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# A Review of Anesthetic Effects on the Developing Brain - Animal versus Human Models

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**Abstract**

In the last 30 years a large amount of data, both animal and human, has come out indicating that perhaps the most commonly used general anesthetics (inhaled anesthetics such as nitrous oxide and iso/sevo/desflurane, but also propofol) may have an effect on the neurodevelopment of an unborn fetus. The neurotoxic effects of volatile anesthetics have been tested numerous times in animal models ranging from rats to primates, and there is a large amount of reliable data which have confirmed that these agents do, in fact, cause interruption and even degeneration of neuronal development, with clinically significant cognitive and behavioural changes neonatal. Does this data apply to the human model?

**Keywords:** Neurotoxicity; Anesthetics; Prenatal; Exposure; Anaesthesia; Apoptosis

## Introduction

In the last 30 years a large amount of data, both animal and human, has come out indicating that perhaps the most commonly used general anesthetics (inhaled anesthetics such as nitrous oxide and iso/sevo/desflurane, but also propofol) may have an effect on the neurodevelopment of an unborn fetus. The neurotoxic effects of volatile anesthetics have been tested numerous times in animal models ranging from rats to primates, and there is a large amount of reliable data which have confirmed that these agents do, in fact, cause interruption and even degeneration of neuronal development, with clinically significant cognitive and behavioral changes neonatally. Does this data apply to the human model?

## Analysis of the Variables at Play and Limitations Thereof

The degree of fetal neurotoxicity has been attributed to several factors, many of which are inherent qualities of the agent used or the animal tested on, but all having an influence on the amount of neuronal death. The primary factors that have been identified to have the most impact are the duration and frequency of exposure, the absolute dosage of agent, the bioavailability and pharmacodynamics of the agent itself, the metabolic competency of the organism, and finally the timing of the exposure with regard to neuronal maturity of the fetus [1-4].

This final factor has proven to be both one of the most important aspects of possible neurotoxic effect and also the most elusive, as animal models across varying species have both different timings for the period of maximal brain growth (called the brain growth spurt period or BGSP) but also the quality and nature of the neuronal connections formed for that specific species during this period [5-7]. The initial stages are neurulation and neural proliferation occur so early in gestation that there is little clinical data in either human or animal models to support any teratogenic effects of anesthetic agents [8]. The following stages of neural migration varies greatly between species, however, with the degree of apoptosis and synaptogenesis, and their temporal relationship to each other, often being so disparate in animal models that it is not necessarily correlatable to the human model. In rats and many other rodents, the peak period of synaptogenesis actually begins and rapidly ends postnatally whereas in most primates and the human brain this period begins in the second trimester and continues on through the end of gestation and generally is completed within the the first year of life [6,7,9]. There is also a strong degree of neuroplasticity at work in the fetal brain which could lead to some degree of compensatory response to exposure, and this also varies between species and is yet another confounding factor which prevents the generalizability of animal model data to the human model [10].

Metabolism of anesthetic agents by both the mother and the fetus similarly varies between species, as does the degree of placental transfer of certain agents, for example propofol [2,11,12]. In the case of propofol specifically, there are several other compounds in the solution (such as EDTA) and these solutions also vary between manufacturers, and these fractional amounts of diluent could themselves be potentially neurotoxic [3]. The act of establishing IV access or any other form of noxious stimuli, for example surgery, on the mother has also been shown to cause physiologic changes in both the placenta and the fetus and something as minor as a variation in transplacental blood flow could have a marked effect on these developmental changes. [3,13,14].

All of these variables have generally been studied in a retrospective manner on humans [14,15], while the two most recent and largest prospective human studies, the Pediatric Anesthesia Neuro-development Assessment Study (PANDA) and the GAS study (which compares Regional vs. General Anesthesia for Neurodevelopmental Outcomes) are both focused on anesthetic exposure in neonates and infants rather than the developing fetus [10,16-18]. Because neurodevelopment continues postnatally in humans, the argument could be made that anesthetic exposure in infancy could also have

neurotoxic effect; however the GAS study has shown that single exposure anesthetics have no effect on cognitive function [18].

## What We Currently Know

The anesthetic agents of highest concern for fetal neurotoxicity all share a common site of action in that they all exert their effect on the GABA and NMDA receptors in the CNS of the developing foetus. [8,17,19]. This is of specific concern in the developing brain because early neuronal organization depends on on-going electrical activity in immature neurons to aid in directing the growth of synapses, a process called activity-dependent network formation [5,7]. GABA and NMDA receptors indirectly regulate calcium channels in immature neurons, and this is the primary mechanism of action theorized to be responsible for neurotoxic effects, specifically "unplanned" apoptosis [17,20]. Multiple animal studies have demonstrated that one of the primary features of anesthetic neurotoxicity is apoptotic neuronal death during the synaptogenesis period [17,19,21], with other complications including suppression of neurogenesis [4,17,22], morphologically abnormal synapse formation [23], altered dendritic spinogenesis [8,24], impairment of hippocampal long-term potentiation [1,25,26], deformation of glial cytoskeletal actin [8,10], and impair mitochondrial function directly by changing the morphology and functional capacity of neuronal mitochondria in the developing brain [8,10,17].

Further, it is well established that longer and more frequent durations of exposure to anesthetic agents lead to more clinically significant neurodevelopmental effects [4] and various combinations of agents can have either an exacerbating effect on the neurotoxicity experienced or, in some cases, certain commonly used anesthetic agents may mitigate or even protect the developing brain from toxic effect [27]. Statistically significant behavioural defects have been reliably reproduced in the rodent model and suggest that affected rodents developed difficulties with spatial awareness and reference memory in the form of decreased ability to navigate and explore novel environments and standardized mazes, as well as delayed development of multiple primitive reflexes and slower growth of body and brain weight [25,28,29].

Finally, analysis on human subjects on the transfer and concentration of anesthetic agents through the placenta into the fetus has been performed, and preliminary studies indicate that even with short periods (<5 min) of anesthetic exposure to the mother at the time of delivery via caesarean section, clinically significant levels of anesthetic agent could be detected in the plasma of the neonate, often with gross signs of induced anesthesia on the infant itself [12,15]. Multiple agents have been explored for a possible method to mitigate the neurotoxic effects of anesthetics, however of these agents dexmedetomidine has shown the most promising data, particularly with relation to propofol exposure, and it is an anesthetic in its own right and thus is an excellent adjunctive medication to use for surgery [30,31].

## Conclusion

While human model data is limited due to the nature of the studied outcomes and difficulty in acquiring a large enough standardized patient population to generate statistically significant data, it is clear that further study is of the utmost priority for future use of anesthetic agents in the pregnant mother, regardless of gestational age [16]. Even very brief exposures of anesthetic levels adequate to induce anesthesia in the mother have been shown to cause significant levels in the term infant, and as previously established the most important phase of fetal/neonatal neurodevelopment is synaptogenesis, which is very much still occurring at the time of delivery and for months afterward. Animal data clearly demonstrates the neurotoxic effect of volatile anesthetic gases and propofol on the developing brain, but due to a myriad of confounding factors such as neuroplasticity, as well as the extremely variable progression of neurodevelopment across mammalian species, we cannot definitively make any concrete statements as to the neurotoxic effects of these agents in the human model [16,18].

While there are multiple national and international large scale prospective studies currently underway to test these theories, it may take several years, if not decades, before they produce both clinically and statistically significant outcomes to lead us toward a more definitive conclusion. These same studies are further limited due to their focus on neonates and infants, rather than prenatal neurobehavioral and cognitive development. Further study focusing on the human model of neurotoxicity is clearly needed. In the interim, it has been suggested that limiting exposure pre-emptively until the role of anaesthetic agents on the developing brain has been more clearly established or using dexmedetomidine routinely as a primary anaesthetic agent, however this is a simplistic solution that may or may not be feasible as well as cost prohibitive. [16,30-36] At this stage of understanding it is instead imperative for paediatric and obstetric anaesthesiologists to be engaged with the surgical team when it comes to the operative plan when weighing the benefits and possible risks of all anesthetic options [16].

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