3 years. The objective of this article is to highlight how the FDA warning may impact the anesthetic and surgical management of the obstetric patient. Neuraxial anesthesia (epidural or spinal anesthesia) is more commonly administered for cesarean delivery than general anesthesia. The short-duration of fetal exposure to general anesthesia during cesarean delivery has not
been associated with learning disabilities. However, the fetus can also be exposed to both intravenous and inhalation anesthetics during non-obstetric or fetal surgery in the second and third trimester; this exposure is typically longer than that for cesarean delivery. Very few studies address the effect of anesthetic exposure on the fetus in the second trimester when most non-obstetric and fetal surgical procedures are performed. It is also unclear how the plasticity of the fetal brain at this stage of development will modulate the consequences of anesthetic exposure. Strategies that may circumvent possible untoward long-term neurologic effects of anesthesia in the baby include: (i) Use of non-implicated (non-GABA agonist) agents for sedation such as opioids (remifentanil, fentanyl) or the alpha-2 agonist, dexmedetomidine, when appropriate. (ii) Minimizing the duration of exposure to inhalational anesthetics for fetal, obstetric and non-obstetric procedures in the pregnant patient, as much as possible within safe limits. (iii) Commencing surgery promptly and limiting the interval between induction of anesthesia and surgery start time will help decrease patient exposure to inhalational agents. While the FDA warning was based on duration and repetitive nature of exposure rather than concentration of inhalational agents, intravenous tocolytics can be considered for use intra-operative, to provide uterine relaxation for fetal surgery, in lieu of high concentrations of inhalational
anesthetic agents. Practitioners should consider the type of anesthesia that will be administered the potential risks when scheduling patients for non-obstetric and fetal surgery.

Key words: anesthesia, general anesthesia, inhalation anesthesia, sedatives, propofol, isoflurane, desflurane, sevoflurane, midazolam, food and drug administration, fetus, development, brain, cesarean delivery, fetal surgery.
On December 14, 2016, the U.S. Food and Drug Administration (FDA), issued a warning that “repeated or lengthy use (>3 hours) 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”\(^1\) The agents implicated are of two major classes of anesthetic agents: Gamma amino butyric acid (GABA) receptor agonists and N-methyl D-aspartate (NMDA) antagonists.\(^2\) Gamma amino butyric receptor (GABA) agonists are drugs that enhance activity at the GABA receptors resulting in sedation, decreased anxiety and muscle relaxation. The GABA receptor agonists include the inhalational anesthetics (Isoflurane, sevoflurane and desflurane), benzodiazepines (specifically midazolam), and the sedative-hypnotic agent, Propofol. The N-methyl D-aspartate (NMDA) antagonist class of drugs include anesthetic agents that inhibit or antagonize the N-methyl D-aspartate receptor and subsequently cause a dissociative anesthesia. An example of an anesthetic agent in the NMDA antagonist class of drugs is ketamine which is seldom used in the pregnant patient population. For the past, several years, one or more of these drugs have been associated with anesthesia-induced neurotoxicity (characterized by loss or death of cells in the brain) in preclinical studies on rodents and non-human primates when used as either the sole anesthetic agent or in combination with other agents.\(^2-9\)

**Pre-clinical studies**

Many of these studies were performed in neonatal animals. A few studies have specifically examined the *in-utero* exposure of rodent and non-human
primate fetuses to the anesthetic agents, isoflurane and propofol.\textsuperscript{8,10} These \textit{in-utero} studies involved administration of anesthesia for 4 – 5 hours at gestational ages equivalent to the second and late third trimesters in humans and demonstrated anesthesia-induced neuronal cell death also referred to as neuroapoptosis.\textsuperscript{11} An ovine study using clinically relevant doses and duration of isoflurane exposure in the mid-gestation period did not demonstrate any neuroapoptosis in response to single anesthetic exposure but significant neuronal cell damage was observed following repeated anesthetic exposure.\textsuperscript{12} These observations were however characterized by anesthetic exposure only without concomitant surgery, a scenario which does not occur in clinical practice (except for sedation for diagnostic procedures). Preclinical studies in rats that involved surgical or noxious stimulation in association with anesthesia exposure have shown conflicting findings.\textsuperscript{13,14} It is therefore not clear how these findings would translate to the human clinical situation.

\textbf{Anesthesia and the pregnant mother}

Most surgical procedures to which a pregnant woman is exposed to, occur at or near term. Surgery at other times during gestation is usually precipitated by
urgent maternal or fetal indications. Most commonly, neuraxial anesthesia involving local anesthetic administration in the epidural or intrathecal space is employed in the third trimester for cesarean deliveries.\textsuperscript{15} However, in emergency conditions or situations in which there is a maternal contraindication to neuraxial anesthesia, a general anesthetic with inhalational agents is administered. Regardless of the nature of the cesarean delivery (elective or emergent), the duration of surgery and anesthesia is typically short and would not be characterized as lengthy, even if general anesthesia is utilized. A retrospective population study by Sprung and colleagues,\textsuperscript{16} examining the medical and educational profiles of a cohort of patients in the United States who were delivered via cesarean delivery with general or regional/neuraxial anesthesia and vaginal delivery without any anesthetic, found no association between perinatal exposure to anesthesia and the development of learning disabilities. In fact, there was no difference in the incidence of learning disabilities in children delivered via cesarean delivery under general anesthesia compared to those delivered under regional (neuraxial) anesthesia. This study does not support a link between general anesthesia and impaired neurological development. However, other investigators, who performed a population based study of neonates following cesarean delivery noted an increased incidence of autism in children who had
received general anesthesia at the time of cesarean delivery when compared to neonates delivered vaginally or via cesarean delivery with regional anesthesia.\textsuperscript{17} The specific nature of the general anesthetic was not described in this paper but general anesthesia typically involves the use of an intravenous sedative-hypnotic, of which Propofol is the most commonly used agent, together with an inhalational anesthetic (e.g. sevoflurane, desflurane, isoflurane or, in developing countries, halothane).

More than 80,000 pregnant women require anesthesia for non-obstetric surgery annually in the United States.\textsuperscript{18} Concern for possible teratogenicity with surgery and anesthesia during pregnancy is highest during the first trimester, however emergency surgery may be necessary at any time during gestation. Typically, for these emergent non-obstetric surgeries or for some fetal surgery procedures, inhalational anesthetics are administered. Even for image guided fetal interventions, sedation using benzodiazepines (e.g. midazolam) is frequently employed.

**Anesthesia and the Fetus**

With recent advances in fetal surgery,\textsuperscript{19} more fetuses are undergoing \textit{in-utero} surgery; approximately 1500 cases occurred in the USA in 2015.\textsuperscript{20} In addition to
fetuses undergoing fetal myelomeningocele repair, those undergoing in-utero resection of sacrococcygeal teratomas, large fetal lung masses refractory to steroid therapy, or other congenital anomalies managed at or near term, via ex utero intrapartum therapy (EXIT), will very likely receive general anesthesia via maternal inhalational gases supplemented with direct fetal intramuscular administration of opioids and muscle relaxants. The provision of adequate uterine relaxation (a necessity for in-utero, open fetal surgery), in a controlled and predictable fashion, makes the utilization of inhalational anesthetics for uterine relaxation a universally preferred method for in-utero surgery. Other procedures such as fetoscopy for selective laser photocoagulation for twin-twin transfusion syndrome (TTTS) and tracheal occlusion for congenital diaphragmatic hernia (CDH) can be performed with maternal local anesthesia supplemented with intravenous sedation using opioids such as fentanyl or remifentanil as well as fetal medications mentioned above.

Based on the recent FDA announcement, one may question the utility or need for fetal intervention which unavoidably involves exposure of the fetus to intravenous or inhalation general anesthetics. However, fetal therapy has been proven to be beneficial for some of these conditions in randomized controlled trials (Myelomeningocele and TTTS), while other procedures such as fetal
tracheal occlusion for CDH are still undergoing scientific review. The ideal pre-clinical scenario will be to study the effects of anesthesia on fetuses that receive both anesthesia and concomitant surgical stimulation. Myelomeningocele and late stage twin-twin transfusion syndrome are frequently associated with some degree of neurological impairment a priori, but many other conditions currently managed with fetal surgery or intervention have not been reported to be specifically associated with impaired brain development in affected children. However, further study is clearly needed, given the increasing body of reliable evidence that abnormalities in hemodynamics (which play both a primary and secondary role in the need for the fetal intervention or therapy, e.g. large fetal lung masses or sacrococcygeal teratomas with hydrops), can significantly affect functional and structural aspects of the central nervous system. In support of this concept, we now know that a significant percentage of children with congenital cardiac anomalies, have impaired neurological development independent of treatment.

Lengthy anesthetics in the pregnant woman is fortunately, a rare situation but may still occur in different scenarios including urgent and emergency surgeries as well as for in-utero surgeries. There is limited information about the metabolism and pharmacodynamics on many of these drugs in the fetus. The blood: gas partition
coefficient determines the rate of uptake and elimination of inhalational agents from maternal lungs; the latter determines the rate of emergence from general anesthesia. With regards to uptake of inhalational agents by the fetus, dual human perfused placental models demonstrate that hypoperfusion on the fetus impairs placental transfer of these agents further compounding the effects of the drugs. This may be the clinical scenario in the hydropic fetus undergoing fetal surgery.

The ability to properly study any potential effect of anesthesia on fetal and neonatal neurocognitive function in humans presents an obvious ethical issue. Most patients undergoing open fetal surgery (where a hysterotomy is performed to access the fetus) currently receive general anesthesia for a variety of reasons including need for fetal analgesia, uterine relaxation, and appropriate surgical access. Any study that proposes randomization of these patients to general versus neuraxial anesthesia may pose an ethical dilemma: how to deal with potential deviations from what is considered the norm with regards to anesthetic management, the definition of what constitutes appropriate maternal and/or fetal care, and even the pragmatic questions of adequate sample size and power. A reasonable compromise solution may be to prospectively follow children that have received in-utero therapy and to assess neurological and neurobehavioral development. To this end an international fetal anesthesia database has been
established with the intent of studying the long term neurodevelopmental outcomes of individuals who have undergone fetal intervention. (Clinical Trials.gov identifier NCT02591745)

The FDA warning regarding commonly utilized anesthetic agents in the third trimester is based on concerns about the exposure of the fetal brain to these agents at a time when synaptogenesis (formation of intricate connections between brain cells) occurs in the third trimester of pregnancy and up to 2-4 years postnatally. What remains unknown, is the effect of surgery of any duration or type performed during mid-gestation, at a time when early brain cell (neuroblast) formation is occurring. The plasticity/ability of the fetus to adapt to potential neuronal/axonal injury during this early phase of brain development is unclear. More research in this area is warranted.

**Impact on Non-obstetric and Fetal Surgery**

While general anesthesia via inhalational anesthetics remains the more common approach for emergent non-obstetric or open fetal surgery, neuraxial anesthesia will continue to be the primary mode of anesthesia offered in the management of the obstetric patient. General anesthesia with inhalational anesthetics should also be reserved for emergency cases or for
procedures/patients not amenable to neuraxial anesthesia. Many non-obstetric procedures are of an emergent nature and will require a general anesthetic; for others, a neuraxial anesthetic may possibly be an alternative option. For fetal procedures that only require sedation i.e. fetoscopic procedures, the intravenous agents implicated in the FDA warning (e.g. Midazolam and Propofol) should be avoided. Alternative options to consider include the use of intravenous opioids such as remifentanil, fentanyl or morphine as monotherapy, as well as neuraxial techniques that employ local anesthetics such as lidocaine and bupivacaine with/without opioids in the epidural or intrathecal space as appropriate. The importance of constant communication with the patient and the utilization of non-pharmacologic techniques to allay anxiety during fetal interventions cannot be overemphasized. More invasive fetal surgical procedures require inhalational anesthetics to maintain uterine relaxation. While neuraxial anesthesia with the supplemental use of intravenous nitroglycerin for uterine relaxation is an option, the prolonged duration of some of the procedures, lack of easy titratability of nitroglycerin to effect, and the possible complications of nitroglycerin, make it a less preferred option for routine use as a sole agent for uterine relaxation during fetal surgery. Most of the preclinical studies that suggest detrimental effects of inhalational anesthetic agents are characterized by either very high
concentrations of anesthetic gases or very long duration of exposure both of which do not routinely occur in clinical practice. The exact concentration and/or dose at which the implicated anesthetics can be administered without associated neurotoxicity have not been elucidated in preclinical studies. However, clinical studies in children have shown that short duration general anesthesia and single exposures are not associated with neurocognitive impairment. Unfortunately, the FDA warning does not provide guidelines on the recommended dose or concentration of the anesthetic agents to be used to avoid neuronal injury. Indeed, current publications provide no specific recommendations to practitioners.

In the absence of specific guidelines, we suggest that in pregnant patients who require general anesthesia, the duration of general anesthesia should be limited as much as possible within safe limits. In those patients in whom the procedure is likely to take more than 3 hours, strategies to reduce the dose and concentration of the anesthetic agent may be helpful (Table 1). For example, for in-utero surgery, where inhalational anesthetic gases are typically utilized for uterine relaxation, the intra-operative administration of tocolytic drugs e.g. intravenous Magnesium sulfate or Atosiban where available, may enhance uterine relaxation and reduce the anesthesia dose from the typically required 2-3 times MAC.
(minimal alveolar concentration) to a lower dose. Atosiban, an inhibitor of both oxytocin and vasopressin, available only in Europe, is another tocolytic, also administered intravenously to halt premature labor. Magnesium Sulphate has limited effectiveness as a tocolytic agent and is used in conjunction with indomethacin and nifedipine. In the absence of Atosiban in the USA, intravenous Magnesium Sulphate is used in the perioperative phase.

Minimal alveolar concentration (MAC) is the term used to describe the concentration of inhalational anesthetic agent in the lungs that is required to prevent movement (motor response) in 50% of subjects in response to surgical (pain) stimulus. Another strategy worth considering may be to decrease duration of exposure to concentrations of agents required for uterine relaxation. This can be accomplished by supplementing inhalational anesthetics with intravenous opioids for the majority of in-utero surgery and limiting the high concentration of 2-3 MAC of inhalation anesthetic to the critical period when fetal manipulation is required and uterine relaxation is most needed; a technique that has been employed in order to avoid the fetal dysrhythmic effects of the inhalational agent, desflurane.  

In conclusion, the FDA warning has clearly raised the concern about potential risks to fetal brain development with inhalational agents, intravenous propofol and
midazolam, the common agents administered during pregnancy for general anesthesia and sedation. We believe that as a general principle, minimizing fetal exposure to these agents is important and advisable. The strengths of this warning for the obstetric population lie in the fact that it was based on multiple observations that have been consistent across many animal models. It highlights the need to limit the duration of exposure of the developing fetus to certain anesthetic agents. The main limitations of this warning are also that it was based primarily pre-clinical studies. Many of the preclinical studies use doses and gestational age equivalent durations of anesthetic exposure far in excess of that used in clinical practice. In addition, to date, no human studies have unequivocally determined an association between anesthetic exposure and impaired memory or neurocognitive function in humans. The complete avoidance of the implicated anesthetic agents may be impractical, and further research is urgently needed to clarify the urgency with, and degree to, which we as practitioners need to respond to this warning. It must be remembered as we respond, that available data are minimal in humans and that this warning has been released based on data generated from animal experiments under conditions of isolated anesthesia exposure without concomitant surgery. It behooves us to exercise caution and to base any major changes in practice on appropriate and stringent human evidence.
wherever possible, to avoid the proverbial metaphorical mistake of throwing the baby out with the bathwater.
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Table Legend

Table 1. Strategies to minimize patient exposure to, as well as dose and duration of anesthetics.

(IV – intravenous. *Atosiban is not approved for use in the United States by the FDA. #Nitroglycerin is difficult to titrate to effect, may result in intractable hypotension and/or pulmonary edema.)
Table 1

<table>
<thead>
<tr>
<th>Type of Surgery</th>
<th>Anesthetic technique</th>
<th>Suggested Modification/Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Obstetric</td>
<td>Neuraxial (Epidural or Spinal) utilizing local anesthetics +/- opioids</td>
<td>None</td>
</tr>
<tr>
<td>Non-Obstetric</td>
<td>Neuraxial as above (if applicable) or Neuraxial utilizing inhalational agents</td>
<td>None</td>
</tr>
<tr>
<td>(Non-Emergent)</td>
<td>General Anesthesia utilizing inhalational agents</td>
<td>&lt; 3 hrs. duration – No change</td>
</tr>
<tr>
<td></td>
<td></td>
<td>&gt; 3 hrs. durations – consider deferring until postpartum</td>
</tr>
<tr>
<td>Non-Obstetric</td>
<td>General Anesthesia utilizing inhalational agents</td>
<td>Limit times:</td>
</tr>
<tr>
<td>(Emergent)</td>
<td></td>
<td>(a) Between induction and start of surgery and</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(b) Between end of surgery and end of anesthesia</td>
</tr>
<tr>
<td></td>
<td>Fetal procedures</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Local anesthesia</td>
<td>No change</td>
</tr>
<tr>
<td></td>
<td>Neuraxial anesthesia</td>
<td>No change</td>
</tr>
<tr>
<td></td>
<td>IV sedative-hypnotic – propofol</td>
<td>&lt; 3 hrs. duration – no change</td>
</tr>
<tr>
<td></td>
<td></td>
<td>&gt; 3 hrs. duration – discuss risk/benefit</td>
</tr>
<tr>
<td></td>
<td>IV sedative – Midazolam</td>
<td>Consider IV opioids (fentanyl or remifentanil) or IV dexmedetomidine</td>
</tr>
<tr>
<td></td>
<td>General anesthesia with inhalational agents</td>
<td>&lt; 3 hrs. duration – no change</td>
</tr>
<tr>
<td></td>
<td></td>
<td>&gt; 3 hrs. duration – discuss risk/benefit</td>
</tr>
<tr>
<td></td>
<td>General Anesthesia with increased concentration of inhalational agents for uterine</td>
<td>Consider supplementing with magnesium sulfate, Atosiban* or Nitroglycerin* for intra-operative tocolysis</td>
</tr>
<tr>
<td></td>
<td>relaxation</td>
<td></td>
</tr>
</tbody>
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