Fetal Pain and Fetal Anesthesia

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Abstract

This revue presents the latest data on fetal pain and on safe and effective techniques for providing direct fetal anesthesia or analgesia in the context of therapeutic procedures or abortion. Pain is a subjective experience occurring in response to impending or actual tissue damage. Pain perception requires conscious recognition or awareness of a noxious stimulus. Neither withdrawal reflexes nor hormonal stress responses to invasive procedures prove the existence of fetal pain, because they can be elicited by nonpainful stimuli and occur without conscious cortical processing. Current theories of pain consider an intact cortical system to be both necessary and sufficient for pain experience. Good evidence exists that the biological system necessary for pain is intact and functional from around 26 weeks' gestation. Pain invasive fetal procedures clearly elicit a stress response, and attenuation of this response may be beneficial.
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Former president Ronald Reagan said once, "When the lives of the unborn are snuffed out, they often feel pain, pain that is long and agonizing" (New York Times, Jan. 31, 1984). Many people disputed this statement, but the president received a letter from many doctors, including two former presidents of the American College of Obstetrics and Gynecology, 2 weeks later, in witch they concluded: "Mr. President, in drawing attention to the capability of the human fetus to feel pain, you stand on firmly established ground"[1].

During the last few years a vivid debate, both scientifically and emotionally, has risen in the medical literature as to whether a fetus is able to feel pain during abortion or intrauterine surgery. This debate has mainly been inspired by the demonstration of various hormonal or motor reactions to noxious stimuli at very early stages of fetal development. While a cortical processing of pain theoretically becomes possible after development of the thalamo-cortical connections in the 26th week of gestation, noxious stimuli may trigger complex reflex reactions much earlier. However, more important than possible painfulness is the fact that the noxious stimuli, by triggering stress responses, most likely affect the development of an individual at very early stages[2].

The neurobiology of the fetus: anatomical pathways

Free nerve endings, begin to develop at about seven weeks' gestation[3,4]; projections from the spinal cord can reach the thalamus at seven weeks' gestation[5]. An intact spinothalamic projection might be viewed as the minimal necessary anatomical architecture to support pain processing, putting the lower limit for the experience of pain at seven weeks' gestation.

At this time, however, the nervous system has yet to fully mature. No laminar structure is evident in the thalamus or cortex, a defining feature of maturity[6,7]. The external wall of the brain is about 1mm thick and consists of an inner and outer layer with no cortical plate. The neuronal cell density of the outer layer is much higher than that of a newborn infant or adult and at seven weeks' gestation has yet to receive any thalamic projections. Without thalamic projections, these neuronal cells cannot process noxious information from the periphery.

The first projections from the thalamus to cortex appear at 12-16 weeks' gestation. By this stage the brain's outer layer has split into an outer cortical rim, with a subplate developing below. The thalamic projections that develop from 12-16 weeks penetrate the subplate[8,9].The major afferent fibres (thalamocortical, basal forebrain, and corticocortical) can wait in the subplate for several weeks, before they penetrate and form synapses within the cortical plate from 23-25 weeks' gestation. Subsequent dissolution of the subplate occurs through prolonged growth and maturation of associative connections in the human cerebral cortex.

Spinothalamic projections into the subplate may provide the minimal necessary anatomy for pain experience, but this view does not account for the transient nature of the subplate and its apparent role in the maturation of functional cortical connections[10]. A lack of functional neuronal activity within the subplate calls into question the pain experience of a fetus before the penetration of spinothalamic fibres into the cortical plate.

Current theories of pain consider an intact cortical system to be both necessary and sufficient for pain experience[11,12]. In support are functional imaging studies showing that activation within a network of cortical regions correlate with reported pain experience[11]. Furthermore, cortical activation can generate the experience of pain even in the absence of actual noxious stimulation[12]. These observations suggest thalamic projections into the cortical plate are the minimal necessary anatomy for pain experience. These projections are complete at 23 weeks' gestation. The period 23-25 weeks' gestation is also the time at which the peripheral free nerve endings and their projection sites within the spinal cord reach full maturity[3]. By 26 weeks' gestation the characteristic layers of the thalamus and cortex are visible, with obvious similarities to the adult brain[8,9], and it has recently been shown that noxious stimulation can evoke haemodynamic changes in the somatosensory cortex of premature babies from a gestational age of 25 weeks. Although the system is clearly immature and much development is still to occur, good evidence exists that the biological system necessary for pain is intact and functional from around 26 weeks' gestation[13].

Fetal psychology

The stereotypical hormonal stress response of adults or older infants, of about 18 months onwards, reporting pain is

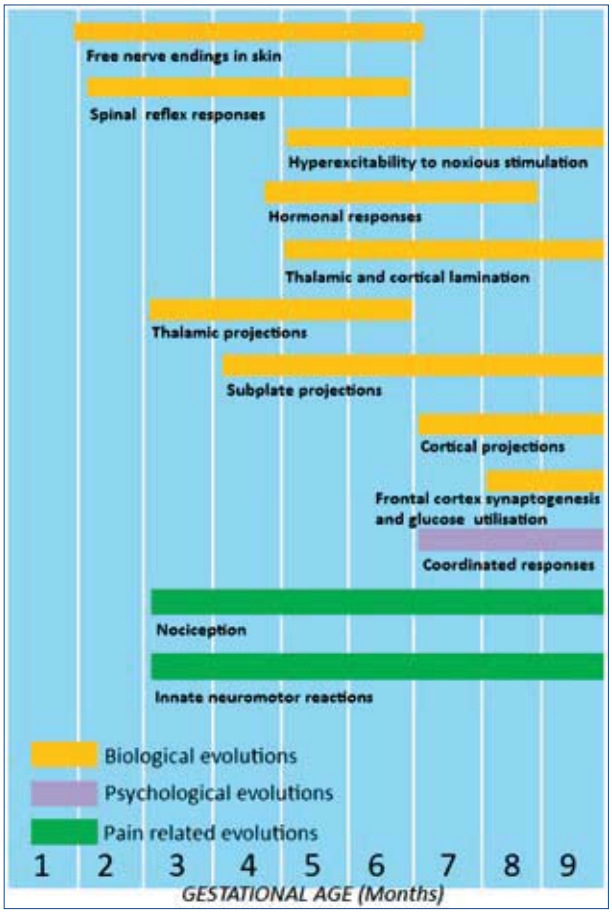

Figure 1. Developmental stages before and after birth

observable in fetuses at 18 weeks' gestation[14]. Behavioural reactions and brain haemodynamic responses to noxious stimuli, comparable to adults or older infants, occur by 26 weeks' gestation[13,15]. These and other observations (figure 1) are taken to suggest that the fetal mind can support an experience of pain from at least 26 weeks' gestation[10,16,17].

Inferences of fetal pain from such indirect evidence, however, present considerable difficulties. The placenta provides a chemical environment to encourage sleep and to suppress higher cortical activation in the presence of intrusive external stimulation. The environment of the womb consists of warmth, buoyancy, and a cushion of fluid to prevent tactile stimulation. In contrast to this buffered environment, the intense tactile stimulation of birth and the subsequent separation of the neonate from the placenta, facilitate the rapid onset of behavioural activity and wakefulness in the newborn infant. Birth marks the transition from laying down brain tissue while in the womb to organising that tissue for the wider world outside the womb[18].

The content of pain

The International Association for the Study of Pain defines pain as "an unpleasant sensory and emotional experience associated with actual or potential tissue damage", or described in terms of such damage. By this definition pain is not merely the response to noxious stimuli or disease but is a conscious experience. The definition further states that "pain is always subjective. Each individual learns the application of the word through experiences related to injury in early life". Without consciousness there can be nociception but there cannot be pain. Thus to understand how pain experience becomes possible it is necessary to understand the origin and developmental course of conscious experience. It is reasonable to assume that conscious function can only emerge if the necessary neural circuitry to carry out that function is fully developed and functional[19,20].

Stuart Derbyshire, a psychologist at the University of Birmingham, UK said that "true pain requires not only development of the brain but also development of the mind to accommodate the subjectivity of pain". "This mental development occurs only outside the womb", he added, "through the baby's actions and interactions with caregivers". The chemical environment in the uterus encourages sleep and suppresses higher-level brain activity necessary for pain perception[21].

In conclusion, pain is a subjective experience occurring in response to impending or actual tissue damage. The subjective experience of pain requires nociception and an emotional reaction. Nociception requires an intact sensory system, and an emotional reaction requires some form of consciousness.

But there are many examples of the ability of babies of this gestation to feel pain. In the first few moments after birth, even with extremely premature neonates (23-26 weeks), a noxious stimulus - for example, phlebotomy - can cause bradycardia, desaturation, and hypertension as a stress response. A neonatologist would seek to relieve this distress with analgesia, and a parent would seek to soothe. Also, fetal procedures (such as in utero chest drain placement) are increasingly being carried out with analgesia[22].

Fetal pain relief during procedures

Invasive diagnostic and therapeutic techniques are increasingly applied to the fetus. It is difficult to know the extent to which the fetus experiences pain. However, several indirect methods have suggested that the fetus at least can feel pain. Robinson and Gregory suggested the importance of providing analgesia in preterm neonates[23]. Anand and colleagues[24-26], Fisk and coworkers[27], and Giannakoulopoulos and colleagues[28] demonstrated that premature infants and fetuses display several humoral stress responses during invasive procedures. These data indicate that the mid-gestational fetus responds to noxious stimuli by mounting a distinct stress response, as evidenced by an outpouring of catecholamines and other stress hormones as well as hemodynamic changes. And, in analogy to what has been documented in neonates, prenatal stress can be expected to affect later neurodevelopment. Theoretically, in utero experienced pain may be "remembered" by the fetus, which could in turn lead to altered sensory patterns or abnormal behavioral patterns in postnatal life. Consequently, management of fetal pain and associated stress response in utero during invasive fetal interventions is important[27]. Even if it remains unproved whether this results in improved neurodevelopment and improved long-term outcome, it is prudent to take preemptive action and manage potentially painful procedures accordingly. Several treatment protocols have been proposed[29] and, in general, a policy of administration of fetal analgesics for any invasive procedures where the fetus might experience pain should be adopted, certainly from 18 to 20 weeks onward. Sufentanil (1 to 2µg/kg) or fentanyl (10µg/kg) can be given intramuscularly or intravenously to the fetus. Should

the mother undergo general analgesia, the fetus should be sufficiently anesthetized through transplacental passage[30]. Ongoing research about whether to administer postoperative fetal pain relief for some procedures may lead to new routes of pain relief, such as intraamniotic injection of long-acting opioids[31].

Anesthetic considerations for fetal surgery

Providing anesthesia for fetal surgery is challenging for many reasons. It requires integration of both obstetric and pediatric anesthesia practice. Two patients must be anesthetized for the benefit of one, and there is little margin for error. Many disciplines are involved, and communication must be effective. Conducting anesthetic research with vulnerable populations, such as pregnant women and their fetuses, is difficult, and many questions remain unanswered. Work must be done in the study of possible neurotoxicity caused by exposure of developing brain to anesthetic agents. The effects of stress on the developing fetus must also be further examined. Optimal anesthetic regimens remain to be determined.

Anesthetic plan:

1.Teamwork/communication. Fetal surgical cases require teamwork. The disciplines that interact may include pediatric general surgery, obstetrics, pediatric anesthesia, obstetric anesthesia, cardiology, radiology, neonatology, neonatal nursing.

2. Preoperative preparation. Specific fetal information is needed. Location of the placenta affects patient positioning. The estimated fetal weight is used to determine dosage of fetal drugs. The actual disease process and pathophysiology, and the extent of anatomic or physiologic derangement, will give the providers an idea of the physiologic reserve of the fetus. Fetal studies to elucidate the lesion and extent of physiologic derangements include ultrasound, echocardiography, and fetal magnetic resonance imaging. Serial studies track the changes. Lung lesions may grow or shrink, airway compression may worsen or resolve, combined cardiac outputs may change, hydrops fetalis may ensue, and polyhydramnios may develop at any time.

Aspiration prophylaxis in the obstetric population includes oral sodium citrate, histamine receptor blockers or proton pump inhibitors, and prokinetic agents such as metoclopramide.

3. Minimally invasive. An anesthetic plan can range from local anesthetic infiltration to sedation to neuraxial to general anesthesia. Medications can be given directly to the mother by the anesthesia team and, thus, indirectly to the fetus by placental transfer. Medications can also be given directly to the fetus by the surgical team. Route of direct administration can be variable; intramuscular, intravenous, and intracardiac routes have been described[32,33,34]. Maternal analgesia can often be accomplished with local anesthetic infiltration, whereas in other cases, a neuraxial technique or general anesthesia may be necessary. Fetal monitoring is typically limited to measurement of the fetal heart rate by the obstetricians with an ultrasound. Echocardiography may be used in cardiac interventions.

Instrumentation for treatment of twin-to-twin transfusion syndrome has shrunk in size and invasiveness has decreased. Previously, at the author's institution, these procedures were performed with general anesthesia or neuraxial techniques. These procedures are now done with sedation. The current practice at our institution includes maternal fasting, one intravenous (IV) catheter, aspiration prophylaxis, and tocolysis with preoperative indomethacin. Light sedation is administered to the mother to provide maternal comfort and decreased fetal movement. Multiple regimens have been used successfully, including combinations of opioids and other sedatives such as benzodiazepines or propofol. In a randomized double-blind trial comparing diazepam and remifentanil for fetal immobilization in minimally invasive surgery, the remifentanil group (0.1µg/kg/min) had significantly less fetal movement and surgeons reported better operating conditions[35]. Initially tocolysis involved preoperative indomethacin, postoperative magnesium infusions, and postdischarge oral nifedipine or subcutaneous terbutaline.

By contrast with the anesthetic for complicated twin gestations, providing anesthesia for balloon dilation of fetal aortic stenosis involves maternal general endotracheal anesthesia and intramuscular administration of fentanyl, vecuronium, and atropine to the fetus[36]. The potential risks of administration of general anesthesia in a pregnant woman are outweighed by the need for a completely immobile mother and fetus, along with the potential need for fetal analgesia as the catheters and needles are advanced through the fetal chest wall and heart. These two different techniques, both for minimally invasive surgery, illustrate the need for collaboration between the teams to prioritize needs and balance risks and benefits to arrive at an optimal anesthetic plan.

4. Open mid-gestation. Open mid-gestation surgery requires significant uterine relaxation. General endotracheal anesthesia with high-dose volatile (two times the minimum alveolar concentration) is most often used to achieve uterine relaxation for open surgery. Intravenous nitroglycerin can also be used to augment uterine relaxation. Relaxation may allow increased uterine blood flow as long as maternal blood pressure is maintained, and results in fetal exposure to some volatile anesthetic agents.

After exposure of the fetus, an intramuscular injection of fentanyl (20µg/kg), atropine (20µg/kg), and vecuronium (0.2mg/kg) is given by the surgical team. Amniotic fluid is lost through the hysterotomy, but is replaced with a continuous infusion of warmed Ringer's lactate using a Level 1 infusion device. If fetal IV access is necessary it is obtained, and IV tubing is handed over the drapes to the anesthesia team. Monitoring of the fetus in these cases may include direct observation, heart rate by ultrasound, fetal echocardiography, and pulse oximetry[37,38]. If a pulse oximeter is placed by the surgical team, the hand is covered with sterile foil to prevent artifact from the operating room lights, and a sterile cable is passed to the anesthesia team. Fetal oxygen saturation ranges from 40% to 70%[39,40]. Fetal echocardiographic monitoring is continuous. Cardiac filling, contractility, and rate, along with patency of the ductus arteriosus, are helpful in anesthetic management of the fetus. Umbilical blood gas measurement may be used in selected cases.

5. EXIT. EXIT (*ex utero* intrapartum treatment) procedure is increasingly used for selected fetal conditions. The purpose of the EXIT procedure is typically to establish functional and reliable fetal airway control while keeping the fetus attached to the uteroplacental circulation. This is accomplished by delivering only a portion of the fetus through a hysterotomy incision. To permit ample time to perform a potentially complex fetal airway procedure, EXIT is done under maximal uterine relaxation, and thus the maternal risks of this procedure are mainly hemorrhagic.

Uterine relaxation is only needed intraoperatively, not postoperatively. Magnesium sulfate is not given. Another difference is the need for two operating rooms and a resuscitation area for the neonatal team. General endotracheal anesthesia is used at our institution to provide high dose volatile anesthetics, but adequate uterine relaxation with neuraxial anesthetic and nitroglycerin infusion has been reported[41,42]. After the patient has been adequately anesthetized, the surgical team passes sterile items off the field for the anesthesia team. These may include tubing for IV fluids, pulse oximeter cables, and oxygen tubing for a sterile Mapleson D circuit. Distinguishing fetal fluids and medication from maternal fluids and drugs is important to avoid confusion especially in emergent or urgent parts of the procedure. Fetal well-being is monitored with pulse oximetry, heart rate, and possibly echocardiography. Following maternal laparotomy, placental mapping and hysterotomy, the fetus is externalized as little as possible to permit surgical approach to the lesion while continuing umbilical blood flow. An intramuscular injection of narcotic and muscle relaxant is given. Once the airway is secured or lesion resected, surfactant is given to the fetus if premature and the lungs are ventilated. It is important that no ventilation take place until the umbilical cord is ready to be divided. Increases in oxygen saturation, the presence of end-tidal CO_2, and good chest movement are indicators of successful intubation. Fiberoptic bronchoscopy can be also be used as confirmation. The baby is delivered for care by the neonatal surgical team.

Pain, stress, and neurotoxicity

Invasive fetal procedures clearly elicit a stress response[32], and attenuation of this response may be beneficial[43]. The long- and short-term effects of this response continue to be studied, as well as the potentially neurotoxic effects of the anesthetics used to block the stress response[44]. As procedures and anesthetic techniques evolve, work should be done to quantify human fetal exposure to anesthetic agents and to explore the effects of these agents and surgical stress on the fetus.

Conclusions

Although there have been some developments in research into fetal pain since the publication of the Royal College of Obstetricians and Gynaecologists report, there is still a great need for further research in many areas.The basic molecular and cellular mechanisms of fetal and neonatal pain are still poorly understood, as are the effects of anaesthetics or analgesics. The development of transgenic mice will allow more detailed studies to be carried out. A major concern is the long-term effects of pain and analgesics on the behavioural and physiological development of neonates. Although some studies have been carried out, further research in this area would be important[45]. ■

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