

## Fetal 'awareness' and 'pain': What precautions should be taken to safeguard fetal welfare during experiments?

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### Abstract

The extent to which the fetus may be able to experience sensations, including pain, *in utero* has apparently been greatly overestimated. The misconception that the prematurely born human infant is a good surrogate for the human fetus of the same post-conception age has led to the notion that awareness, pain experience and the potential to suffer, which are observable in premature human infants born at 30 weeks or earlier, should therefore occur in equivalent human fetuses. However, extensive studies of lambs *in utero* have demonstrated that the physiological environment of the fetal brain, and its responsiveness to stimuli, are markedly different from those of the newborn lamb, whether born prematurely or not. The fetus apparently remains in continuous states of sleep-like unconsciousness, which are maintained by a range of neuroinhibitory physiological mechanisms that are unique to fetal life. Moreover, the fetus is not apparently arousable to states of 'awareness' by potentially noxious humoral, auditory or surgical stimuli. These observations question the need to use pain-relieving medication in fetuses during experimental surgery. Also, unique and adverse fetal responses to some analgesics that are effective postnatally indicate that caution should be exercised when considering the *refinement* of giving analgesics to the fetus.

**Keywords:** fetal unconsciousness, pain, analgesia, refinements

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### Introduction

Every mother knows that her baby before birth will often move in response to the physical stimulation of pressing on it through the abdominal wall or it will "jump" in response to a loud and unexpected sound. Indeed, almost immediately after birth many babies can distinguish their mother's voice from the voices of other women. It is therefore easy to arrive at the conclusion that the baby can feel touch and hear sounds *in utero*, especially during late pregnancy. This view is reinforced by the knowledge that otherwise healthy babies born prematurely during the last 10 weeks of the usual 40-week human pregnancy are clearly capable of consciousness and respond to auditory, visual, taste, thermal, touch, painful and other stimuli (Lee et al., 2005; Mellor et al., 2005). As a result, many midwives, obstetricians and paediatricians believe that during late pregnancy babies are conscious and can *experience* noxious as well as pleasant sensations and therefore that they need to be protected against the former (e.g.

pain) and given the opportunity to experience the latter (e.g. relaxing music). It is not surprising, therefore, that some clinicians now advocate that pain relieving medication (analgesics) should be given directly to the fetus during potentially painful invasive procedures (Derbyshire, 2006), even when the mother, and therefore the fetus, are under general anaesthesia.

Given that such ideas are confidently asserted about human fetuses it is understandable that similar views are held with regard to the potential for conscious experience in other mammalian fetuses, especially those that are neurologically mature at birth (e.g. most farm animal species). Indeed, regulations designed to protect the welfare of animals explicitly include prenatal stages from halfway through pregnancy (e.g. Anonymous, 1999), in order to deal with the possibility that potentially noxious stimulation of individuals during these early developmental stages may lead to suffering.

Such thinking is increasingly leading members of Animal Ethics Committees to consider requiring that analgesics be given to fetuses to protect them during and after surgical or other potentially noxious manipulations. While this trend reflects a sincere commitment to protect animals from unnecessary harm through an act of *refinement*, it raises an important question: Is giving analgesia to the fetus really beneficial or even safe?

The purpose of this paper is to examine this question using as a basis some recent detailed reviews about the potential for prenatal "awareness" or consciousness (Mellor and Gregory, 2003; Mellor and Stafford, 2004; Lee et al., 2005; Mellor et al., 2005; Mellor and Diesch, 2006, 2007). As the relevant scientific literature was fully referenced in these reviews, only pertinent additional publications are quoted here.

### **Prerequisites for experiencing pain and suffering**

For a living animal to experience pain and to suffer as a result it must first possess two attributes (Mellor and Diesch, 2006):

1. It must have a nervous system that is sophisticated enough to transduce potentially noxious sensory inputs (e.g. electrical impulses in pain nerve pathways) into experiences that the animal may interpret as sufficiently unpleasant to represent suffering – without such a capacity for sentience animals cannot perceive by the senses and cannot suffer or experience good welfare.
2. It must be conscious – an animal cannot suffer while it is unconscious.

This obviously means that most living and conscious 'higher' animals, when mature, meet these prerequisites and have the capacity to suffer – but what about the mammalian fetus?

### **Early development of the nervous system**

It is apparent that immediately after conception the fertilised ovum has no capacity for sensory perception and conscious awareness. It is equally apparent that almost immediately after birth neurologically mature newborns do possess those capacities, as indicated by their volitional responses to maternal and environmental stimuli (Mellor and Stafford, 2004).

During the intervening period, anatomically there is a progression from rudimentary neural structures towards increasing size, complexity and maturity such that peripheral, visceral, spinal and brain nerve tracts and related neural aggregations develop, proliferate, interconnect and grow (Mellor and Gregory, 2003). Associated with this neuroanatomical development is a progressive functional maturation which is reflected in changes in behaviour and in the electrical activity of the brain.

Behaviourally, initial 'startles' or jerky whole-body movements progress through individual limb, neck or head movements to later apparently purposeful and eventually well-coordinated limb movements or changes in body position within the uterus (Mellor and Gregory, 2003). Paralleling these behavioural changes is a progression of electrical states in the brain, as described below. Electrical activity in the cerebral cortex is of particular note because functional maturation of the cortex is considered to be an essential prerequisite of conscious awareness (Mellor and Gregory, 2003; Lee et al., 2005; Mellor et al., 2005).

Neurophysiologically, pre-cortical and cortical structures are electrically silent initially – i.e. there is no activity in the electroencephalogram (EEG). The EEG then exhibits sporadic spikes, which evolve into short epochs of sustained activity against a background of electrical silence. Continuous mixed sleep-like EEG activity then appears and this subsequently matures into differentiated and alternating rapid-eye-movement (REM) and non-REM sleep-like patterns. Finally, in neurologically mature fetuses EEG patterns indicating repetitive sleep-wake cycles appear soon after birth.

### **Neurological development and states of unconsciousness**

During the early stages of electrical silence and sporadic short epochs of EEG activity the cerebral cortex does not have the functional capacity to support any states resembling consciousness. Thus, movements of the body, limbs, neck or head or changes in facial expression (e.g. grimacing) in response to invasive stimulation at this stage are considered to be subcortical reflexes (Lee et al., 2005). This is also likely to be true during the subsequent stage of continuous undifferentiated sleep-like EEG activity because such activity denotes unconsciousness (Mellor et al., 2005). However, once REM-non-REM differentiation occurs the functional capacity of the brain may have matured sufficiently to support conscious awareness, because it is at this stage that neural connections, which are essential for consciousness, become well established between sub-cortical brain structures and the cerebral cortex (Lee et al., 2005; Mellor et al., 2005; Mellor and Diesch, 2006).

Consistent with this evaluation, human infants who are born prematurely at 28-30 weeks after conception exhibit the capacity for conscious awareness during wakeful phases of their repetitive sleep-wake cycles (Lee et al., 2005). However, as we shall see, the physiological environment of the fetal brain is so markedly different from that of the newborn's brain, that direct extrapolations from newborn brain states to those of the gestational-age equivalent fetus can

be, and probably have been very misleading (Mellor et al., 2005).

### The consciousness status of the fetus

We have already noted that mammalian embryo-fetuses are very likely to be in unconscious states when their EEG is electrically silent, intermittent or continuous with mixed sleep-like patterns, and that it is only after REM-non-REM differentiation occurs later in pregnancy that consciousness might be possible. However, three lines of evidence, *taken together*, strongly support the view that even when they have matured neurologically fetuses do not normally exhibit conscious awareness before or during birth (Mellor and Gregory, 2003; Mellor et al., 2005, Mellor and Diesch, 2006).

First, fetal EEG patterns and fetal behaviour demonstrate that sleep-like states of unconsciousness are continuously present throughout the last half of pregnancy (Mellor et al., 2005). This is because the continuous undifferentiated EEG patterns, which exhibit a mixture of REM-non-REM features, and the differentiated and alternating REM-non-REM patterns, which appear later and are indistinguishable from those seen during postnatal sleep, are all incompatible with consciousness. In addition, during labour there is a shift in the balance between the REM and non-REM states of unconsciousness such that the deeper non-REM state predominates (Mellor and Diesch, 2006).

Second, at least eight fetal, placental and uterine factors with well-demonstrated inhibitory effects on the fetal EEG apparently operate throughout the last half of pregnancy (Mellor and Gregory, 2003; Mellor et al., 2005), as summarised below.

- *Adenosine* is a potent neuroinhibitor and sleep-inducing agent. It is present in high concentrations in the fetus and its tissue concentrations are inversely correlated with the levels of oxygen in fetal tissues. This is important because, during fetal oxygen shortages, adenosine can shut down cortical electrical activity and rapidly produce a silent EEG trace. This has the protective effect of decreasing the oxygen required by the cerebral cortex in such circumstances.
- *Allopregnanolone and pregnanolone* are neuroactive steroids with well-established and potent anaesthetic, sedative and analgesic (pain relieving) effects. They are synthesised from progesterone and cholesterol by the fetal brain and placenta, and act via a specific neuroinhibitory system in the fetus (the  $\gamma$ -aminobutyric acid or GABA system).
- *Prostaglandin D<sub>3</sub>* is a potent sleep-inducing hormone which is also synthesised by the fetal brain and has neuroinhibitory effects.

- One or more *placental peptides* have demonstrated fetal neuroinhibitory effects.
- *Warmth, cushioned tactile stimulation and buoyancy* of the fetal environment also promote general suppression of brain activity.

It is apparent, therefore, that mature fetal cerebrocortical function occurs in an inhibitory physiological environment which is unique to prenatal life.

Third, the neurologically mature fetus is not arousable from non-REM or REM sleep-like states to conscious wakefulness by potentially noxious interventions such as induced hypercapnia (high carbon dioxide), sounds loud enough to cause intense auditory pain and surgery-induced tissue damage (Mellor et al., 2005). This contrasts strikingly with the situation after birth where these potent stimuli do arouse the sleeping young to conscious wakefulness.

This prenatal non-responsiveness to potentially noxious stimulation is a further indication of the unique inhibitory functional environment of the fetal brain. It also suggests that expulsion from the uterus at birth would lead to a marked reduction in overall neuroinhibitory influences on the brain. Indeed, this appears to be the case, because immediately after birth the major neuroinhibitors are substantially withdrawn and are replaced by a range of potent neuroactivators that support the onset of conscious awareness (Mellor and Diesch, 2006, 2007).

### Implications for the use of pain relief in fetuses

In light of the above observations, three questions are relevant to the use of analgesics during invasive fetal procedures. Is analgesic use required? Do impulse barrages in pain nerves matter during fetal procedures? What analgesics could be used?

#### Is analgesic use required?

With regard to preventing the embryo-fetus from *experiencing* pain, the answer appears to be that analgesics are not required. The reasons for this are as follows. During the early stages of neurological immaturity, indicated by EEG silence, progressing to sporadic spikes and short intermittent epochs of electrical activity, and then to continuous mixed EEG patterns, the fetus has not yet developed the capacity for sentience. Thereafter, once REM-non-REM differentiation has occurred, by which stage the capacity for sentience apparently has appeared, the fetus normally remains in continuous states of sleep-like unconsciousness which are probably maintained by the range of neurological factors (mentioned above) with demonstrated inhibitory effects on the fetal EEG. Thus, initially the embryo-fetus is insentient and so does not meet the first prerequisite of pain *experience*, and subsequently, the mature fetus is potentially sentient, but does not meet the

second requirement of being *conscious*. It follows that conscious pain perception cannot occur before birth, so that giving analgesics to the fetus to prevent the *experience* of pain is apparently not necessary.

Even if it were necessary to provide such pain relief, the fetus would in any case be protected by the usual practice of giving general anaesthesia to the dam before any acute surgery — as long as sufficient time is allowed for the general anaesthetic to cross the placenta, even neurologically mature fetuses do not respond behaviourally to very invasive surgical procedures (Mellor and Gregory, 2003). General anaesthesia therefore provides a significant safeguard for fetal welfare and should help to reassure those who, despite the evidence presented above, remain convinced that the fetus is capable of consciousness.

It may be concluded, therefore, that the use of analgesics is not required to protect fetal welfare because the initial neurological immaturity, the naturally maintained states of fetal unconsciousness in older fetuses and the use of general anaesthesia individually and collectively ensure that the fetus is not capable of consciously perceiving pain or any other sensations.

#### **Do impulse barrages in pain nerves matter during fetal procedures?**

Although the fetus is not apparently able to experience pain, invasive procedures nevertheless stimulate pain receptors and elicit impulse barrages in those pain nerve tracts that have developed by the time of the procedure. This is indicated by withdrawal of the stimulated body part and other behavioural responses, stress hormone release and changes in the rates of blood flow to the brain and other organs during and shortly after invasive fetal procedures (Lee et al., 2005; Mellor et al., 2005). However, none of these responses requires an intact cerebral cortex — they occur in anencephalic babies and decorticate animals — so that they are elicited by brain and other neural mechanisms below the level of the cerebral cortex (Lee et al., 2005; Mellor et al., 2005; Mellor and Diesch, 2006, 2007). Nevertheless, they raise the following question: Could such potentially noxious fetal stimulation initiate responses in the developing nervous system that would make the individual more sensitive to pain in the long term, i.e. after birth? In other words, might there be longer-term benefits of pharmacologically blocking such sensory inputs during fetal surgeries even though the fetus cannot *experience* them as pain? In considering these questions it is important to appreciate that there are apparently no studies which have robustly tested these speculations about fetal noxious stimulation, and thus there are no empirical data to demonstrate a causal relationship between such sensory input and the presumed potential for a subsequent greater

sensitivity to pain (Mellor et al., 2005). Indeed, robust clinical studies of newborn and young human infants are increasingly suggesting that this is not an important effect (Moiniche et al., 2002).

#### **What analgesics could be used?**

Notwithstanding all of the above evidence, there may still be some researchers or clinicians who have lingering doubts about whether or not it is necessary to use analgesics to protect fetuses against the immediate presumed noxious effects of invasive procedures and/or possible longer term effects. Thus, they may continue to recommend that the adage "If in doubt, treat" should be applied. This would be most incautious because this approach is based on the presumption that fetal responses to analgesics can be accurately predicted from responses of prematurely born individuals of the same post-conception age, and therefore that we have sufficient knowledge of mechanisms of analgesic action in the fetus for this strategy to be adopted without significant hazard. Neither of these presumptions is true.

We have already seen that the physiological environment *in utero* is markedly different from that of the newborn, whether prematurely born or not. It is therefore entirely possible that the effects of at least some analgesics may be different when administered to the fetus. Also, we are strikingly ignorant of the effects of most analgesics on the fetus. For instance, we do not know what to give, when to give it, how to give it or how often it should be given. We do not even know whether or not drugs that are demonstrably analgesic in the newborn actually do have analgesic effects in the fetus.

We do know, however, that morphine, which is a respiratory depressant in the newborn, elicits several hours of continuous deep breathing in the fetal lamb, and that the muscular activity associated with this increases oxygen consumption so much that the fetal oxygen status declines, sometimes to fatal levels (Bennet et al., 1986). In addition, morphine also stimulates fetal release of the stress hormone cortisol (Taylor et al., 1997) and is associated with prolonged abnormality of sleep state. Clearly, morphine administration has a demonstrated capacity to compromise the physiological state of the fetus that would cast doubt on the scientific validity of any observations made when morphine is given.

Further, non-steroidal anti-inflammatory analgesics in the fetus are strongly contraindicated because of their demonstrated capacity to cause fetal hypoxemia and increase the incidence of cerebral haemorrhage in growth-retarded fetuses (Doyle et al., 2005). Finally, there is increasing evidence that anaesthetics such as ketamine may cause a dramatic increase in the rate of programmed cell death in the developing brain of many species (Mellor et al., 2007).

On the basis of all of the above observations, therefore, we recommend in the context of analgesic administration to the fetus that the "If in doubt, treat" strategy should be discarded, at the very least until we understand better what we are doing.

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