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Fetal pain perception and pain management

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Summary This paper gives an overview of current science related to the concept of fetal pain. We have answered three important questions: (1) does fetal pain exist? (2) does management of fetal pain benefit the unborn child? and (3) which techniques are available to provide good fetal analgesia?

Introduction

Pain is a subjective experience occurring parallel to a physiologic response in reaction to impeding or actual tissue damage. The subjective experience of pain requires nociception and an emotional reaction. Nociception requires an intact sensory system, whereas an emotional reaction requires some form of consciousness. As the fetus cannot tell us whether it feels pain, and as pain cannot be assessed using objective measures, only indirect methods are useful to determine whether the fetus feels pain.

The concept of fetal pain and fetal analgesia is becoming more and more relevant as in-utero interventions to relieve prenatally diagnosed diseases are rapidly becoming a clinical reality.[1–5] Thanks to advances in high-resolution ultrasound and other diagnostic techniques, increasing numbers of conditions are diagnosed early in gestation and insight into their pathophysiology has been gained. Some of these conditions are life threatening in utero and might benefit from prenatal surgical intervention. In-utero surgery is increasingly applied to the unborn child, placenta, membranes or cord.

Since Robinson and Gregory published their landmark paper demonstrating the necessity and safety of analgesia in preterm neonates,[6] pain in neonates and adequate analgesia drew more and more attention. Thanks to the outstanding work by Anand et al. and Fisk et al., it becomes increasingly clear that premature infants and fetuses experience stress during invasive procedures and that, as a consequence, their long-term neurodevelopmental status might be affected.[7–15] Some current publications have suggested that fetal analgesia can be performed efficiently, eliminating the fetal stress response.[16] It remains unclear whether this results in improved neurodevelopment and improved long-term outcome.

This paper focuses on the evidence that fetal pain is a realistic problem and on the current status of fetal pain management during in-utero procedures.

Does the fetus experiences pain?

The question of whether a fetus experiences pain is an immense challenge. There is no objective measurement of

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'pain'. The fetus is unable to tell us if it feels pain, so other evidence must be used to decide whether the fetus feels pain. Because of the obvious difficulties in studying fetal behavior, activation of the hypothalamic—pituitary—adrenal axis (the 'stress response') has been proposed as a surrogate indicator of fetal pain. This has limitations: stress responses do not necessarily signify pain (e.g. during exercise) and stress responses do not involve the cortex. However, in the absence of a stress response the fetus is unlikely to experience pain. Also, one could argue that the stress response is more relevant in terms of immediate and long-term sequelae, whether or not associated with pain in the fetus.

The idea that a fetus will experience stress when an invasive stimulus is imposed on it and that therefore analgesia will be necessary, originated from the work by Anand on preterm neonates.[7—9] The rationale was that if a premature infant was capable of feeling pain then there is no reason why a fetus of the same gestation should not also feel pain. Fisk and co-workers continued this work and provided direct evidence that premature fetuses have hormonal and hemodynamic responses to invasive stimuli.[10—15] They also showed that these responses can be blocked by analgesia.[16]

Hemodynamic responses

It is well known from animal studies that the fetus in late gestation has a remarkable capacity to redistribute its blood flow in response to acute stressors (hypoxemia, hemorrhage) to protect its more vital organs, such as the brain and myocardium, at the expense of other organs such as gut, kidneys and the extremities.[17,18] Similarly, some chronic stressors, such as sustained hypoxemia or prolonged reductions in uterine blood flow, are also associated with increased brain blood flow.[19,20] In the human fetus, Doppler ultrasonography studies have shown an association between chronic hypoxemia of intrauterine growth restriction and redistribution of blood flow.[21] Fisk and colleagues demonstrated that acute painful stimuli (transgression of the fetal abdominal wall during in-utero transfusion) were associated with a significant hemodynamic response in the fetus.[14] This hemodynamic stress response is consistent with redistribution of blood supply to the brain.

Hormonal responses

Due largely to the research work of Anand and co-workers, we know that preterm neonates have hormonal stress responses following invasive interventions.[7—9] These hormonal responses can be prevented by analgesia. A decade after this earlier work, similar studies were performed in the unborn child. Activation of the fetal hypothalamic—pituitary—adrenal (HPA) stress response can be assessed by measuring stress hormones such as noradrenaline, cortisol, β-endorphin, and corticotrophin. Fisk et al. studied samples obtained before and after in-utero fetal blood transfusion and compared levels of these hormones before transfusion (immediately after access to the fetal circulation was established), with levels at the end of transfusion (just before the needle was removed).[10—12] Fetal plasma was obtained during fetal blood sampling for intrauterine transfusion either by needling the fetal intrahepatic vein (IHV) or by needling the placental cord insertion (PCI). As the PCI is not innervated, no stress response was observed, whereas in the IHV-transfused fetus a significant increase in stress hormones was recorded. The fetal HPA system seems functional from at least the beginning of the second trimester.

Anatomical considerations

To experience pain, an intact system of pain transmission must be available. Peripheral receptors develop from the seventh gestational week.[22] From 20 weeks gestation, peripheral receptors are present on the whole body.[23,24] From 13 weeks gestation, the afferent system located in the substantia gelatinosa of the dorsal horn of the spinal cord is developing.[24,25] Development of afferent fibers connecting peripheral receptors with the dorsal horn starts at 8 weeks gestation.[25] Spinothalamic connections start to develop from 14 weeks and are complete at 20 weeks gestation, and thalamocortical connections are present from 17 weeks gestation and completely developed at 26—30 weeks gestation.[26] From 16 weeks gestation, pain transmission from a peripheral receptor to the cortex is possible and certainly completely developed from 26 weeks gestation. It is important to note that serotonin-releasing inhibitory descending pain fibers only develop after birth. It is therefore safe to assume that the fetus feels more pain then the small infant.

Neurophysiological data

A primitive electroencephalogram (EEG) is present from 19 weeks gestation and from 22 weeks it is feasible to register a continuous EEG. More advanced EEG recordings, such as a sleep/wake pattern, somatosensory evoked potentials and visually evoked potentials, are measurable from 24 weeks gestation.[22,27]

According to the definitions of pain and feeling, a fetus definitely cannot feel pain. But we cannot deny that the fetal nervous system mounts protective responses to tissue injury. Based on the data mentioned above, we can safely assume that the fetus reacts to painful stimuli from 24 weeks gestation and that it is possible that this occurs from 16 weeks gestation.

Do we need to provide adequate fetal anesthesia?

The fetal nervous system mounts protective responses to tissue injury. The evidence for early exposure to noxious stimuli resulting in adverse effects on future neural development is increasing. This means noxious stimulation might not need to penetrate consciousness to substantially alter the course of sensory development. Ruda reported that localized inflammation during the neonatal period permanently alters neuronal circuits that process pain in the spinal cord.[28] Preterm neonates who had experienced 4 weeks of neonatal intensive-care unit therapy manifested decreased behavioral responses and increased cardiovascular responses to the pain of a heel prick when compared

with neonates born at 32 weeks.[29] Differences in these response patterns were strongly correlated with the number of invasive procedures experienced since birth, rather than other clinical factors (such as age, Apgar score, birth weight, severity of illness, or weight at 32 weeks postconception). These data suggest that repetitive pain and stress might alter the neurologic substrate associated with pain, leading to altered neurobehavioral responses from subsequent pain.

According to Anand, repetitive pain in neonatal rat pups can lead to an altered development of the pain system associated with decreased pain thresholds during development.[30] Increased plasticity of the neonatal brain might allow these and other changes in brain development to increase their vulnerability to stress disorders and anxiety-mediated adult behavior. Similar behavioral changes have been observed during later childhood of ex-preterm neonates who were exposed to prolonged periods of neonatal intensive care.[31] Recent studies suggest that although early painful memories are not accessible to conscious recall, they might be encoded in 'procedural memory' and lead to abnormal behavioural patterns or altered sensory processing in later life. Taddio et al. demonstrated that children undergoing a ritual circumcision immediately after birth (without pain relief) react much more vigorously to painful stimuli later in life, such as vaccination at 2 months of age, then those who underwent the procedure with analgesia or those that did not undergo the procedure.[32]

It is becoming increasingly clear that experiences of pain will be 'remembered' by the developing nervous system, perhaps for the entire life of the individual.[22,33] These findings should focus the attention of clinicians on the long-term impact of early painful experiences, and highlight the urgent need for developing therapeutic strategies for the management of neonatal and fetal pain.

Which techniques are useful to provide adequate fetal anesthesia? (Table 1)

Because fetal pain is a realistic problem, we must provide, or attempt to provide, adequate pain relief during every situation in which the unborn child might experience potentially painful stimuli. Fisk et al. showed that direct administration of 10 μg/kg fentanyl intravenously to the fetus blunts the fetal stress response to intrauterine needling.[16] The magnitude of the β-endorphin and cortisol response was halved, and the cerebral Doppler response was ablated. They showed that successful analgesia in the fetus is achievable.

In various clinical situations it is appropriate to consider fetal analgesia. First, clinicians might consider fetal analgesia during in-utero invasive therapeutic or diagnostic procedures, such as blood transfusions, shunt placements, endoscopic laser coagulation of vascular anastomoses in twin-to-twin transfusion syndrome, fetoscopic endotracheal occlusion for congenital diaphragmatic hernia and open fetal surgery. Second, some might advise providing analgesia during late termination of pregnancy. Third, it might be worth considering administering constant pain relief to fetuses in serious, painful but viable fetal conditions. Finally, one might suggest pain relief during vaginal childbirth, especially when instrumental.

Several ways of administering analgesics to the fetus are available: transplacentally (after maternal oral or parenteral administration) or directly to the fetus, using the intravenous, intramuscular or intra-amniotic approach. The available drugs include anesthetic agents such as halogenated agents, opioids and benzodiazepines. Essentially, the mode of administration and drug of choice depend on the type of intervention planned.

During open fetal surgery under maternal general anesthesia, inhalational agents are considered to provide adequate fetal anesthesia and produce uterine relaxation essential for successful surgery. So additional analgesia for the fetus is unnecessary. Direct fetal administration of fentanyl and pancuronium is reserved for cases where the fetus moves during the procedure.[34]

Some endoscopic procedures performed directly on the fetus, such as tracheal occlusion or repair of meningomyelocele, are usually performed under maternal local or regional anesthesia. As these procedures do not require maternal general anesthesia, additional fetal anesthesia is desired and is usually done by direct administration of opioids and muscle relaxants to the fetus. Two possible routes of administration for these drugs are injection into the umbilical cord and intramuscular injection into the fetus.[34] A similar approach could be used for late termination of pregnancy: administration of analgesics directly intravenously before a lethal fetal injection of potassium chloride or lidocaine is administered.

The term 'obstetric endoscopy' was proposed for procedures on the placenta, the umbilical cord and fetal membranes. Obstetric endoscopic procedures do not require direct contact with the fetus. The risks of maternal (and consequently fetal) general anesthesia are unlikely to be justified by the degree of stress response inflicted on the fetus. However, immobilization of the fetus is required to prevent accidental fetal movements complicating these procedures. In these instances, fetal immobilization is possible using maternally administered sedative drugs such as diazepam. However, recent studies by Dewolf et al. and Van de Velde et al. have determined that maternally administered remifentanil in doses as low as 0.1 μg/kg per min produces effective maternal sedation and fetal immobilization, through transplacental passage, during these procedures.[35,36]

Long-term pain management following invasive fetal surgery or in cases of non-lethal painful in-utero conditions is somewhat more challenging. Most anesthetic drugs have serious side effects to the mother when administered orally or parentally to the pregnant women. Strumper et al. recently showed that intra-amniotic sufentanil was easily resorbed by the sheep fetus and suggested that the intra-amniotic administration of analgesics might provide a simple and effective means of reassuring good and prolonged fetal analgesia.[37]

Conclusion

Evidence is increasing that, from the second trimester, the fetus reacts to painful stimuli and that these painful interventions might cause long-term effects. It is therefore

Table 1 Overview of management options for fetal and maternal anesthesia during in utero interventions

	Maternal anesthesia	Fetal anesthesia
Open surgery	General anesthesia with or without epidural anesthesia	Fetus is anesthetized through placental passage, additional anesthesia can be obtained by direct fetal administration (IM or cord) of opioids (e.g. fentanyl 10 μg/kg or sufentanil 1 μg/kg) and muscle relaxants (e.g. pancuronium 0.3 mg/kg)
Fetoscopic fetal surgery	Local anesthesia or regional anesthesia (spinal, epidural of combined spinal epidural)	Direct fetal administration (IM or cord) of opioids (e.g. fentanyl 10 μg/kg or sufentanil 1 μg/kg) and muscle relaxants (e.g. pancuronium 0.3 mg/kg). Atropine (0.02—0.03 mg/kg) can be added
Fetoscopic surgery on placenta and cord	Local anesthesia or regional anesthesia (spinal, epidural of combined spinal epidural)	Maternal IV administration of remifentanil 0.1—0.2 μg/kg/min or maternal IV administration of benzodiazepines
Late termination of pregnancy	Local anesthesia or regional anesthesia (if labor is induced and patient requests regional analgesia for labor; epidural or combined spinal epidural)	Direct fetal administration (IM or cord) of opioids (e.g. fentanyl 10 μg/kg or sufentanil 1 μg/kg) and muscle relaxants (e.g. pancuronium 0.3 mg/kg), followed by drugs to perform feticide (potassium or lidocaine)
Chronic in utero pain management or postoperative fetal pain management	None	Intra-amniotic administration of lipid soluble opioids

recommended to provide adequate fetal pain relief during potentially painful procedures during in-utero life. The optimal mode of drug delivery and the optimal dose and drug to be used remain the subject of further study.

Practice points

- Fetal analgesia has to be provided as a routine during potential painful interventions.
- The fetal HPA system should be considered as functional from the beginning of the second trimester.

Research agenda

- Determination of the optimal mode of drug delivery.
- Determination of the optimal dosage and drug for fetal analgesia.
- Effect of prenatal analgesia on postnatal pain threshold and long-term effect.

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