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Pediatric RESEARCH

REVIEW ARTICLE

Analgesia for fetal pain during prenatal surgery: 10 years of progress

Carlo V. Bellieni[1]

Some doubts on the necessity and safety of providing analgesia to the fetus during prenatal surgery were raised 10 years ago. They were related to four matters: fetal sleep due to neuroinhibitors in fetal blood, the immaturity of the cerebral cortex, safety, and the need for fetal direct analgesia. These objections now seem obsolete. This review shows that neuroinhibitors give fetuses at most some transient sedation, but not a complete analgesia, that the cerebral cortex is not indispensable to feel pain, when subcortical structures for pain perception are present, and that maternal anesthesia seems not sufficient to anesthetize the fetus. Current drugs used for maternal analgesia pass through the placenta only partially so that they cannot guarantee a sufficient analgesia to the fetus. Extraction indices, that is, how much each analgesic drug crosses the placenta, are provided here. We here report safety guidelines for fetal direct analgesia. In conclusion, the human fetus can feel pain when it undergoes surgical interventions and direct analgesia must be provided to it.

Pediatric Research (2021) 89:1612–1618; https://doi.org/10.1038/s41390-020-01170-2

IMPACT:

- Fetal pain is evident in the second half of pregnancy.
- Progress in the physiology of fetal pain, which is reviewed in this report, supports the notion that the fetus reacts to painful interventions during fetal surgery.
- Evidence here reported shows that it is an error to believe that the fetus is in a continuous and unchanging state of sedation and analgesia.
- Data are given that disclose that drugs used for maternal analgesia cross the placenta only partially, so that they cannot guarantee a sufficient analgesia to the fetus.
- Safety guidelines are given for fetal direct analgesia.

INTRODUCTION

Exactly 10 years ago, the Royal College of Obstetrics and Gynecology released an outstanding report on fetal awareness,[1] based on previous works.[2] This report concluded that the fetus cannot experience pain in any sense prior to 24 weeks of gestation. Neither after this epoch, the authors write, fetuses can feel any pain, because they are constantly in a state of sedation. Thus, they concluded, "fetal analgesia should not be employed where the only consideration is concern about fetal awareness or pain."[1]

This report excluded the possibility of fetal pain on three main bases: (a) the need of complete thalamocortical connections to feel pain, (b) the presence in fetal blood of neuroinhibitors capable to anesthetize the fetus, and (c) the nonarousablility of fetuses from sleep with any stimulation. The authors also ruled out that fetuses feel pain during potentially painful in-womb surgery, because "Open uterine surgery on the fetus is extremely unusual," and "these procedures are performed under maternal general anesthesia, the fetus is also anaesthetized as a result of transplacental passage of the high concentrations of volatile agents given to the mother." Nonetheless, this report could not predict the relevant progress of fetal surgery in the following years, and that much evidence would have shown that fetal anesthetics are not enough to overcome fetal pain.

This report has been a sort of guideline for a decade, during which fetal surgery has soared as never before (Fig. 1). Meanwhile, several papers have analyzed the issue of fetal pain, and the data they gathered have led the authors to admit the possibility of fetal pain in the second half of the pregnancy and the evidence of fetal pain in the third trimester on the basis of fetal neurologic maturity of pain pathways.[3–12] Recently, Stuart Derbyshire, one of the most prominent researchers in this field, who had always excluded the eventuality of fetal pain,[13,14] has changed his conclusions, due to the new evidence: "Overall, the evidence, and a balanced reading of that evidence, points towards an immediate and unreflective pain experience mediated by the developing function of the nervous system from as early as 12 weeks. That moment is not categorical, (…) Nevertheless, we no longer view fetal pain (as a core, immediate, sensation) in a gestational window of 12–24 weeks as impossible based on the neuroscience."[10]

The first aim of this review is to focus on whether a fetus can feel pain and when. The second aim is to assess if current fetal analgesia is safe and effective, and if it either should be directly administered to the fetus, or if current anesthetic doses provided to the pregnant woman are sufficient.

[1]Neonatal Intensive Care Unit, University Hospital, Viale M Bracci, 53100 Siena, Italy
Correspondence: Carlo V. Bellieni (cvbellieni@gmail.com)

Received: 11 February 2020 Revised: 26 August 2020 Accepted: 26 August 2020
Published online: 24 September 2020

FETAL NOCICEPTIVE PATHWAYS

The first necessary requirement for pain perception is the presence and activation of nociceptors. These organs appear in the skin of the human fetus in an epoch between 10 and 17 weeks of gestational age (GA).[15] From 6 weeks of GA, nerve terminals that have already formed synapses with the spinal cord are present in the skin of the human fetus,[16] but they are fibers for the sensation of touch, not for the determination of temperature or pain.[17,18] The nerve terminals appear in the internal organs later than on the skin, that is, from 13 weeks of GA;[19] for example, the pancreas will only have them around 20 weeks of GA.[20] Myelination of nerve fibers begins between 12 and 14 weeks of GA.[21] The appearance of neuromediators is also precocious: substance P appears at 10–12 weeks of GA and enkephalins at 12–14 weeks of GA.[22] Opioid production begins in the brain around the 20th week of GA.[23] The spinothalamic tract for the conduction of touch and pain stimuli and the mesodiencephalon with the thalamus are present since the 15th week of GA.[24] The thalamus is the gateway to the cerebral cortex; it is sufficiently developed at 17 weeks of GA. All cortical-bound somatosensory inputs relay through the thalamus. One major group of these somatosensory inputs is the nociceptive input. The thalamus appears to be the essential organ of the affective side of our sensation, especially pain.[25] The pivotal importance of the thalamus and diencephalic structures in fetal pain is highlighted by several authors: "Bearing in mind the dominant role of the reticular formation of the brain stem, which is marked by a wide divergence of afferent information, a sense of pain transmitted through it is diffuse and can dominate the overall perception of the fetus."[26]

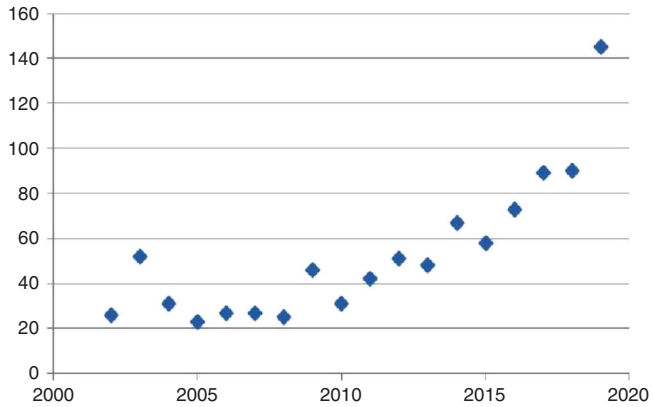

Fig. 1 Fetal surgery: number of clinical studies per year. Data are retrieved from the PubMed database.

The amygdala, the processing center for emotional stimuli and anxiety, is present toward the middle of gestation.[27] The thalamocortical fibers appear in the second half of pregnancy at 23–30 weeks of GA, but already in the previous period, they reach the subplate.[28] The subplate is a transition structure of the cerebral cortex to which the projection fibers from the thalamus arrive.[29] It is a transitory but active and functioning station, where the fibers arrive waiting to find a mature cerebral cortex; it is present between 10 and 35 weeks of GA.[30] Then it disappears. Recent work with ferrets has shown that auditory stimuli trigger a neural activity in the subplate, which is topographically very similar to the activity observed in the more mature auditory cortex.[31]

Between 24 and 32 weeks of GA, the cortical thalamus fibers begin to colonize the cortex, increasing this colonization after 34 weeks of GA[30–32] (Fig. 2). The process of formation of the neocortex begins in the first trimester of pregnancy: the neurons that will form it migrate from the periventricular area to the periphery and the first cortical fold begins to form. The insula, one of the main centers for the perception of pain, begins to form between these folds.[33] For some scholars, the presence of the cortex is essential for the conscious perception of pain, while for others it is not.[34] Several papers have now been published, suggesting that the necessity of the cortex for pain experience may have been overstated;[35–38] even in hydranencephalic children, that is, with almost total absence of the cortex, it is possible to receive visual information,[39,40] and the responses to noxious stimulation of children with hydranencephaly are purposeful, coordinated, and similar to those of intact children.[41,42]

Toward mid-pregnancy, the human fetus responds to external stimuli, and in particular to those that are potentially stressful or painful with body movements,[43] facial mimicry,[44–46] and hormonal production.[47] The fetus in the second half of pregnancy, in reaction to a potentially painful stimulus, produces stress hormones. After a potentially painful stimulus (a puncture in the suprahepatic vein), an increase in blood cortisol and adrenaline was seen in fetuses of 16–25 weeks of GA, which was not found in the control fetus group;[48,49] by administering fentanyl to the fetus before the puncture, the increase in these hormones is significantly reduced.[50]

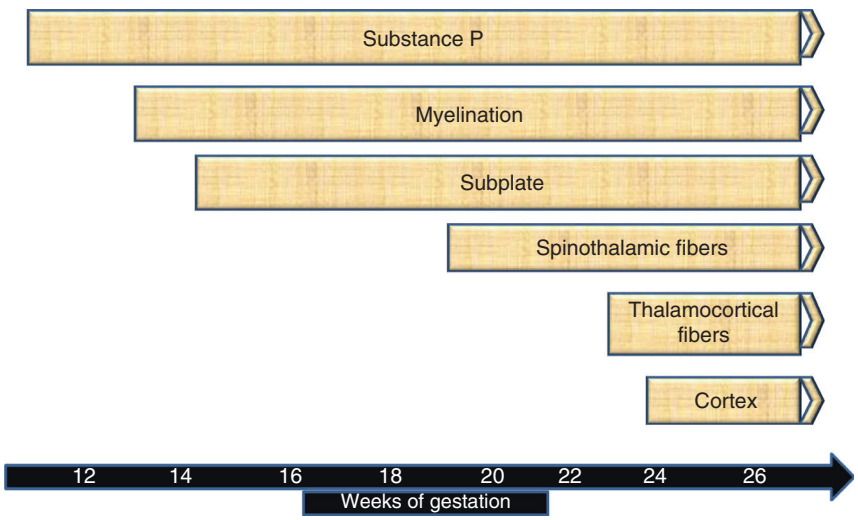

Fig. 2 Fetal pain. Age of appearance of the main brain structures related to pain sentience.

FETUSES ARE NOT IN A STATE OF CONTINUOUS INVARIABLE SLEEP

Human fetuses have a rich repertoire of general movements, which turn into more coordinated responses to stimuli after 26 weeks of EG. Many data suggest that these movements indicate the differentiation of fetal behavior in various states.[44,51] Prechtl described fetal behavioral states, named them from F1 to F5, analogous to those of the newborn, and his seminal descriptions are still valid.[44] To the aims of this review, it is noteworthy that the behavioral states F3 (calm wake), F4 (active wake), and the state F5 (crying) are present in human fetuses[52,53] and are easily detectable with the joint evaluation of body movements, the regularity of the breath, and eye movements measurable with fetal ultrasound. Using ultrasounds, it was possible to see that human fetuses show well-established sleep–wake states at the end of pregnancy, spending time that varies between 9 and 20% in active wakefulness[54] and that it can be woken up with appropriate stimuli.[55–63] Fetuses between 30 and 40 weeks have wide variations in the percentage of time spent in sleep–wake states,[55] and refined methods of coding fetal facial movements allow to identify the progression of increasingly complex facial movements in utero, as well as the formation of the fetal facial pain/distress gestalt.[64] A startle reaction is easily provoked in healthy fetuses after a sudden external noise.[65] Stone et al.[66] recently correlated the presence of fetal active wake state with the sleep posture of the mother, and fetal behavioral states, including active wake, have been described to influence its autonomic activity.[67] In prematurely born fetuses, it is possible to record the waking state from the 30th week of GA via electroencephalogram (EEG),[68] and the somatosensory evoked potentials are recordable at 26–28 weeks of GA.[69] Fetal magnetoencephalography has shown positive responses since the 27th week of GA, and with functional magnetic resonance imaging, the activation of the fetal brain to sounds at 33 weeks of GA has been seen.[70] Fetuses respond with movements and facial expressions to external stimuli and in particular to music:[71,72] this is not compatible with the deep and irreversible state of sleep.

FETUSES ARE NOT ANESTHETIZED BY THEIR BLOOD NEUROINHIBITORS

Some substances with neuroinhibiting activity in the fetal blood have been hypothesized to be sufficient to anesthetize the fetus.[2] In reality, these substances keep the fetus in a state of continuous sleep, which is defined in the RCGO (Royal College of Obstetricians and Gynaecologists) report as "sedation," but this is different from anesthesia. In fact, anesthesia implies immobility (lack of movements to pain), amnesia, and hypnosis (defined as lack of perceptional awareness), while sedation is just a state of more or less deep sleep that can be reversed by noxious or stressful stimuli. This would be sufficient to remove any doubt. But even sedation and sleep are not continuous in the fetus, despite these neuroinhibitors. These substances are adenosine, progesterone, allopregnenolone, pregnenolone, and prostaglandin D2 (PGD2). No molecular targets involved in anesthesia have been identified in neuroinhibition of the fetus. Adenosine is a purinergic messenger, which regulates many physiological processes in excitable tissues, particularly in the brain. PGD2 is a hormone that induces sleep through the release of adenosine and the consequent GABAergic inhibition of wakeful neurons. Pregnenolone and allopregnenolone also have an analgesic effect: they increase the activity of the inhibitory pathways of GABA in the central nervous system. Progesterone and its metabolites are strongly implicated as inhibitors of fetal EEG activity and behavior. Some[1,2] claimed that these substances are present in fetal blood in greater concentration than in maternal blood, producing fetal sedation. Nonetheless, the fetus can skip from sleep to wake (see the previous section) at least in the third trimester of pregnancy, and "sedation" does not mean that the subject is insensitive to pain at that stage; the effect of a sedative substance, such as benzodiazepines or barbiturates, is very different from an anesthetic substance. These two observations downsize the possibility of a pain-relieving effect of the aforementioned neuroinhibitors. But there is more: the neuronal inhibitory effects of both adenosine and PGD2 were recorded after being artificially administered in the brains of the test animals and, also in this case, the effect of these substances was not analgesic but only sedative;[73] the anesthetic effect of pregnenolone is observed only if "injected in high doses that result in high blood levels (2 µg/ml),[74] far higher than those present in physiological fetal blood (0.5 µg/ml)."[75]

We must also underline another evidence: several neuroinhibiting substances are found in fetal blood at levels equal to, if not lower than, the concentration of the same substances in the blood of the pregnant woman, which is certainly neither sedated nor anesthetized by their presence. A pregnant woman's blood pregnenolone is higher than blood fetal pregnenolone, but the opposite is true for allopregnenolone.[76] Allopregnenolone blood levels are similar in maternal and fetal blood,[77] while pregnenolone sulfate values are much higher in fetal blood,[77] but its isomers appear at similar levels in maternal and fetal blood.[78] Adenosine levels are higher in normal fetuses than in the blood of uncomplicated pregnant women,[79] but in women with hyperemesis gravidarum, it is much higher than in fetal blood.[80] We have no data on fetal blood concentration in pregnancy with regard to prostaglandins; however, the concentration of PGD2 synthase in human amniotic fluid increases during the gestational weeks 12–25, and decreases slowly until the end,[81] with the effects of a possible increase, but then a decrease in the synthesis of PG. The average progesterone concentration is twice as high in fetuses than in mothers,[76] but also in preeclamptic mothers, progesterone is twice the basic level they had before pregnancy.[82] Thus, the fetuses have an increase in blood values of some of these neuroinhibitors compared to the basic level of a healthy woman, but these values are similar to those of women with the above pathologic states, who certainly will not be anesthetized: the logic follows that the fetus will neither be sedated nor anesthetized by these levels of circulating hormone.

MATERNAL ANESTHESIA IS NOT SUFFICIENT TO GUARANTEE FETAL ANESTHESIA

The anesthesia that women receive for fetal surgery is not sufficient to anesthetize the fetus. One hint is the fact that fetuses born by cesarean section performed under general anesthesia of the mother are born in a waking state, and only in some cases in moderate sedation, but never anesthetized: tactile stimuli at birth are enough to awaken them. Nonetheless, one might say that maternal anesthesia provided to the mother for cesarean section is limited in an amount to minimize the exposure of the fetus, for a short surgery. More evidence is needed, and here it is described.

Anesthetic drugs given to the mother

These drugs can arrive to the fetus, but, while the glomerular filtration rate and hepatic metabolism of the drug are reduced and the drug half-life are prolonged, the placenta filters many drugs that cannot arrive to the fetus in sufficient amounts. Moreover, the placenta expresses some metabolic enzymes, inducing an increase in the metabolism of drugs such as dexamethasone[83] or remifentanyl.[84] For each drug, passive placental transfer depends on the fat solubility, the charge, the molecular weigh, and the concentration gradient across the membranes. The fetal/maternal (F/M) ratio, also known as extraction index, is used to study placental transfer for a given drug. Usually, drugs that cross the blood–brain barrier cross the placenta. Transfer of the placental drug is also influenced by changes in the acid–base state of the

mother and/or fetus; this is known as fetal ion trapping and its clinical relevance is unclear. For example, lidocaine is a weak base that increases in fetal blood in the case of acidosis, leading to fetal toxicity;[85] however, lidocaine is not used for anesthesia in prenatal surgery, and fetuses who undergo surgery have usually no acidosis. Placental transfer of muscle relaxants is also very low, with a fetal concentration ~10–20% of the maternal plasma concentration.[86] Furthermore, maternal anesthetics arrive to the fetus in an insufficient amount, so that doses potentially lethal for the mother should be given to anesthetize the fetus: because the fetal/maternal blood ratio of most anesthetics is low.

While some agents like morphine are not ideal, others, for example, remifentanil are highly lipophilic, they readily cross the placenta so that they can be given maternally, are readily metabolized by the placenta, and can provide fetal analgesia. Remifentanyl has been used to provide fetal immobilization and analgesia when fetal surgery is performed under regional anesthesia, for example, EXIT procedures.[87]

Halothane, isoflurane, and sevoflurane extraction index is 0.78, 0.71, and 0.38, respectively;[86] that of propofol ranges from 0.5 to 0.8;[88] maternal blood concentrations of propofol are 14 times higher than in fetal blood after 5 min after the infusion and twice higher after 180 min.[88] Morphine and fentanyl extraction index is 0.6 and 0.5, respectively.[89–92] Morphine concentration in fetal blood after intrathecal anesthesia given to the mother is almost undetectable,[92] and this is particularly important, since most prenatal surgery is not performed in general maternal anesthesia, but spinal maternal anesthesia is preferred. For fetal procedures such as EXIT technique, where the fetus is partially delivered but not separated from the placenta when operated, and in fetal blood transfusions, fetal direct analgesia is required.[93]

Anesthetic drugs given to the fetus

Fetal direct anesthesia seems correct because in many cases, fetal surgery is performed by giving the mother a spinal anesthesia and not a general anesthesia. In 2012, fetal direct analgesia was provided in about a third of cases of prenatal surgery,[94] but several studies report that anesthesia to the fetus is now a widespread and accepted practice.[95–100] Obviously, if the surgery takes place on the placenta or on the umbilical cord, both organs not innervated by nociceptors, fetal analgesia is not necessary.

Some researchers recommend that 20 µg/kg of intramuscular fentanyl be administered to the fetus before the procedure,[94] while others recommend that a continuous infusion rate of remifentanil 0.1 µg kg^{-1} min^{-1} be administered to the mother to obtain the fetal immobilization and maternal sedation, although they do not exclude the direct administration of analgesics to the fetus.[101] Some researchers have used intra-amniotic opioids for fetal analgesia on lamb fetuses,[102,103] and have shown that higher plasma concentrations of opioids have been obtained in the fetal lamb than in their mother sheep, suggesting that this pathway could be used for humans. Van de Velde and De Buck[95] as well as Pelizzo[104] have provided useful schemes for the administration of analgesics to the mother and fetus during surgery. Adverse effects on fetuses or mothers due to fetal analgesia have rarely been reported.[105]

Safety and risks of analgesic drugs for the fetus

A clear knowledge of the risks of analgesic drugs for the fetus is necessary, to understand if the risk is such as to discourage their use. Let us examine recent studies that have assessed their teratogenicity and impact on synaptogenesis.

Teratogenicity

Administering opioids in high doses to rat fetuses can induce malformations in the skeleton and central nervous system; but when opioids such as morphine or sufentanil were administered at relevant concentrations through a mini osmotic pump in pregnant rat females, the defects in the birth were no longer observed.[85] In human studies, no evidence supports a teratogenic effect of opioids. Several retrospective human studies have reported an increased rate of cleft palate in infants exposed to diazepam during the first trimester of pregnancy. Subsequently, a prospective cohort study did not find a significant association between benzodiazepine therapy and cleft palate.[106] Finally, no evidence suggests that a single dose of benzodiazepine for induction of anesthesia is harmful to the fetus. The teratogenicity of muscle relaxants was explored in the rat, but growth restriction and skeletal abnormalities were observed only at concentrations 30 times higher than those found in clinical practice.[85]

Nitrous oxide is considered a weak teratogenic agent in rats and mice, but the negative effects are observed in animals only after prolonged exposure to high concentrations that are unlikely to occur in humans under anesthesia and reversed by its combination with halogenation.[107] In conclusion, although some anesthetic agents are teratogenic in animal studies under specific conditions, no anesthetic drug has been shown to be teratogenic in humans.

Neurologic risks

In recent years, warnings have been launched about studies showing accelerated neuronal apoptosis associated with abnormal behavior in immature rodents exposed to anesthetic agents, such as propofol,[108] sevoflurane,[109] or isoflurane.[110] However, the extrapolation of the results from animal studies to the human brain is questionable, since brain development and synaptogenesis differ between species.[111,112] Furthermore, in 2016, the United States Food and Drug Administration (FDA) issued a warning that "repeated or prolonged use (>3 h) of general anesthetic drugs and sedation during surgery or procedures in children under the age of 3 years or pregnant women during their third trimester can affect children's brain development."[113] The drugs involved belong to two main classes of anesthetic agents: gamma-aminobutyric acid receptor agonists (inhalation anesthetics isoflurane, sevoflurane, and desflurane, benzodiazepines, in particular, midazolam, and the sedative–hypnotic agent propofol) and *N*-methyl D-aspartate antagonists (e.g., ketamine). Based on the recent FDA announcement, the usefulness or need for fetal interventions that inevitably involves exposure of the fetus to general intravenous or inhalation anesthetics has been questioned: fetal surgery has been shown to be surely useful for some anomalies (myelomeningocele and twin-to-twin transfusion syndrome),[114] while less unanimous are the evidences for the advantages of other in utero procedures, such as fetal tracheal occlusion for congenital diaphragmatic hernia.[115] Long-lasting administrations of anesthetics in pregnant women are fortunately a rare situation. In fetal procedures that require only sedation, that is, fetoscopic procedures, the intravenous agents implicated in the FDA report (e.g., midazolam and propofol) should be avoided.[116]

We should highlight an important issue: most preclinical studies suggesting harmful effects of inhalation anesthetics are characterized by very high concentrations of anesthetic gases or by a very long duration of exposure, both of which do not routinely occur in clinical practice. However, clinical studies in children have shown that short-term general anesthesia and individual exposures are not associated with neurocognitive impairment.[117]

We report in Table 1 the strategies to reduce fetal risks from maternal exposure to analgesics/anesthetics.

Neuroimaging methodologies have shown some of their most significant promise in studies of anesthetic-induced developmental neurotoxicity.[118] Duration-dependent increased apoptosis and necrosis was detected in young rhesus monkeys after ketamine exposure at 9 h (relatively long exposure) and 24 h (extremely long exposure), but not at 3 h (short exposure, which more closely mimics typical general pediatric anesthesia),[119] while 5 h was sufficient to induce extensive neurodegeneration in another study.[120] In an in vitro experiment, researchers incubated frontal cortical cells isolated from the neonatal monkeys with different

Table 1. Strategies to minimize dose and duration of anesthetics in pregnant women.

Type of anesthesia	Changes suggested
Local anesthesia	No change
Neuraxial anesthesia	No change
I.v. sedative–hypnotic propofol	<3 h duration: no change >3 h duration: discuss risk/benefit
I.v. sedative midazolam	Consider i.v. opioids (fentanyl or remifentanil) or i.v. dexmedetomidine
General anesthesia with inhalational agents	<3 h duration: no change >3 h duration: discuss risk/benefit
General anesthesia with increased concentration of inhalational agents for uterine relaxation	Consider supplementing with magnesium sulfate, atosiban[a], or nitroglycerin[b] for intraoperative tocolysis

i.v. Intravenous.
[a]Not approved for use in United States by Food and Drug Administration.
[b]Difficult to titrate to effect, may result in intractable hypotension and/or pulmonary edema. Modified from ref. [116]

doses of ketamine administration. After the administration of 1 μM ketamine, there were no significant neurotoxic effects. However, ketamine caused enhanced apoptosis in cultures treated with doses of 10 or 20 μM.[121] Five hours of isoflurane is sufficient to induce extensive apoptosis in neonatal macaque as is 8 or 9 h (but not 5 h[122]) of sevoflurane.

Ongoing studies are aimed to determine whether sevoflurane-induced neuroapoptosis was reduced by cotreatment with dexmedetomidine.[123] These are based on previous trials on animals, where the rat pups were treated with sevoflurane (2.5% for 6 h) alone, dexmedetomidine alone, or sevoflurane in combination with various doses of dexmedetomidine. These studies were stimulated by reports showing that dexmedetomidine was neuroprotective in several models of brain injury.[124]

CONCLUSION

An important amount of scientific literature has been produced in the past decade on the subject of fetal surgery,[125] fetal pain, and fetal direct analgesia.[126–132] In the fetus, "Whereas evidence for conscious pain perception is indirect, evidence for the subconscious incorporation of pain into neurological development and plasticity is incontrovertible."[133] Our review shows that maternal anesthesia provided with either volatile analgesics or opioids is unlikely to harm the fetus if the surgery does not exceed 3 h; they should be integrated with a direct administration of analgesics to the fetus.

Our review opportunely focused on administering analgesic drugs to the fetus either directly or by getting them through the mother. The extraction index had not been considered in previous reviews, and this was one of the reasons some authors argued that maternal anesthesia was sufficient for both mother and fetus. The risks reported by giving fetuses anesthetic drugs are overcome by the relatively short length of these surgery interventions and by the safety of the drugs if given at appropriate doses. We highlight that the FDA warning was based primarily on the results from studies of laboratory animals, including nonhuman primates. The evidence from human studies that informed the FDA warning was far less compelling. In fact, resolving the question of whether anesthetic drugs are neurotoxic to patients has proven difficult. No single randomized controlled clinical trial will provide the answer to this central question because of various confounding factors.[134]

Platt,[6] so commented the RCOG report:[1] "We could rewrite this [report] as 'in theory they can't feel pain, therefore they don't.'" This image is significant and shows better than many words the weakness of those argumentations. Overcoming fetal pain is the new frontier of clinical analgesia. How much this pain is really strong and conscious, we do not know yet, and we should delve into it. A pain scale to assess pain level during fetal surgery has recently been proposed by a Brazilian study group, assessing facial movements in real time with 3D scans, according to the NFCS (Neonatal Facial Scoring System), which is validated to detect pain behaviors and suffering of healthy and preterm infants,[135] but never used before during intrauterine life in acute pain conditions.[136] It has recently been shown that fetuses during fetal surgery can respond to pain with bradycardia and also this can be a useful tool to assess fetal pain.[137] Furthermore, we are aware that denying fetal pain not only concerns fetal surgery, but can lead to underestimating the pain of the fetus born before the end of pregnancy, that is, of the premature infant,[8] despite the victorious efforts to overcome many oppositions done at the end of the last century.[138–140]

ADDITIONAL INFORMATION

Competing interests: The author declares no competing interests.

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