ISSN-E: 2617-9563

‘’Effects of General Anesthesia on the Neurocognitive Development of the Fetus during Pregnancy’’

ISSN-E: 2617-9563

Abstract

The effects of general anesthesia on the developing brain continue to be a major concern in the medical community and among the general public, with the majority of studies focusing on infants and children. In recent years, as a result of the continual advancement of medical technology, the number of surgeries performed during pregnancy has increased; yet, there are relatively few research on general anesthesia during pregnancy. The FDA has issued a warning that general anaesthetic use during pregnancy may have negative effects on the developing brain of the baby. This review reviews methodically the evidence supporting this warning. From their creation until April 2020, PubMed, EMBASE, and Web of Science were queried. Both preclinical and clinical research was admissible. Studies both preclinical and clinical were accepted. The researchers ruled out case reports, in vitro models, long-term exposures, and prenatal exposures. The impact on learning and memory as a whole was viewed as the most important finding. Markers of neuronal injury (such as apoptosis, synapse formation, neurone density, and proliferation) and subgroup analyses were considered secondary outcomes. Preclinical studies consistently demonstrate that anaesthetics cause neurotoxicity during pregnancy.

Key Words: General Anesthesia, Neurocognitive development, Fetus, Pregnancy.

الملخص

لا تزال آثار التخدير العام على نمو الدماغ مصدر قلق كبير في المجتمع الطبي وبين عامة الناس، حيث تركز غالبية الدراسات على الرضع والأطفال. في السنوات الأخيرة، نتيجة للتقدم المستمر في التكنولوجيا الطبية، زاد عدد العمليات الجراحية التي يتم إجراؤها أثناء الحمل؛ حتى الآن، هناك عدد قليل نسبيًا من الأبحاث حول التخدير العام أثناء الحمل. أصدرت إدارة الغذاء والدواء الأمريكية (FDA) تحذيرًا من أن استخدام التخدير العام أثناء الحمل قد يكون له آثار سلبية على نمو دماغ الطفل. تستعرض هذه المراجعة بشكل منهجي الأدلة الداعمة لهذا التحذير. منذ إنشائها حتى أبريل 2020، تم الاستعلام عن PubMed وEMBASE وWeb of Science. كان كل من البحث قبل السريري والسريري مقبولاً. تم قبول الدراسات قبل السريرية والسريرية. استبعد الباحثون تقارير الحالات، في النماذج المختبرية، والتعرضات طويلة المدى، والتعرض قبل الولادة. تم النظر إلى التأثير على التعلم والذاكرة ككل على أنه أهم اكتشاف. واعتبرت علامات الإصابة العصبية (مثل موت الخلايا المبرمج، وتشكيل المشبك، وكثافة الخلايا العصبية، والتكاثر) وتحليلات المجموعات الفرعية نتائج ثانوية. تظهر الدراسات قبل السريرية باستمرار أن التخدير يسبب السمية العصبية أثناء الحمل.

الكلمات المفتاحية: تخدير عام، نمو معرفي عصبي، جنين، حمل.

Introduction

In newborn mice, rats, piglets, and primates, preclinical investigations have demonstrated that exposure to a number of clinically used general anesthetic and sedative medications results in extensive age-dependent neurotoxicity linked with learning problems (McCann & Soriano, 2019). On account of these findings, anesthesiologists, parents, and other practitioners are extremely concerned about the safety of general anesthesia for young children. The long-term effects of general anesthesia on the fetus are poorly understood.

Recent animal studies have demonstrated the neurotoxic consequences of anesthetics, which result in long-lasting cognitive abnormalities. These harmful consequences are primarily detectable in infants born prematurely and newborns, as well as elderly animals (Vutskits, L., & Xie, 2016). The examination of potential mechanisms is now underway. A number of retrospective studies have been done in the United States and Europe to obtain further insight into the probable neurotoxic effects on the brains of newborns and young children.

In the past 15 years, animal research has revealed the potential for routinely used anesthetics and sedatives to promote neuroapoptosis and other neurodegenerative alterations in the developing mammalian brain. This concern has prompted a number of retrospective investigations on human newborns and early children, some of which found a link between infant exposure to general anesthesia and subsequent neurobehavioral issues in childhood (Andropoulos, 2018). This correlation is especially pronounced for extended or repeated exposures. This issue concerning anesthetic neurotoxicity is pertinent to the unborn due to the substantial increase in fetal interventions requiring sedation and analgesia for the fetus or due to maternal anesthetic effects. The possibility of anesthetic neurotoxicity is the most significant clinical and scientific issue in pediatric anesthesiology.

As medical technology has advanced, the number of fetus and infant surgeries has increased. Medical professionals and the general public are increasingly concerned about whether early-life exposure to general anesthetics has long-term negative effects on the central nervous system. Animal studies have confirmed, after years of research and observation, that anesthetics cause neurodegenerative changes and abnormal learning abilities in brain development. Since 2017, the Food and Drug Administration (FDA) of the United States has issued a warning regarding anesthetics and the developing brain, where the neurotoxicity of anesthetics has captured the public's attention (Olutoye et al., 2018).

Because medical advancements have made it possible to perform more operations on fetuses' and newborns, the rate of fetal anesthesia exposure increases during the period of brain development. Although the use of sedation or general anesthesia is generally regarded as safe, recent animal and child studies have raised a concern: general anesthesia may have detrimental effects on neurodevelopment (Li, Jiang & Zhao, 2021). In late pregnancy or in children younger than 3 years old, repeated or prolonged (greater than 3 h) use of general anesthetics or sedatives may have adverse effects on neurodevelopment. For other stages of brain development, however, the conclusion is not yet clear. The neurotoxicity of anesthetics is affected by drug toxicity, dosage, duration of exposure, and the stage of embryonic brain development. A genetic predisposition may also play a role.

Traditionally, pregnant anesthesiologists have had difficulty administering anesthesia for obstetric and nonobstetric surgery. Statistics from the developed world indicate that 1-2% of all obstetric patients will require emergency non-obstetric surgery at least once in their lifetimes, despite the paucity of data from developing nations. Several disorders and associated complications during pregnancy may necessitate hospitalization and surgical intervention for a pregnant woman (Ramirez, V., Valencia, G., & Catalina, 2020). During pregnancy, surgical emergencies such as ovarian cyst torsion, appendicitis, strangulated hernias, and severe injuries require immediate attention. Despite the fact that the risk of surgery is comparable to that of the general population, anesthetic management is currently exceedingly difficult. The safety of the mother and fetus in utero is the top priority when administering anesthesia during these emergency surgical procedures. In spite of recent advances in the clinical arena and in technology, anesthesiologists face a number of challenging obstacles when providing safe anesthetic services. Clinical problems, including but not limited to changing demographic characteristics, such as advanced maternal age, obesity, and comorbidities, such as diabetes, severe anemia, and heart diseases, etc., present an anesthesiologist with a monumental uphill battle.

Problem Statement

Long regarded as a safe method for facilitating pediatric surgery, unpleasant treatments, and medical imaging, general anesthesia has been utilised for decades. Concerns have accumulated, however, that fetuses', infants, and young children exposed to general anesthesia may experience neurotoxic consequences with permanent implications. Approximately 200,000 of the 4 million children under the age of six in the United Kingdom get general anesthesia each year (5%), making the danger of anesthetic-induced neurotoxicity a significant public health concern (Jeske, 2019).

Anesthesia practitioners are gravely concerned about the potential harm that could result from giving general anesthetics to the developing brains of infants and pregnant women. By possibly interfering with normal neuroapoptosis, anesthetics and medicines may have negative effects on the developing brains of children (DeGrange, 2019). Neuroapoptosis is the body's normal, regulated cell death, which plays a critical part in brain development. Controlled cell death is essential for neurodevelopment because it prevents redundant, defective, or useless neurons from clogging the developing brain (Creely, 2016)

This natural development can be disrupted by anesthesia, which alters neuroapoptosis and increases neurodegeneration, causing unintended harm. Animals exposed to high amounts of general anesthesia are susceptible to neurodegeneration, according to studies with juvenile rats and nonhuman primates. This injury could also result in learning delays, long-term memory problems, and worse spatial identification in the human population. In addition, investigations of infants and children exposed to excessive amounts of anesthetics have revealed a rise in learning difficulties and an increase in behavioral issues compared to the general population of the same age.

As an increasing number of pregnant women and young children undergo general anesthesia for surgical procedures, it is essential to know how anesthesia affects the maturing brain. The importance of research focusing on inhalation agents, intravenous drugs, and methods to safeguard the developing brain is growing. To discover the safest and most effective manner to deliver anesthesia to this fragile population, research-based knowledge is required.

Research Objective

To show the effect of general anesthesia on the neurocognitive development of the fetus during pregnancy.

Research Significance

The introduction of general anesthesia (GA) in 1846 changed the practice of surgery. In 2007, the United States performed over 40 million anesthetic procedures annually, and 21 million patients received GA for surgical procedures. Enhanced monitoring, delivery systems, pharmacology, and care standards have enhanced the safety of GA. However, clinical brain monitoring has failed to enhance standards of care in populations that may be at risk of GA-induced neurotoxicity.

Anesthesiologists have a number of significant obstacles while delivering anesthesia to pregnant patients undergoing surgery. Optimal management needs a comprehensive grasp of maternal and fetal physiology, altered medication pharmacodynamics and pharmacokinetics, and a sympathetic approach to the parturient, who must be properly advised about the risks and advantages of intervention. The ultimate objective is to provide safe anesthesia for the mother while minimizing the danger of preterm labour and fetal death. Throughout the perioperative phase, surgeons, anesthesiologists, and obstetricians must collaborate to safeguard the health of the fetus and mother. A positive outcome for the mother and fetus is contingent on professional management of both the surgical disease process and anesthetic.

Definition of Key Terms

General anesthesia: consists of a combination of drugs that induce a sleep-like state prior to surgery or other medical procedures. Under general anesthesia, there is no sensation of pain because the patient is fully asleep.

Neurocognitive: Neurocognitive functions are cognitive functions intimately related to the function of certain brain regions, neural pathways, or cortical networks, which are ultimately supported by the brain's neurological matrix (Cohen Kadosh et al., 2021).

Fetus: A human or other mammal's offspring in the stages of prenatal development that follow the embryonic stage.

Pregnancy: is the period during which one or more embryos develop inside a woman's uterus (Fleischman, Oinuma & Clark, 2010).

Literature Review

Anesthesia practitioners are preoccupied with the potential harm that could result from giving general anesthetics to the developing brains of infants and pregnant women. This injury may result in learning delays, long-term memory problems, and impaired spatial identification. In utero, the growing brain typically undergoes neuroapoptosis, which is defined as the natural, controlled death of brain-forming cells.

Development of Fetal Brain

The brain is the most complicated of all human organ systems. It consists of more than 100 billion information-processing cells called neurons (Stiles & Jernigan, 2010). Neurogenesis is the process of creating new neurons. Large networks of these cells are responsible for thoughts, emotions, behaviors, and sensations. Early in fetal development, brain tissue is derived from the ectoderm, which begins as a neural plate on day 16 of gestation and produces a neural tube by day 21. The neural tube divides into three distinct regions: the forebrain, the midbrain, and the hindbrain. In the seventh week of development, the brain undergoes encephalization, a process that increases the brain's size and capability. The majority of brain development happens during the prenatal period; by the third trimester, the brain will enlarge by 260%. Between the third trimester to the age of three, the human brain develops rapidly. Neurogenesis will

continue in the postnatal period, albeit to a considerably smaller extent than before birth (Lippert & Brüning, 2021). Every minute, approximately 250,000 neurons are created and connected via synapses, a process known as synaptogenesis. There are an estimated 60 trillion neural connections in adults.

Synaptogenesis, neurogenesis, and gliogenesis are physiological processes that allow neurons to mature and differentiate. Synaptogenesis is dependent on continuous neural signaling, communication, and feedback processing in order to establish meaningful neuronal connections. There is an overproduction of neurons, synapses, glial cells, and neurological processes during various stages of development. Neurons that are redundant or have no function are eliminated through neuroapoptosis (Singh, 2022).

In order for these brain development physiologic processes to occur, it is necessary that the mother receives an adequate diet. Adequate vitamin and mineral intake promote healthy brain development (Khayat, Fanaei & Ghanbarzehi, 2017). Iron plays a role in baby neuronal myelination and the development of the frontal cortex. The use of vitamin B12, which is needed for neurologic and sensory development, is another great example. A malnourished mother may give birth to children with a smaller head size and lower brain weight, which can contribute to a negative neurodevelopmental result.

During development, the brain is also vulnerable to external stimuli from the outside world. The cognitive and motor skills of a child born to a woman who has been exposed to lead, mercury, and radiation may be impaired. Particularly, lead is known to harm growing neurons. Nicotine, alcohol, and cocaine used by the mother can be neurotoxic to the developing fetus, resulting in a lower IQ, developmental delays, and growth retardation.

Excessive alcohol use by the mother can result in fetal alcohol syndrome in the newborn, which is characterized by several problems that cause intellectual and behavioral deficits. These conditions are known as fetal alcohol spectrum diseases and are characterized by a wide range of teratogenic and psychological problems that, depending on the quantity of alcohol use, can result in non-hereditary mental impairments (Hoyme et al., 2016). Even moderate alcohol consumption during pregnancy has been linked to cognitive and behavioral problems. Negatively impacting neuronal and central nervous system development in utero, these problems include mood disorders, aggressiveness, and addictive behaviour.

The developing brain of the fetus is seen to be extremely fragile. It is subject to numerous external stimuli and requires a healthy diet from the mother. Neurotoxicity of the brain can result from exposure to teratogens such as medicines, environmental pollutants, and alcohol, leading to aberrant neuronal development and later cognitive impairments.

Anesthesia

Anesthesia is described as the insensitivity to pain that is artificially created by the administration of gases or injectable medications prior to surgical procedures. Greek philosopher Dioscorides coined the term anesthesia to describe the narcotic-like effects of the mandragora plant. Oliver Wendell Holmes later used the term to describe a state of amnesia, analgesia, and narcosis that made painless surgery possible (Tranquill & Grimm, 2015). General anesthesia is a combination of many forms of anesthetics, including inhalation and intravenous anesthetics. General anesthesia utilizes a mix of medications to induce unconsciousness. The combination of medications induces muscular relaxation, analgesia, and forgetfulness to allow patients to endure surgical operations safely and successfully.

Inhalation agents

Prior to the advent of the hypodermic needle, inhalation anesthesia was the first type of anesthetic used for surgery in the nineteenth century. In 1846, WTG Morton showed diethyl ether as the first general anesthetic (Butterworth et al., 2014). Diethyl ether is the precursor to volatile inhalation anesthetics such nitrous oxide, sevoflurane, desflurane, and isoflurane. These current gases are liquid at normal temperature, making them easy to transport and relatively inexpensive to produce (DeGrange, 2019). These liquids evaporate rapidly with the use of a vaporizer, making them excellent for use as an anesthetic gas. All volatile inhalants act on inhibitory neurotransmitters in the brain known as GABAA receptors (Garcia, Kolesky, & Jenkins, 2010). Nitrous oxide is a non-volatile anesthetic gas that is kept and supplied from a gas cylinder and is commonly referred to as "laughing gas." Compared to other inhalation anesthetics, nitrous oxide differs in that it operates on NMDA receptors.

Intravenous agents

As the science of anesthesia has advanced, novel methods of administration have also emerged. In 1872, Pierre Ore' proposed the use of intravenous drugs as a sort of anesthesia utilizing the sedative Chloral Hydrate. Drugs such as morphine, barbiturates, and sedatives/hypnotics are utilised in numerous anesthetic-required procedures nowadays. These medications may be administered alone or in conjunction with inhalants as part of general anesthesia (Robinson & Toledo, 2012).

Propofol is one of the most often used hypnotic intravenous anesthetics. When administered for sedation, Propofol possesses amnestic characteristics. Its primary effect on the brain is on GABAA, a crucial neurotransmitter for neurodevelopment. Propofol interacts with the major inhibitory neurotransmitter in the brain, GABAA, to induce dissociation, resulting in unconsciousness and retrograde amnesia (Lee et al., 2015). It has been discovered that

intravenous anesthetic drugs, such as Propofol, have negative effects on the growing brains of animals. Certain intravenous anesthetics may modify GABA receptors in developing fetuses' and children, putting them at risk for neurodegenerative alterations, according to some research.

General Anesthesia and Neurodevelopment

Extensive research over the past three decades has uncovered disturbing consequences of general anesthetics on the developing brain. In diverse species (from nematodes to nonhuman primates), these impacts include neuronal and glial damage, functional abnormalities in neural communications, and long-lasting socioaffective and cognitive deficiencies. Given that the bulk of currently used general anesthetics are known to be harmful to a very young brain, the most pressing priority has been the development of neurotoxic-free, safe general anesthetics.

Numerous preclinical studies (Maksimovic et al., 2022) suggest that the mammalian brain is at its most vulnerable during the intense period of synaptogenesis, when trillions of neuronal synapses are being formed and the neurons actively migrate to their final destination while connecting and maturing, thereby forming a complex and robust network known as neuronal circuitries, which are crucial for proper behavioral and cognitive development. Notably, synaptogenesis depends on the timely maturation and proliferation of glial cells, which provide a nurturing environment and thus set the stage for developing synaptogenesis. The species of rodents (mice and rats) have been utilised most frequently in published preclinical investigations. Their synaptogenesis is mostly a postnatal occurrence that lasts around three weeks, with a peak around postnatal day 7, which has been frequently documented as the most vulnerable time period for general-anesthesia-induced developmental neurotoxicity. It is crucial to note that synaptogenesis in humans, despite being diverse among brain regions, begins during fetal development and reaches its peak by the second year after birth.

Significant neuronal death during this critical period has been shown to result in long-lasting disruptions in neuronal synaptic communications within the remaining neuronal networks, which are thought to be, at least in part, the functional correlates of cognitive, affective, and motor deficits observed later in life. Concerning is the rapidly expanding body of clinical evidence indicating that early exposure to general anesthetics appears to have negative consequences on adolescent behavioral performance, which is not surprising in light of accumulating animal research (e.g., learning disabilities, attention deficit disorders, poor school performance, socioaffective impairments, etc.). A few years ago, the U.S. Food and Drug Administration released a Drug and Safety Communication regarding the potential risk of neurodevelopmental deficits in infants prenatally or postnatally exposed to repeated or protracted general anesthesia (McCann & Soriano, 2019). This was done to keep the public informed. Although the necessity to provide comfort during painful procedures is indisputable, the struggle to ensure that we do not cause harm to our youngest patient population throughout crucial periods of brain development continues to be our top priority.

Neuronal network impairment caused by early general anesthesia exposure of the developing brain

Although our initial efforts in the field of developmental neurotoxicity were focused on examining the nature of easily detectable morphological changes using histological assessments, we discovered that the general-anesthesia-induced impairment of synaptogenesis is multifaceted, and that seemingly subtle changes that cannot be detected morphologically remain in surviving 'normal' neurons after the grossly damaged neurons have been removed. Based on current findings, these neurons may not be fully functioning; that is, their transmissions may be flawed.

We originally discovered that early general anesthesia induces long-term impairment in synaptic transmission in the hippocampus of adolescent rats (postnatal days 27-33) subjected to anesthesia during the peak of synaptogenesis (postnatal day 7). Despite the presence of robust short-term potentiation, long-term potentiation was significantly hindered (Jevtovic-Todorovic,). This finding showed a long-term disruption in neuronal circuitries in the developing hippocampus, a brain region critical for appropriate learning and memory formation. Synaptic transmission was investigated utilizing patch-clamp recordings of evoked inhibitory postsynaptic current (eIPSC) and evoked excitatory postsynaptic current (eEPSC) from the pyramidal layer of control and anesthesia-treated rat subiculum, a key component of the hippocampus complex. Again, anesthesia-treated rats had decreased synaptic transmission, with inhibitory transmission being considerably disrupted.

Y-aminobutyric acid (GABA) and N-methyl-D-aspartate are two important neurotransmitter systems in the developing brain that are modulated by the general anaesthetics often employed in clinical settings (NMDA). Historically, general anaesthetics were regarded as "muddy players" in terms of their capacity to interfere with the existing milieu of brain receptors (Hua, 2020). They have a great potential to temporarily block communication in the central nervous system due to their promiscuity. This inhibition is maintained via inhibiting glutamatergic NMDA receptors and/or enhancing chloride inflow via interaction with GABA receptors, according to the hypothesis. While the initial understanding of excessive excitation via NMDA receptors revealed an increase in cell death, subsequent research confirmed that suppression of glutamate inflow via these receptors was equally deleterious. This behaviour was noticed after ketamine, a common intravenous general anesthetic, was administered. Moreover, propofol in conjunction with the majority of volatile drugs (e.g., sevoflurane, isoflurane, etc.) increases the sensitivity of GABA

receptors, hence amplifying the input of chloride within neurons and inhibiting further transmission. Although the molecular mechanisms of general anaesthetics are not fully understood, the data suggests that unphysiological regulation of these two neurotransmitter systems leads in widespread neurotoxicity during synaptogenesis. Recent research indicates that these deleterious effects may be transgenerational via epigenetic modification of the epigenome, indicating that the effects of general anaesthetics are not only long-lasting, but may also be ingrained in the genome, allowing for transgenerational impairments in offspring never exposed to general anaesthetics. Taking this information into account, we and others have been exerting tremendous effort to identify new molecular targets that could lead the creation of innovative, pediatric-safe general anaesthetics.

Methodology

Information sources and research technique

The following search terms were entered into PubMed, EMBASE, and Web of Science: anesthesia, during pregnancy, embryo/fetus/newborn, and neurological outcome (Supplementary material). In consultation with an expert biomedical librarian, for each topic, pertinent synonyms and subcategories were added.

Eligibility criteria

Studies examining the effects of general anesthesia during pregnancy on the fetal brain development of humans or other mammals were admissible, regardless of the anaesthetics, so long as it was approved for use in humans. Also admissible were studies investigating neuroprotective methods. A group without anesthesia (to assess neurotoxicity) or a group with anesthesia served as the comparison group (neuroprotective strategies). Eligible studies included (pre)clinical interventional and clinical observational research. From the inception of the databases until April 2020, articles could be incorporated.

Exclusion criteria included in vitro models, chronic exposure, exposure solely during delivery, case reports, abstracts, and languages besides English, French, Dutch, and German. When there were confounding factors (such as purposeful hypoxia) or when outcome characteristics were not directly connected to brain development, studies were discarded.

Results

Learning and memory were evaluated in 44 (68%) of the trials. The Morris water maze test was utilised the most, followed by the radial arm maze test.

In 48 (74%) trials, neuronal damage was analyzed. Histology and immunoblotting of biomarkers were the most prevalent methods employed to assess neuronal damage.

For rats, mice, and non-human primates, meta-analyses revealed substantial impairments in at least one outcome parameter per species (e.g., neurone density for rats: 1.07, learning and memory for mice: 1.03, and apoptosis for non-human primates: 2.20. In a meta-analysis of three investigations involving sheep, no impairments were detected. Since there was just one rabbit study and one guinea pig study, no meta-analysis could be done for these species.

The most often studied anaesthetic was sevoflurane, followed by isoflurane, ketamine, Propofol, halothane, nitrous oxide, enflurane, and desflurane. At least one outcome parameter was significantly impaired by sevoflurane, isoflurane, ketamine, and Propofol, according to meta-analyses (e.g., proliferation for sevoflurane: 2.86, learning and memory for isoflurane: 0.96, neurone density for ketamine: 1.28, and Due to the small number of studies, no meta-analyses could be done for halothane, nitrous oxide, enflurane, and desflurane.

In 62 (95%) of the publications, anaesthesia was administered without surgical stimulation. l, halothane, nitrous oxide, enflurane, and desflurane. Significant imp (Zou, et al., 2020; Olutoye et al., 2019; Van der Veeken et al., 2019) was observed when surgery was performed under anaesthesia, allowing just apoptosis to be included in a meta-analysis that revealed no adverse effects (1.31).

In the majority of research, pregnant animals were subjected to anaesthesia during the second trimester (49 studies), followed by the third (12 studies) and the first (4) trimesters. Meta-analyses revealed significant impairments for all outcome parameters in all trimesters, with the exception of learning and memory in the third trimester (learning and memory in the first trimester: 2.07, synapse formation in the second trimester: 1.00, or apoptosis in the third trimester: 1.25.

Discussion

Regardless of the anaesthetics medication or gestational age, fetal exposure to general anesthesia resulted in decreased learning and memory, neuronal damage, or both in various experimental animal species. However, the majority of tests were performed under general anesthesia without concurrent surgical intervention, which is a setting rarely encountered in clinical anesthesia. For VI anaesthetics, these effects were only recorded following exposure to >1 MAC, lasting >3 h, or several administrations. Neurotoxicity was seen at lower doses/duration/frequency for intravenous anaesthetics. In addition, the administration of anesthesia and monitoring were frequently below preclinical standards and well below those typically applied in the clinic. Dexmedetomidine mitigated neurotoxicity generated by anesthesia.

It would be necessary to use animal species with a brain development equal to that of humans, making rodents unsuitable. Due to the availability of established neurobehavioral tests, similar brain histology, and substantial knowledge of molecular pathways, rodents are frequently utilised. (Chinn et al., 2020) However, the brain growth surge in which the brain is at its most sensitive to external stimuli (such as anaesthesia) occurs perinatally in humans but postnatally in rodents (Rizzi et al., 2010). In contrast, the brains of guinea pigs, lambs, and non-human primates develop prenatally. (Li, et al., 2007; Clancy et al., 2007; Workman et al., 2013). In order to adapt findings from animal trials to humans, it would be more appropriate to explore the effects of anaesthesia on fetal brain development in species whose brains develop during the perinatal period, such as rabbits or pigs. However, we located only one study in rabbits (Van der Veeken et al., 2019) and none in pigs.

In every study but three, animals were subjected to a surgical degree of general anesthesia without surgical stimulation. In actuality, pregnant women are subjected to anesthesia nearly solely to facilitate surgery (with the exception of ICU sedation conditions) (Devroe, et al., 2019).

Positive pressure ventilation and conventional ASA monitoring are commonly utilised in pregnant women, but were used in just a minority of research. This is likely due to the fact that the majority of studies used rats, for which these procedures are impractical. Similarly, monitoring standards for preclinical research were adhered to in only roughly half of the investigations. Isoflurane induces respiratory depression leading to hypoxemia, hypercarbia, or both, both of which can trigger apoptosis and decrease neurocognitive performance. (Stratmann et al., 2009; Floyd et al., 2020; Samaiya et al., 2016) Positive pressure breathing lowers apoptosis and improves neurocognitive prognosis. (Wu et al., 2014) In a number of the included trials, it is impossible to determine whether the observed neuronal damage was the direct result of the anaesthetic or the indirect result of respiratory depression.

Low exposure to IV anaesthetics was observed to result in neurological abnormalities, but only excessive exposure to volatile anaesthetics impacted neurological outcome. Notably, intravenous anaesthetics were provided at sedative doses, whereas volatile anaesthetics were administered at doses that produced surgical levels of general anaesthesia. Therefore, intravenous anaesthetics may be more detrimental to the brain than volatile anaesthetics. In contrast, two investigations that directly compared volatile and intravenous anaesthetics (at comparable depths of anaesthesia) concluded that Propofol was safer than isoflurane. (Creeley e al., 2013; Gluncic et al., 2019) The causes of these contradictory observations are simply conjectural. When volatile anaesthetics are inhaled spontaneously, there may be some degree of "autoregulation" of the depth of anaesthesia (a negative feedback mechanism with the animal stopping inhalation and limiting further uptake of anaesthetics when levels of anaesthesia become too deep). (Gibbons, Steffey & Eger, 1977) This mechanism is not present for intravenous anaesthetics. Therefore, it is possible that IV anaesthetics caused a more pronounced respiratory depression. In research utilizing IV anaesthetics, less monitoring was conducted than with volatile anaesthetics, hence this went unnoticed.

Conclusion

This review sought to ascertain the effects of general anesthesia on the developing brains of infants and fetuses. Anaesthetics and medicines can have a negative impact on the developing brain of children.

No matter the animal species, the type of anaesthetic used, or the point in the pregnancy at which the procedure is performed, administering anaesthesia to pregnant laboratory animals causes neuronal damage, which in turn impairs the animals' abilities to learn and remember. Notably, there is a lack of access to human data. The application of the findings from the laboratory to people is made more difficult by the presence of various confounders. The brain development of rodents, which is the animal species that is employed most often in scientific research, is markedly different from that of humans. In the majority of trials, anaesthesia was carried out in the absence of any kind of surgical stimulation. In many of the trials, the physiological monitoring and control of homeostasis fell short of the preclinical and clinical standards. The anaesthetic doses, as well as the duration and frequency of the exposure, were frequently substantially higher than what is typical in clinical practice.

References

Andropoulos, D. B. (2018). Effect of anesthesia on the developing brain: infant and fetus. Fetal diagnosis and therapy, 43(1), 1-11.

Chinn, G. A., Pearn, M. L., Vutskits, L., Mintz, C. D., Loepke, A. W., Lee, J. J., ... & Sall, J. W. (2020). Standards for preclinical research and publications in developmental anaesthetic neurotoxicity: expert opinion statement from the SmartTots preclinical working group. British journal of anaesthesia, 124(5), 585-593.

Clancy, B., Finlay, B. L., Darlington, R. B., & Anand, K. J. S. (2007). Extrapolating brain development from experimental species to humans. Neurotoxicology, 28(5), 931-937.

Cohen Kadosh, K., Muhardi, L., Parikh, P., Basso, M., Jan Mohamed, H. J., Prawitasari, T., ... & Geurts, J. M. (2021). Nutritional support of neurodevelopment and cognitive function in infants and young children—an update and novel insights. Nutrients, 13(1), 199.

Creeley, C. E. (2016). From drug-induced developmental neuroapoptosis to pediatric anesthetic neurotoxicity—where are we now? Brain sciences, 6(3), 32.

Creeley, C., Dikranian, K., Dissen, G., Martin, L., Olney, J., & Brambrink, A. (2013). Propofol-induced apoptosis of neurones and oligodendrocytes in fetal and neonatal rhesus macaque brain. British journal of anaesthesia, 110(suppl_1), i29-i38.

DeGrange, R. W. (2019). The Effect of Anesthesia on the Developing Brain.

Devroe, S., Bleeser, T., Van de Velde, M., Verbrugge, L., De Buck, F., Deprest, J., ... & Rex, S. (2019). Anesthesia for non-obstetric surgery during pregnancy in a tertiary referral center: a 16-year retrospective, matched case-control, cohort study. International Journal of Obstetric Anesthesia, 39, 74-81.

Fleischman, A. R., Oinuma, M., & Clark, S. L. (2010). Rethinking the definition of “term pregnancy”. Obstetrics & Gynecology, 116(1), 136-139.

Floyd, T. F., Khmara, K., Lamm, R., & Seidman, P. (2020). Hypoxia, hypercarbia, and mortality reporting in studies of anaesthesia-related neonatal neurodevelopmental delay in rodent models: a systematic review. European Journal of Anaesthesiology| EJA, 37(2), 70-84.

Garcia, P. S., Kolesky, S. E., & Jenkins, A. (2010). General anesthetic actions on GABAA receptors. Current neuropharmacology, 8(1), 2.

Gibbons, R. T., Steffey, E. P., & Eger 2nd, E. I. (1977). The effect of spontaneous versus controlled ventilation on the rate of rise of alveolar halothane concentration in dogs. Anesthesia and Analgesia, 56(1), 32-34.

Gluncic, V., Moric, M., Chu, Y., Hanko, V., Li, J., Lukić, I. K., ... & Tuman, K. J. (2019). In utero exposure to anesthetics alters neuronal migration pattern in developing cerebral cortex and causes postnatal behavioral deficits in rats. Cerebral Cortex, 29(12), 5285-5301.

Hoyme, H. E., Kalberg, W. O., Elliott, A. J., Blankenship, J., Buckley, D., Marais, A. S., ... & May, P. A. (2016). Updated clinical guidelines for diagnosing fetal alcohol spectrum disorders. Pediatrics, 138(2).

Hua, T. (2020). General Anesthetics Activate a Central Pain-Suppression Circuit in the Amygdala (Doctoral dissertation, Duke University).

Jeske, A. H. (2019). Local Anesthetics. In Contemporary Dental Pharmacology (pp. 9-22). Springer, Cham.

Jevtovic-Todorovic, V. (2016). General anesthetics and neurotoxicity: how much do we know? Anesthesiology clinics, 34(3), 439-451.

Khayat, S., Fanaei, H., & Ghanbarzehi, A. (2017). Minerals in pregnancy and lactation: a review article. Journal of Clinical and Diagnostic Research: JCDR, 11(9), QE01.

Lee, J. H., Zhang, J., Wei, L., & Yu, S. P. (2015). Neurodevelopmental implications of the general anesthesia in neonate and infants. Experimental neurology, 272, 50-60.

Li, X., Jiang, X., & Zhao, P. (2021). Effects of Pregnancy Anesthesia on Fetal Nervous System. Frontiers in Pharmacology, 11, 523514.

Li, Y., Liang, G., Wang, S., Meng, Q., Wang, Q., & Wei, H. (2007). Effects of fetal exposure to isoflurane on postnatal memory and learning in rats. Neuropharmacology, 53(8), 942-950.

Lippert, R. N., & Brüning, J. C. (2021). Maternal metabolic programming of the developing central nervous system: unified pathways to metabolic and psychiatric disorders. Biological Psychiatry.

Maksimovic, S., Useinovic, N., Quillinan, N., Covey, D. F., Todorovic, S. M., & Jevtovic-Todorovic, V. (2022). General Anesthesia and the Young Brain: The Importance of Novel Strategies with Alternate Mechanisms of Action. International journal of molecular sciences, 23(3), 1889.

McCann, M. E., & Soriano, S. G. (2019). Does general anesthesia affect neurodevelopment in infants and children? Bmj, 367.

Olutoye, O. A., Baker, B. W., Belfort, M. A., & Olutoye, O. O. (2018). Food and Drug Administration warning on anesthesia and brain development: implications for obstetric and fetal surgery. American Journal of Obstetrics and Gynecology, 218(1), 98-102.
Olutoye, O. A., Cruz, S. M., Akinkuotu, A. C., Sheikh, F., Zamora, I. J., Yu, L., ... & Olutoye, O. O. (2019). Fetal surgery decreases anesthesia-induced neuroapoptosis in the mid-gestational fetal ovine brain. Fetal Diagnosis and Therapy, 46(2), 111-118.
Ramirez, V., Valencia, G., & Catalina, M. (2020). Anesthesia for nonobstetric surgery in pregnancy. Clinical Obstetrics and Gynecology, 63(2), 351-363.
Rizzi, S., Ori, C., & Jevtovic-Todorovic, V. (2010). Timing versus duration: determinants of anesthesia-induced developmental apoptosis in the young mammalian brain. Annals of the New York Academy of Sciences, 1199(1), 43-51.
Robinson, D. H., & Toledo, A. H. (2012). Historical development of modern anesthesia. Journal of Investigative Surgery, 25(3), 141-149.
Samaiya, P. K., Narayan, G., Kumar, A., & Krishnamurthy, S. (2016). Neonatal anoxia leads to time dependent progression of mitochondrial linked apoptosis in rat cortex and associated long term sensorimotor deficits. International Journal of Developmental Neuroscience, 52, 55-65.
Singh, N. (2022). Long Non-Coding RNA in Neural Stem Cells Self-Renewal, Neurogenesis, Gliogenesis and Synaptogenesis. Recent Advances in Non-Coding RNAs.
Stiles, J., & Jernigan, T. L. (2010). The basics of brain development. Neuropsychology review, 20(4), 327-348.
Stratmann, G., May, L. D., Sall, J. W., Alvi, R. S., Bell, J. S., Ormerod, B. K., ... & Firouzian, A. (2009, April). Effect of hypercarbia and isoflurane on brain cell death and neurocognitive dysfunction in 7-day-old rats. In The Journal of the American Society of Anesthesiologists (Vol. 110, No. 4, pp. 849-861). The American Society of Anesthesiologists.
Tranquilli, W. J., & Grimm, K. A. (2015). Introduction: use, definitions, history, concepts, classification, and considerations for anesthesia and analgesia. Veterinary anesthesia and analgesia. 5th ed. Ames, Iowa: Wiley Blackwell, 3-10.
Van der Veeken, L., Van der Merwe, J., Devroe, S., Inversetti, A., Galgano, A., Bleeser, T., ... & Deprest, J. (2019). Maternal surgery during pregnancy has a transient adverse effect on the developing fetal rabbit brain. American Journal of Obstetrics and Gynecology, 221(4), 355-e1.
Vutskits, L., & Xie, Z. (2016). Lasting impact of general anesthesia on the brain: mechanisms and relevance. Nature Reviews Neuroscience, 17(11), 705-717.
Workman, A. D., Charvet, C. J., Clancy, B., Darlington, R. B., & Finlay, B. L. (2013). Modeling transformations of neurodevelopmental sequences across mammalian species. Journal of Neuroscience, 33(17), 7368-7383.
Wu, B., Yu, Z., You, S., Zheng, Y., Liu, J., Gao, Y., ... & Lian, Q. (2014). Physiological disturbance may contribute to neurodegeneration induced by isoflurane or sevoflurane in 14-day old rats. PloS one, 9(1), e84622.
Zou, S., Wei, Z. Z., Yue, Y., Zheng, H., Jiang, M. Q., & Wu, A. (2020). Desflurane and surgery exposure during pregnancy decrease synaptic integrity and induce functional deficits in juvenile offspring mice. Neurochemical Research, 45(2), 418-427.