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*REVIEW*

# Fetal pain: implications for research and practice

Pain is a subjective experience. The fetus cannot tell us what it is feeling, and there is no objective method for the direct measurement of pain. To address the question of pain in the fetus, one must use indirect evidence from a variety of sources, and then make an informed guess. This approach is similar to that which we use with animals. We cannot ask animals how they feel, but infer from a variety of indirect approaches including study of their behaviour, anatomy, and physiology.

## Does the fetus feel pain?

### *Consciousness*

To feel pain, or suffer discomfort, one needs to be conscious, to be aware. We do not know when, if at all, consciousness starts in the fetus. The biological basis of consciousness is little understood although at least in adult humans, the evidence suggests that it is in some way associated with electrical activity in the cerebral cortex. Crick[1] has suggested that one is conscious of something when there is electrical activity in specific large neural cortical networks, particularly in layers IV to VI of the cerebral cortex[2].

Greenfield has emphasised that one should not think of consciousness as an all or none phenomenon, rather that it may come on like a dimmer switch. This concept of evolving consciousness could apply to the developing fetus, in whom experience is most unlikely to be the same as that of an adult. Furthermore, the fetus may not have the same physical basis for conscious experience as the older human. Frogs, for example, do not have a developed cerebral cortex, lacking layers IV to VI. If they are conscious at all, their experience must be associated with activity in a less complex neuronal network, possibly more analogous to the fetal subplate zone[3].

### *Anatomical evidence*

The most important evidence is anatomical. For the fetus to feel pain, it is necessary for the requisite nociceptive pathways to be developed. This involves neural connections between peripheral receptors and the spinal cord, upward transmission via the spinal cord to the thalamus, and from there to the outer cerebral layers. The development of the human nervous system is a progressive and ascending process, with the cerebral cortex the last region to develop.

Connections from the periphery to the spinal cord are formed early, at about eight weeks; C fibres begin to grow into the human fetal spinal cord at about 10 weeks[4]. The substantia gelatinosa in the dorsal horn is the spinal cord region of interneurones which is thought to play a major part in the modulation of noxious inputs; by 30 weeks of gestation it has most features of the adult[4]. The cerebral cortex starts to form at 10 weeks, although at that stage it is isolated from the rest of the brain[5]. Cortical development involves the structural differentiation and maturation of cortical neurones, fibres, glia and blood vessels, and this starts only at about 17 weeks of gestation with layers VI and V, but continues until long after birth. From 15 weeks, the cortex is underlain by the subplate zone, a layer of neurones below the cortex that is specific to the fetus. Synapses appear within the cortical plate from mid-gestation. The subplate zone expands considerably between 17 and 20 weeks, while from about 17 weeks, there is a shifting population of connections from the thalamus to this region[6]. Thalamic fibres penetrate the cortical plate from 24 to 28 weeks[6,7], and at this stage the full anatomical pathways necessary for nociception are in place.

I. Kostovic, who has been involved in many of the fundamental human fetal neuroanatomical studies[6–9], has written in a personal communication: *Between 22 and 26 weeks of gestation the subplate zone contains an abundant mixture of cholinergic, thalamo-cortical and corticocortical waiting neurones, and there are transient fetal synaptic circuits between the subplate and cortical plate neurones. It seems probable that extrinsic influences (via the thalamocortical pathways at least) could change the activity of the neocortical alange at that stage, and possibly even earlier e.g. in a 20 week fetus when thalamocortical and cholinergic afferents already have synapses with upper subplate neurones, and these neurones very probably send axons into the cortical plate. At least from mid-gestation onwards it seems that extrinsic influences (via thalamo-cortical pathways) can act through demonstrable synapses, which, if physiologically active, may be involved in the modulation of the activity of the fetal neocortex.*

Assuming that activity in the cerebral cortex or subplate zone is necessary for consciousness, then for the

fetus to be conscious of an external experience, these regions need to be connected with incoming nervous activity. Most incoming pathways, including nociceptive ones, are routed through the thalamus and, as stated above, penetrate the subplate zone from about 17 weeks. However, the earliest cortical links with the external world are formed even earlier than this; these comprise the catecholamine pathways of noradrenergic and dopaminergic neurones, and do not pass through the thalamus. These monoamine fibres start to invade the subplate zone at 13 weeks and reach the cortex at about 16 weeks[6,10,11]. This puts an early limit on when it is likely that the fetus might be aware of anything that is going on in its body or elsewhere.

The last pathways in the nociceptive system to be formed are the inhibitory descending serotonin neurones, which can block the ascending pathways. These do not form until after birth[4], raising the possibility that the fetus may actually be more sensitive to noxious stimuli than the older child, and may explain why the newborn shows exaggerated behavioural responses to sensory provocation[4].

### *Physiological evidence*

There is some evidence for a primitive electroencephalogram from 19 to 20 weeks, and sustained electroencephalogram from 22 weeks; these have been obtained from very preterm infants[9,12]. Electroencephalic patterns are clearly measurable in older preterm babies and have been well characterised from 28 weeks to term[9]. Studies of evoked responses in preterm babies show that both visual and somatosensory potentials can be elicited from as early as 24 weeks and are well developed by 27 weeks[13]. The fact that a primitive somatosensory potential can be evoked at 24 weeks suggests that the nociceptive pathways from the periphery to the cortex are functional from that time[14]. The flexor reflex, a measure of nociceptive function in the central nervous system, is also present in preterm infants tested from 26 weeks[4]. This evidence thus suggests that the nociceptive system is functional from at least 24–26 weeks, but gives little information concerning earlier gestations.

### *Behavioural responses*

One has to be cautious about interpreting behavioural responses in terms of conscious experience, for some, at least, could be purely reflex. It is well known that decorticate experimental animals show a wide range of behavioural responses to noxious stimuli.

The fetus starts to make movements in response to being touched from eight weeks[15], and more complex movements build up, as detected by real-time ultrasound, over the next few weeks[16]. It can respond to sound from 20 weeks and discriminate between different tones from 28 weeks[17].

With the preterm baby, who now can be kept alive from 23 weeks, one can observe behavioural responses to various clinical interventions. Such babies show a distinct pattern of behaviour to painful stimuli, such as a heel prick. This includes a wide range of facial expressions and behaviours, including screwing up the eyes, opening the mouth, as well as clenching the hands and limb withdrawal, which an older baby would also show, if in pain[18]. Most nurses and mothers looking after preterm babies are convinced that they are both sentient and feel pain. This type of evidence is similar to that from animals. Most people believe that their cat feels pain if someone treads on its tail.

## Theoretical considerations

### *Does one need previous experience to feel pain?*

It has been argued that the fetus cannot feel pain, because pain is a complex phenomenon affected by previous experience[19,20]. It is generally agreed that stimulation of a particular nociceptive pathway in the adult can be associated with various types of conscious experience, even in the same individual. Such variation may depend on previous experience, or on other simultaneous occurrences. It is well known, for example, that a soldier wounded in battle often feels nothing at the time. It is also possible to sensitise the experience: people who are depressed often feel more pain than at other times. This complexity of the experience of pain in adults is not controversial. However, the fact that the suffering associated with nociceptive stimulation in adults can be affected by activity in other parts of the brain, does not prove that in a naïve being, such as the fetus, there can be no experience of pain. The fact that the sensation of pain can be affected by previous experience, does not entail the conclusion that previous experience is necessary to feel pain. Such an argument would suggest that a newborn baby could not feel pain either. The view that to experience pain it is necessary to have experienced pain previously is self defeating: there could never be a first experience of pain.

### *Is self consciousness needed?*

It has also been suggested that consciousness implies self consciousness, and as the fetus is not self conscious it cannot be conscious either[21]. However, consciousness does not necessarily imply self consciousness in the adult sense. All that is needed for the fetus to feel pain, is that it has a simple awareness of what is going on in

itself. It does not need the more complex understanding that it itself is different from the outside world.

## Stress responses

Recent research has concentrated on the stress responses of the fetus to various interventions, just as neonatal research did in the previous decade[22,23]. It is important to clarify the relevance of this work to a discussion of pain. Stress responses, defined as an activation of specific hormonal and neurotransmitter systems, do not provide a direct index of pain. Although stress hormones are usually increased when a subject is experiencing pain, there are many other situations which are not painful, such as exercise, which also can increase their levels. Furthermore, production and release of stress hormones such as cortisol can be mediated by the hypothalamus, without involvement of the cortex or other higher brain regions involved in sentience.

There is now evidence that the human fetus can mount substantial stress responses[24]. These have been shown both by examining stress hormone levels in the blood before and after invasive procedures[25,26] and by examining the redistribution of blood flow within the fetus[27]. We have shown that after intrauterine transfusions carried out at the placental cord insertion, which is not innervated, there is little or no change in any of these variables. However, after procedures through the intrahepatic vein, that involve piercing the fetal abdomen, which is innervated, there are major changes. Cortisol, β-endorphin and noradrenaline rise substantially after blood transfusions, a slow procedure that takes at least 10 minutes. With shorter interventions, such as fetal blood sampling without transfusion, cortisol and β-endorphin remained constant after procedures at either site. There is, however, evidence of a more rapid increase in noradrenaline, with procedures that involve piercing the fetal abdomen, from at least 18 weeks of gestation, although this response seems variable[26].

With Doppler ultrasound, our group has also shown that with invasive procedures there is a significant fall in the pulsatility index in the middle cerebral artery, consistent with a redistribution of blood flow to the brain ('brain sparing'). It has been found after procedures that involve piercing the fetal trunk, and occurs rapidly, as early as 70 s after the insult[27,28]. These include fetal blood sampling, tissue and urine sampling, body cavity aspirations, and insertion of feto-amniotic shunts. These responses have been found at all gestations studied from as early as 16 weeks. It has been well established that this cerebral redistribution response occurs in the human fetus during the chronic stress associated with intrauterine growth restriction and hypoxaemia, and in response to the acute stresses of haemorrhage or hypoxaemia in animal models[29]. It thus appears that the human, like the ovine, fetus is capable of an acute brain sparing response.

What then is the use of measuring stress responses? In considering stress responses in relation to the question of fetal pain, the 'null hypothesis' is of relevance: if there were no change in stress hormone level, it would be very unlikely that the fetus was experiencing pain. Stress responses can also be used to give some sort of index, though imperfect, of the degree of trauma involved, and further determine the effect of analgesia or anaesthesia. Finally, high levels of stress hormones may have long term consequences, as discussed below[30].

It was the demonstration of stress responses in the newborn during surgery, that precipitated the change in attitude in the medical and nursing care of newborn infants. It must be emphasised, however, with both the fetus and the newborn, that a stress response in itself does not tell us directly what the baby is feeling.

## Long term implications

There is evidence to suggest that a single early painful or stressful experience can have long term effects, and sensitise the child to pain and stress later. A recent prospective study showed that male babies who had been circumcised at five days or less, four to six months later cried more, and showed more often other forms of pain behaviour in response to their vaccination jab, than those who had not been circumcised[31]. It has also been shown that repeated insults, such as heel lancing, may induce a state of hypersenitivity in the response to pain[32]. Reynolds and Fitzgerald[33] have shown in a rat model that in the neonatal period there can be long lasting sensory nerve sprouting at the site of a wound; this could be one mechanism for long term hypersensitivity to pain.

Animal studies suggest that brief fetal or neonatal stress can have long term effects. The developing nervous system appears to be at a very plastic stage and vulnerable to insult. In rats born at a stage equivalent to the late fetus in man early postnatal handling permanently increases both the density of glucocorticoid receptors in the hippocampus[34], and the behavioural responses to stress throughout life. Handled rats secreted less corticosterone and showed a faster return to basal levels in a stressful situation. Handling in the first postpartum week had greater long term effects, than handling in the subsequent two weeks[35].

Fujii *et al.*[36] showed that exposure of pregnant rats to hydrocortisone for only three days, affected the long term development and behaviour of the offspring. A single dose of dexamethasone administered to the rhesus macaque was sufficient to damage fetal hippocampal formation, especially the CA3 region[37]. Prenatal stress

of pregnant rhesus monkeys has also been shown to have long term effects on the offspring, especially augmenting their hormonal and behavioural responses to new stressors[38,39]. This may, at least in part, be due to the direct transfer of some maternal cortisol across the placenta[40].

Whether fetal experience of pain or the activation of major stress responses, either *in utero* or at birth, has any long term effects in humans is not known. These animal experiments suggest that it may be possible and that this is an important area for future research.

## Clinical implications

The fetus is currently treated as though it feels nothing, and is given no analgesia or anaesthesia for potentially painful interventions. This is similar to the way in which newborn babies used to be treated, until the major change of practice which arose out of the work of Aynsley Green, Anand and colleagues[22,23,41]. They compared newborn infants undergoing cardiac surgery who received deep anaesthesia with sufentanil with those given a lighter regimen of halothane and morphine. The sufentanil group, in whom the responses of cortisol and noradrenaline were reduced to the baseline, had a much better post-operative outcome in terms of sepsis and mortality, than the latter, in whom the stress hormone response was not reduced to the same extent[42]. Now such pain relief is routinely given to babies not just for open surgery, but for more minor procedures[43]. However, it is possible that opiate drugs may themselves have long term adverse effects, and research is needed to determine their risk–benefit ratio for different interventions, both in the fetus and in the neonate.

### *Invasive procedures*

There are several areas where it is appropriate to consider pain relief or anaesthesia in the fetus[44]. Firstly, therapeutic interventions, such as shunt insertions or blood transfusions which are carried out for the benefit of the fetus. Many of these procedures are carried out in the third trimester at gestational ages comparable to preterm infants, who would be given analgesia. Secondly, there are diagnostic sampling or aspiration procedures in the fetus which are only of concern in this context if the procedure transgresses the fetal body; this will not be the case with needle insertion of the placenta, amniotic fluid or umbilical cord.

### *Termination of pregnancy*

The majority of terminations of pregnancy are carried out before 13 weeks of gestation, but 10% are performed between 13 and 19 weeks, less than 1% between 20 and 24 weeks and only a very few after that. Late terminations may cause pain to the fetus if they involve an invasive procedure, such as surgical dismemberment. Modification of the technique, such as preparatory occlusion of the umbilical cord, may be appropriate[45]. Whether potassium-induced termination of pregnancy at a viable gestation or the hypoxaemia caused by uterine contractions in terminations induced by prostaglandins cause pain or discomfort is hard to assess.

### *Childbirth*

The experience of the baby during birth is not usually considered. It is generally assumed that as birth is a natural phenomenon, undergone for thousands of years without pain relief, that it is painless for the baby. This may not be the case.

Noradrenaline levels in umbilical cord blood after spontaneous vaginal delivery are 10 to 20 times those before labour[46], and several times higher than contemporaneous maternal levels. Babies born by elective caesarean section have smaller rises in cortisol, noradrenaline, met-enkephalin and β-endorphin than those born by vaginal delivery[47–49]. Vaginal delivery seems advantageous for transitional respiratory adaptation at birth, and catecholamines are known to facilitate resorption of pulmonary fluid[50]. Thus a degree of stress at birth assists the baby's adaptation to the external world. The rise in stress hormones, however, can be considerably greater in assisted than in normal vaginal deliveries[51]. Elevation of fetal catecholamines in the umbilical cord are associated with pO2 and pH levels suggestive of hypoxia[46]. It is likely that the mechanical effects of instrumental delivery may add to this stress, and it may be that in the future obstetricians will consider giving analgesia before, or immediately after, such deliveries.

### *Analgesia for the fetus*

Failure to provide adequate analgesia for preterm babies is now considered substandard and unethical practice[52]. There have been similar calls for fetuses to be given analgesia during invasive procedures[53,54], even though there is no current evidence that analgesia blunts nociceptive responses *in utero,* or how analgesia may be safely and effectively administered.

The opioid agonists, such as fentanyl, are the drugs most widely used for sedation and analgesia in neonatology. Fentanyl has been given directly intravenously to fetuses before open fetal surgery, without apparent adverse effect, but also without any proof that it works[55]. Direct administration requires intravenous injection to the fetus, and this is known to have risks. These could be reduced but not abolished by direct fetal intramuscular

administration, the stress of which is likely to be relatively minor, but would prolong the procedure in order to await absorption. Intra-amniotic injections of lipid soluble opiods results in sub-therapeutic levels in the fetus[56].

Intravenous administration of fentanyl in the mother is unsatisfactory since the rate of transfer across the placenta is slow: 10 minutes after administration of 1 μg/kg the average fetal:maternal ratio was 0·31[57]. Larger doses may cause respiratory depression in the mother. Intravenous benzodiazepines cross freely into the fetal circulation, with fetomaternal equilibrium occurring within 5–10 minutes[58,59]. However, not only do they cause sedation, they may also have adverse behavioural effects if delivery soon follows, impairing fetal responsiveness. General anesthesia has significant risks in pregnancy. The potential benefits of analgesia in the fetus need to be balanced against the risk of additional procedures, and the potential for adverse long term drug effects. Administration of safe and effective analgesia to the fetus, without adverse effects in the mother, is a considerable challenge.

## Medical *versus* scientific caution

There is clearly is not enough evidence to be certain if and when the fetus starts to feel pain. By 26 weeks the full anatomical system for nociception has been formed, the electroencephalogram shows activity in the cerebral cortex, and the preterm baby of the same gestational age, if delivered, shows a complex range of pain behaviour. Some have concluded that it is not possible for the fetus to be aware of events before 26 weeks of gestation[20,60], and not to feel pain until considerably later than that[61]. This seems unduly certain, given the available evidence. Before 26 weeks, too little is known about the physical basis of consciousness in the fetus, the function of the subplate zone, the function of transient connections to the cortical plate and subplate zone, and the role of the monoamine innervation, to be sure that the fetus has no awareness. Given the anatomical evidence, it is possible that the fetus can feel pain from 20 weeks and is caused distress by interventions from as early as 15 or 16 weeks. This sets a limit to the earliest stage that analgesia might be considered.

## Conclusion

It is not possible to measure pain directly in the fetus. Studies of stress responses can be used to give an index of the degree of trauma induced by different interventions, and also the response to analgesia or anaesthesia, but they do not indicate what the fetus actually experiences. The assessment of whether or when the fetus is likely to feel pain has to be based on an evaluation of the available anatomical and physiological evidence. The physical system for nociception is present and functional by 26 weeks and it seems likely that the fetus is capable of feeling pain from this stage. The first neurones to link the cortex with the rest of the brain are monoamine pathways, and reach the cortex from about 16 weeks of gestation. Their activation could be associated with unpleasant conscious experience, even if not pain. Thalamic fibres first penetrate the subplate zone at about 17 weeks of gestation, and the cortex at 20 weeks. These anatomical and physiological considerations are important, not only because of immediate suffering, but also because of possible long term adverse effects of this early experience. Research in these areas is urgently required.

The eighteenth century philosopher, Jeremy Bentham, wrote of animals *The question is not Can they reason?, nor, Can they talk?, but Can they suffer?*. This caused a change in attitude towards animals and their treatment that is continuing to day, such that in the UK, even frogs and fishes are required by Act of Parliament to be protected by anaesthesia from possible suffering due to invasive procedures. Why not human beings?

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**Vivette Glover, Reader & Nicholas M. Fisk, Professor**
*Division of Paediatrics, Obstetrics and Gynaecology, Imperial College School of Medicine, Queen Charlotte's and Chelsea Hospital, London*

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