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The Effects of General Anesthetics on the Developing Brain of Fetus

Sucharitha A*, Bhuvana D and Shrisha S Raj

Omega College of Pharmacy, Affiliated to Osmania University, India

***Corresponding author:** Are Sucharitha, Pharm D, Omega College of Pharmacy, Affiliated to Osmania University, Edulabad (V), Medchal (dist), Hyderabad, Telangana, India, Tel: 7416215939; Email: aresucharitha29@gmail.com

Review Article

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Abstract

General Anesthesia is a practice of medically inducing temporary loss of consciousness accompanied by complete or partial loss of pain reflexes. Anesthesia for obstetrics and pediatric surgery is unpreventable for pregnant women and newborn infants with life-threatening disorders requiring a prolonged stay in the intensive care unit (ICU). Despite this, fetal brain development begins in the third week of gestation of intrauterine life. Volatile anesthetics such as sevoflurane, desflurane, isoflurane nitroprusside, etc are used during pregnancy to prevent preterm contractions and inhibit uterine contractility. These volatile anesthetic agents are highly lipid soluble and are of low molecular weight which readily favors for transplacental passage of the volatile anesthetics by simple diffusion and shows numerous effects on the neuronal transmission system. The basic principles of embryo-fetotoxicity were evaluated in the aspects of embryo-fetal effects of drugs such as anesthetics analyzed, and the most commonly used anesthetics were presented with teratogenic risks. Various studies suggested that prolonged exposure to general anesthetics might result in extensive neuroapoptosis (neuronal death), anesthetic neurotoxicity, neuroinflammation, synaptic loss, activation of caspase, and other neurodegenerative changes in the developing human brain. This review briefly summarizes the growth and development of the brain in fetuses and neonates, the data regarding neurotoxicity, and a few key components accountable for neuroapoptosis and causes long-lasting cognitive impairment in fetuses induced due to general anesthetics that is the progress in neurodevelopment in the offspring on anesthetic exposure will be reviewed.

Keywords: General Anesthetics; Volatile Anesthetics; Sevoflurane; Desflurane; Isoflurane; Nitroprusside; Preterm Contractions; Transplacental Passage; Embryo-fetotoxicity; Teratogenic Risks; Neuroapoptosis; Neurotoxicity; Neuroinflammation; Synaptic Loss; Neurodegeneration; Cognitive Impairment

Abbreviations: CNS: Central Nervous System; NSC: Neural Stem Cells; NGF: Nerve Growth Factor; BDNF: Brain Derived Neurotrophic Factors; GABA: Gamma Aminobutyric Acid; NMDA: N-methyl D-aspartate; ADHD: Attention-Deficit/Hyperactivity Disorder; ASD: Autism Spectrum Disorder.

Introduction

General anesthesia is a state of intended loss of consciousness that renders the patient unresponsive even with pain or stimulus. This result is achieved by administering the general anesthetics either by intravenous administration or by inhalation of these drugs, which frequently act as both analgesics and neuromuscular blocking agents. The biochemical mechanism of general anesthetics remains contended as they induce unconsciousness and affect the central nervous system (CNS) at a multitude of levels. The goal of anesthetics during the pregnancy is to ensure a noteworthy recovery of the mother and to maintain a safe and secure continuation of pregnancy without damaging the fetus [1]. The placental transfer of these drugs depends on factors such as their highly lipid-soluble resulting in the trapping of these drugs in the placenta. This gives rise to teratogenic issues such as major congenital malfunctions. During pregnancy in the first trimester, many physiological parameters are modified when compared to the normal responses due to the effect of anesthetics. These physiological changes have a great impact nearly on all major organ systems, including the nervous system, cardiovascular system, hepatic, and pulmonary, and also lead to various changes in the metabolic activities of the body. It is mandatory and highly recommended that the requirement for anesthetics should be reduced during this period administered either by inhalations or intravenous administration. In the second trimester, the management of anesthetics becomes much safer than that of the first and third trimesters as the second trimester is considered the safest other trimesters. However, the gravid uterus begins to compress the larger vessels, and the compression of the aortocaval vessel can be dangerous during the administration of general or regional (local) anesthetics. All other difficulties that are experienced during the first and second trimesters are increased during the period of the third trimester. The precautions implemented in the second trimester are held good for the third trimester [2]. No matter what the general anesthetics need a lot of attention as the inhalant anesthetics can intensify uterine relaxations and have a chance of causing post-partum hemorrhage. Most of the anesthetic drugs can pass through the breastmilk at a very low level, and few anesthetics can suppress lactation very rarely, but there is a possibility. One of the biggest concerns is about the effects on the newborn infant due to general anesthetics.

Neurodevelopmental Vulnerability The developing brain undergoes complex processes of neurogenesis, synaptogenesis, and neuronal maturation, which are highly susceptible to external influences. Animal studies have demonstrated that exposure to general anesthetics during critical periods of brain development can disrupt these processes, leading to structural and functional abnormalities. Similarly, human epidemiological studies have suggested associations between early exposure to anesthesia and adverse neurodevelopmental outcomes, although causality remains uncertain [3].

Intravenous Anesthetics (IV)

IV anesthetics are drugs administered directly into the bloodstream, typically via injection. These drugs act quickly and are often preferred for their rapid onset of action. Common IV anesthetics include propofol, etomidate, ketamine, and benzodiazepines like midazolam [4].

Propofol: It is one of the most widely used IV anesthetics due to its rapid onset and short duration of action. It provides smooth induction and recovery, making it ideal for short procedures or for maintaining anesthesia during longer surgeries.

Etomidate: This IV anesthetic is commonly used for induction of anesthesia, particularly in patients with compromised cardiac function as it has minimal effects on the cardiovascular system.

Ketamine: It is known for its dissociative effects and analgesic properties. Ketamine is often used in pediatric anesthesia and in patients with bronchospasm or hypovolemic shock due to its minimal respiratory depression and ability to maintain cardiovascular stability [5].

Midazolam: This benzodiazepine is frequently used for preoperative sedation and anxiolysis. It has an amnestic effect, making it useful for procedures where the patient may need to forget the events during surgery.

Inhalational Anesthetics

Inhalational anesthetics are gases or volatile liquids that are administered via inhalation. They are often used for maintenance of anesthesia once the patient has been induced with IV drugs. Common inhalational anesthetics include sevoflurane, desflurane, isoflurane, and nitrous oxide.

Sevoflurane: It is commonly used due to its pleasant odor, rapid onset, and relatively quick recovery. Sevoflurane is often used in pediatric anesthesia and outpatient surgeries.

Desflurane: This inhalational anesthetic has a very rapid onset and offset of action, making it suitable for fast recovery. However, it is known to irritate the airways and is often avoided in patients with respiratory conditions [6].

Isoflurane: It is a potent inhalational anesthetic with a rapid onset and offset of action. Isoflurane is commonly used in both adult and pediatric patients for maintenance of anesthesia.

Nitrous Oxide: Also known as laughing gas, nitrous oxide is often used in combination with other inhalational or IV anesthetics to provide analgesia and reduce the concentration of other anesthetic agents required [7].

Dosage and Duration of Exposure

The dosage and duration of exposure to both IV and inhalational anesthetics are carefully monitored to minimize the risk of adverse effects and ensure patient safety.

Dosage: The dosage of anesthetics is tailored to each patient based on factors such as age, weight, medical history, and the type of surgery being performed. Anesthesia providers calculate dosages carefully to achieve the desired level of sedation or unconsciousness while minimizing the risk of complications.

Duration of Exposure: The duration of exposure to anesthetics varies depending on the length of the surgical procedure and the patient's individual response to the drugs. Anesthesia providers continuously monitor the patient's vital signs and adjust the dosage of anesthetics as needed to maintain anesthesia while minimizing the risk of prolonged exposure.

Development of the Human Fetal Brain

The brain begins to form early in the first trimester and continues to develop until the birth. The basis of the human brain from an extremity of a 3-millimeter neural tube is worth admiring. The development of the fetal brain begins just after three weeks of fertilization but, in the third week the primitive neural cell divides and begins to differentiate, the neuronal plate folds onto it and forms a neural tube that closes by the fourth week (28 days) of pregnancy and is a derivative of the brain and spinal cord of the embryo. The process by which the neural tube forms from the neural plates is called neurulation. The neural plates lengthen and eventually start folding and forming a groove after the closure of the neuronal groove, resulting in the formation of three distinct regions of the brain- the forebrain, the midbrain, and the hindbrain [8]. These structures develop from the vesicles and area also known as the prosencephalon, the mesencephalon, and the rhombencephalon, individually. Later the prosencephalon develops into the diencephalon and telencephalon. The diencephalon initiates the thalamus, hypothalamus, neurohypophysis, and optic cups whereas, the rhombencephalon gives rise to the fourth ventricle and metencephalon which further differentiates into the pons and the cerebellum [9].

Synaptic Pruning and Circuit Formation: The complex process of circuit formation and synaptic pruning that takes place during embryonic brain development may be interfered with by general anaesthesia. In order to optimise neuronal circuits and remove unnecessary connections, synaptic pruning is crucial in deciding how the brain functions. Later in life, abnormal brain connections and functional abnormalities may result from disturbances in this process. The production of neural stem cells (NSCs) from the subventricular and subgranular zones is known as neurogenesis. Few neural stem cells are found in the foetal brain at different gestational ages. These cells are asymmetrical, round, oval, and triangular in shape. However, the number of NSCs is reduced with an increase in the gestational age. The NSCs are extensively distributed in the subventricular zone, hippocampus, and cortex. The NSCs have a solid potential to give rise to different types of cells in the central nervous system (CNS) which are- the neurons, astrocytes, and oligodendrocytes. In humans, neurogenesis begins at the fifth gestational week of pregnancy and is limited to the subventricular zone by the lateral ventricles and sub-granular zone [10].

The five developmental stages in hippocampal neurogenesis are-

- Activation of quiescent radial glia-like cells in the sub-granular zone
- Proliferation of intermediate progenitor and non-radial precursor
- Generation of neuroblast
- Integration of immature neurons
- Post-mitotic maturation of neurons

Synaptogenesis- A fundamental element of the nervous system and its network is synaptogenesis. Axonal pathfinding results in synaptogenesis. The process of synapse, which allows information to be transferred between neurons and the nervous system, is known as synaptogenesis. The last stage of axonal pathfinding involves the axon tip approach its target tissue through the terminal cells, which have a significant impact on the developing axons in order to create a synapse. Regardless of the neurotransmitter, synaptophysins are the structural glycoproteins that form the main base of the synaptic vesicular membrane [11]. Synaptogenesis is an integral process for creating a network of information for the overall framework of brain connectivity electrochemical in nature. A pocket percent of neurons fail to make relevant connections and give faulty feedback during synaptogenesis these neurons are observed as inessentials and are predestined to die through a natural process of programmed cell death, called apoptosis [12].

The neurotrophins are the proteins that are released from the parts of presynaptic and postsynaptic synapses that induce the development, survival, and differentiation of mature neurons. The neurotrophins, the family of growth factors that consist of nerve growth factor (NGF), neurotrophin 3, neurotrophin 4, and brain-derived neurotrophic factors (BDNF) play a vital role in synaptogenesis. In a mature nervous system, the neurotrophic factors induce synaptic plasticity and regulate the formation of long-term memory. Two different types of plasma receptors – P75 neurotrophic receptor (P75ntr) and tropomyosin receptor kinase receptors (Trk receptor) initiate the neurotrophins that mediate the signal transduction [13]. The neurotrophins are released by the neurons, their neural actions depend on the source of neurotrophic ligand, secretion, and signaling at the synapse. A failure to communicate a synaptic signal leads to impairment of the neural network which then curatively contributes to neuronal apoptosis.

Neurotoxicity: Preclinical studies in animal models have provided evidence suggesting that exposure to general anesthetics during critical periods of brain development can lead to neurotoxicity. Agents such as isoflurane, sevoflurane, and propofol have been shown to induce apoptosis (cell death) and disrupt neurogenesis and synaptic development in the fetal brain. These neurotoxic effects may have long-lasting consequences on brain structure and function [14].

Neuronal Apoptosis/Neuroapoptosis: The fetal and neonatal duration period is very critical and responsive to neuronal development which involves, a brisk brain development tallying the apoptosis (programmed cell death) and synaptic pruning naturally. Extensive research has shown that exposure to several classes of drugs, such as gamma-aminobutyric acid (GABA) agonists, N-methyl D-aspartate (NMDA) antagonists, including anesthetics shows immense neuronal apoptosis which causes neurotoxic insult that causes neurodevelopmental interferences with an inalterable cognitive, and behavioral orientation, and variations in intellectual disability. It is generally accepted that general anesthetics can decrease the excitatory transmission of the N-methyl D-aspartate receptor, a receptor of glutamate that plays a major role in synaptic plasticity at the peak of synaptogenesis causing apoptotic neurodegeneration leading to cognitive impairment and lack of memory [15].

Nevertheless, in the developing brain the concentration of chloride (Cl-) intracellularly is high particularly, during the peak of synaptogenesis this results in the activation of GABAA receptors leads to Cl- efflux and neuron depolarization accordingly due to depolarization, there is an increase in the concentration of the intracellular calcium (Ca+2) which might reach to an extent where it is harmful to the neurons, and may contribute to neuronal injury caused by excitotoxicity of GABAA receptors. Hence, any fundamental variance between the excitatory and inhibitory influx/efflux in the central nervous system might trigger the apoptosis of neurons exceptionally during the phase of synaptogenesis it can also change the structure of dendritic spines- help in transmitting neural signals, and play a role in memory and learning [16].

Timing of Exposure: Anesthesia's effects on the development of the prenatal brain are largely dependent on when it is applied. According to research on animals, exposure during particular windows of vulnerability—such as the equivalent of the third trimester in rodents—may be more risky. The foetal brain is developing and developing fast during this time, which makes it more prone to anesthesia's effects [17].

- **First Trimester:** During the first trimester of pregnancy, which spans approximately weeks 1 to 12 post-conception, the fetal brain undergoes rapid and critical development. This period is characterized by neurulation, the formation of the neural tube, and the early differentiation of brain structures. Exposure to environmental insults, including teratogens or medications, during this period can have profound and lasting effects on brain development [18]. However, surgical interventions requiring general anesthesia are relatively uncommon during the first trimester due to the lower risk of complications and the preference for delaying elective procedures until later in pregnancy when possible.
- **Second Trimester:** The second trimester, from approximately weeks 13 to 26 post-conception, is a period of extensive neurogenesis, neuronal migration, and synaptogenesis in the fetal brain. Major brain structures continue to develop and mature, including the cerebral cortex, which undergoes significant expansion and folding. During this period, exposure to anesthesia may disrupt these critical processes, potentially leading to alterations in brain structure and function. However, the risk of anesthesia-related complications may be lower compared to the first trimester, as organogenesis is largely complete, and the fetus may be more resilient to external insults [19].
- **Third Trimester:** The third trimester, spanning approximately weeks 27 to 40 post-conception, is a period of rapid growth and refinement of neural circuits in the fetal brain. Synaptogenesis intensifies, and the fetal brain undergoes significant structural and functional maturation in preparation for extrauterine life. Exposure to anesthesia during this critical period may have particularly pronounced effects on neurodevelopment, as the fetal brain is highly vulnerable to external insults, and disruptions in synaptic development and circuit formation could have long-lasting consequences. Additionally, concerns have been raised about the potential impact of anesthesia on fetal stress responses and the developing stress regulatory systems in the brain [20].

Neurodevelopmental Outcomes: Epidemiological studies investigating the long-term neurodevelopmental outcomes of infants exposed to anesthesia in utero have yielded mixed results. While some studies have reported associations between early exposure to anesthesia and an increased risk of neurodevelopmental disorders such as learning disabilities, attention-deficit/hyperactivity disorder (ADHD), and cognitive impairments, others have found no significant associations. It is challenging to establish causality in observational studies due to confounding variables and the complexity of neurodevelopmental outcomes [21].

- **Perioperative Considerations:** In clinical practice, the timing of exposure to anesthesia during pregnancy is often dictated by the urgency of the surgical procedure and the gestational age of the fetus. Whenever possible, elective procedures requiring general anesthesia may be deferred to the second trimester or later to minimize potential risks to fetal brain development. However, in cases of emergent or essential surgeries, anesthesia exposure may be unavoidable, necessitating careful consideration of the potential risks and benefits for both the mother and the fetus. Anesthesiologists strive to use the lowest effective dose of anesthetic agents and minimize the duration of exposure while ensuring adequate maternal and fetal physiological stability during surgery [22].

- **Learning Disabilities:** A range of neurodevelopmental disorders that impact a person's capacity to learn and apply social and academic skills are included in the category of learning impairments. Research examining the long-term neurodevelopmental consequences of prenatal anaesthetic exposure has found correlations with a higher likelihood of learning impairments. These could show themselves as challenges in arithmetic, reading, writing, and other academic subjects. Learning difficulties can have a major impact on one's ability to obtain an education, find job, and lead a generally better life [23].

- **Attention-Deficit/Hyperactivity Disorder (ADHD):** ADHD is a neurodevelopmental disorder characterized by persistent patterns of inattention, hyperactivity, and impulsivity that interfere with daily functioning and academic performance. Several epidemiological studies have suggested an association between early exposure to anesthesia and an increased risk of ADHD later in childhood [24]. However, the causal relationship between anesthesia exposure and ADHD remains unclear, as other factors, such as genetic predisposition and environmental influences, may also contribute to the development of the disorder [25].

- **Cognitive Impairments:** Cognitive impairments refer to deficits in intellectual functioning, including problems with memory, attention, executive function, and problem-solving skills. Some studies have reported associations between exposure to anesthesia during early development and cognitive impairments later in life. These impairments may manifest as difficulties in academic performance, social interactions, and adaptive functioning. However, the specific cognitive domains affected and the severity of impairment may vary widely among individuals [26].

- **Behavioral Disorders**: Exposure to anesthesia during critical periods of brain development has also been associated with an increased risk of behavioral disorders, such as conduct disorder, oppositional defiant disorder, and autism spectrum disorder (ASD). Behavioral disorders can significantly impact social relationships, school performance, and overall functioning. While some studies have reported associations between anesthesia exposure and behavioral outcomes, the evidence is not conclusive, and further research is needed to elucidate the underlying mechanisms [27].

- **Language and Communication Disorders:** Language and communication disorders encompass difficulties in understanding and using spoken or written language, as well as deficits in social communication skills. Although less extensively studied than other neurodevelopmental outcomes, some research suggests a potential link between anesthesia exposure during pregnancy and language and communication impairments in offspring. However, additional research is needed to better understand the nature and extent of these associations [28].

- **Motor Coordination and Developmental Delay:** Exposure to anesthesia during critical periods of brain development may also impact motor coordination and contribute to developmental delays in gross and fine motor skills. Motor coordination difficulties can affect activities such as walking, running, and manipulating objects, potentially leading to challenges in daily functioning and participation in physical activities [29].

- **Emotional Regulation and Mental Health:** Emerging evidence suggests that exposure to anesthesia during pregnancy may influence emotional regulation and mental health outcomes in offspring. Disruptions in early brain development, including alterations in stress regulatory systems, may predispose individuals to anxiety, depression, and other psychiatric disorders later in life. However, the specific mechanisms linking anesthesia exposure to mental health outcomes require further investigation [30].

Mitigating Strategies: In clinical practise, precautions are taken to reduce the possibility of pregnant women being exposed to anaesthesia [31]. When using anaesthetic medications, anesthesiologists try to use the lowest effective dose and limit exposure time as much as they can. For some surgical procedures, regional anaesthesia techniques like epidural or spinal anaesthesia may be preferable to general anaesthesia in order to minimise foetal exposure. Furthermore, to ensure safety during surgery, close monitoring of the physiological parameters of the mother and foetus is necessary [32].

Conclusion

In conclusion, the effects of general anesthetics on the developing brain of infants and fetuses represent a multifaceted and complex area of concern within the medical community. While general anesthesia is often necessary for surgical procedures in pregnant individuals and infants, there is growing evidence suggesting potential risks to fetal and neonatal neurodevelopment. Understanding these risks is essential for informing clinical decision-making and optimizing outcomes for vulnerable patients. Research, both preclinical and clinical, has shed light on the mechanisms through which general anesthetics may exert neurotoxic effects on the developing brain. Animal studies have demonstrated disruptions in neurogenesis, synaptogenesis, and neuronal apoptosis following exposure to anesthetics during critical periods of brain development. Observational studies in humans have reported associations between anesthesia exposure in early life and an increased risk of neurodevelopmental disorders such as learning disabilities, ADHD, and cognitive impairments. However, translating these findings into clinical practice presents significant challenges. Causality remains difficult to establish in observational studies, given the presence of confounding variables and the complexity of neurodevelopmental outcomes. Additionally, ethical considerations limit the feasibility of conducting controlled trials to directly assess the effects of anesthesia on fetal brain development in humans.

In light of these challenges, healthcare providers must approach the use of general anesthesia during pregnancy and infancy with caution. Strategies to minimize potential risks include judicious use of anesthesia, consideration of alternative anesthesia techniques, such as regional anesthesia, and careful monitoring of maternal and fetal physiological parameters during surgery. Moreover, ongoing research efforts are needed to elucidate the underlying mechanisms of anesthesia-induced neurotoxicity and identify strategies to mitigate potential harm. Ultimately, while general anesthesia remains a vital tool in medical practice, its effects on the developing brain of infants and fetuses warrant continued attention and investigation. By advancing our understanding of anesthesia-induced neurotoxicity and implementing evidence-based practices, healthcare providers can strive to ensure the safety and well-being of vulnerable patients undergoing surgical procedures during pregnancy and early infancy.

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