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Does the fetus feel pain, and why do we care to know?

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Abstract

As adults we experience pain as the unity of two components: physiological and psychological. We feel the sensation and translate it into an emotional context. The fetus has rudimentary physiological nociceptive pathways from around 24-26 weeks of gestation, and behavioural and physiological responses to nociceptive stimuli. Preterm newborns have observable emotional pain responses to nociceptive stimuli and it has been suggested that if they "feel" pain so must fetuses. However, it is a mistake to consider the newborn at any age as a good surrogate for the human fetus when considering the psychological component of pain. The psychological component of pain requires that we are conscious and aware. The newborn infant experiences consciousness, but there is considerable evidence to show that the fetus does not. The fetus appears to remain in continuous states of sleep-like unconsciousness. These states are maintained by a range of neuro-inhibitory physiological mechanisms that are unique to fetal life and in large part mediated by the placenta. Moreover, the fetus does not appear to be aroused or woken up when exposed to noxious stimuli, suggesting that this sleep-like state of unconsciousness is actively maintained. Thus it is vitally important when considering fetal pain, to remember to take account of the environment the fetus lives in. Further, the temptation to follow the maxim "if in doubt treat" should be tempered by the evidence that analgesics can cause adverse fetal responses, and may lead to damage of organs such as the brain. Conversely, there are little or no data to suggest pain itself can cause injury during fetal life. Much remains to be studied on this subject, but the science, not our heart, should rule our decision-making processes if we are to approach the treatment of the fetal pain in a truly ethical manner.

Introduction

When we undertake surgery or painful procedures on the animals in our care, we are ethically bound to give those animals analgesics to prevent or reduce the experience of pain. However, in many institutions there is no clear policy on how to treat the fetus when considering the care of pregnant animals in teaching and research. Yet, when asked the question do you think that a fetus that undergoes manipulations such as surgery needs analgesia, many of us will firmly answer yes. For those who are not sure, the answer is frequently: "If in doubt treat, better to be safe than sorry." However, neither is a satisfactory place to start the decision-making processes needed to develop effective and safe treatments, and to judge whether treatment is even needed.

The provision of analgesia is a complex task when one can readily access the animal, but the problem gets even tougher when we consider treating the fetus. The development of treatment regimes for the fetus brings with it a host of questions that must be addressed: how do we gain access to treat, what should we treat with, how long for and what are the doses, how can we judge efficacy if we cannot see the

fetus, does the fetus respond to the analgesics like an adult, what is the clearance of medication, are there side effects, and how high is the potential to do more harm than good? The last question is crucial. Unlike the adult, the growing and developing organs of the fetus are at risk of injury when exposed to exogenous factors like anaesthetics and analgesics (Mellor et al. 2005; Drasner 2010; Jevtovic-Todorovic 2011). While we feel comfortable emotionally in advocating treatment on a "just in case" basis, we must in fact use evidence-based medicine and science in order to prevent injury and follow the maxim often ascribed, potentially incorrectly (Smith 2005), to Hippocrates of "*Primum non nocere*; above all, do no harm."

To start our thinking on this subject we need to ask the fundamental question of whether the fetus actually ever feels pain, in the way we as adults understand pain. As adults we understand pain as an adverse emotional sensation. We translate nociceptive (pain) stimuli into an emotional response, and thus our understanding of pain is governed by both physiological, and equally importantly, psychological components. The psychological component requires us to be consciously aware of the stimulus. For example, under anaesthesia, surgical manipulation results in nociceptive stimuli being sent to the brainstem and subcortex, and activation of these regions in turn elicits a physiological response, for example the release of cortisol and catecholamines (Smith et al. 2000). However, we do not "feel" this stimulus as pain, as defined by the emotional component of pain perception, because we are unconscious and thus unaware of the stimuli. While tempting to treat the terms nociceptive stimuli and pain as meaning the same thing, it is vitally important to understand the difference between a nociceptive stimuli and the feeling (emotional/psychological) of pain, when assessing the fetus, for the evidence strongly suggests that the fetus is never conscious and thus the psychological component of pain is not likely to be part of fetal pain processing.

The physiological component: nociceptive circuits in the fetus

In the human fetus, neuro-anatomical studies show that after 23 weeks of gestation, there are connections between nerve endings and the spinal cord, and between the thalamus and preliminary projections to the cortex (Fitzgerald 2005). These connections are necessary to provide the capacity for physiological processing of nociceptive stimuli from the periphery to the brain. It is suggested that this rudimentary circuit may be sufficient to provide the "minimal necessary pathway to feel pain" (Derbyshire 2010). If physiological and behavioural responses to nociceptive stimuli can be taken as evidence that "pain" is being experienced, this may be said to potentially occur from 24 weeks (Derbyshire 2010).

Many studies have indeed suggested that the fetus "feels" pain (in the adult physiological/psychological holistic sense) because there are measurable physiological and behavioural responses to nociceptive stimuli (Smith et al. 2000). For example, fetal needling for blood and biopsy samples, and vibroacoustic stimulation (loud vibrating noise used as a stress test) both result in fetal behavioural changes such as abrupt body movements or limb withdrawal, and the production of "stress" hormones such as cortisol and catecholamines, and changes in cardiovascular variables such as increased heart rate (Abrams & Gerhardt 2000; Smith et al. 2000; Gitau et al. 2004). However, as discussed by Maria Fitzgerald and colleagues, maturation of cortical projections is required for full processing of nociceptive stimuli, and this is a process which is incomplete in fetal life (Fitzgerald 2005; Slater et al. 2007). Further, and importantly, cortical activation does mean consciousness or psychological awareness of the stimulus is painful. These fetal responses primarily reflect subcortical and brainstem responses, reflex in nature, and indeed can be elicited in anencephalic fetuses (i.e. those without a cortex due to failure of neural plate fusion) (Visser et al. 1985; Park et al. 2010), and thus can occur without a cortex and thus without the means to achieve consciousness.

Physiologically, nociceptive pathways in the fetus differ from those seen in the adult. Peripheral sensory receptive fields are large and diffuse in sensitivity, there is immaturity of A and C fibres and thus immaturity of sensory processing within the spinal cord, and there is an imbalance of excitatory and inhibitory control leading to a relatively more excitable state of spinal cord processing (Fitzgerald 2005; Derbyshire 2010). Thus, the reflexes of the fetus and newborn to even mild non-painful stimuli are often initiated at lower thresholds and result in large magnitude, exaggerated movements (Fitzgerald

2005). In adults, acute nociceptive information is conducted within the spinal cord via small myelinated A fibers and larger non-myelinated C fibers. Other afferent sensory information from touch or pressure receptors is conducted via A beta fibers. In the fetus and newborn, however, A beta fibers also appear to conduct nociceptive information Thus stimuli which are not pain-related can activate spinal pathways that are selectively related to pain processing in adults (Fitzgerald 2005).

In the past these responses have led to the concept that the newborn has a greater sensitivity to pain and thus needs more medication (Fitzgerald & Walker 2009). For newborns at least, immaturity of the nociceptive circuit means that analgesia can last longer, and they are more sensitive to analgesics necessitating lower doses (Fitzgerald & Walker 2009). Newborns also change their responses to analgesics during the first month of life, and this may in part be due to the changing role of the rostroventral medulla of the brainstem (Hathway et al. 2009). An example of this is the response to the sedative/analgesic midazolam where in rats before 3 weeks of age midazolam does not induce sedation and may even potentiate pain responses, whereas by 4 weeks the response begins to resemble that of the adult (Koch et al. 2008).

Despite relative immaturity of the nociceptive pathways, newborns nonetheless feel pain psychologically because they are conscious and thus can be aware of the stimuli, and repeated exposure to pain is associated with adverse outcomes (Fitzgerald & Walker 2009). However, this does not mean that the age-equivalent fetus is also conscious and psychologically aware of pain *in utero*. To determine this, one must evaluate what it means to be a fetus, living as it does in a confined, dark and sheltered environment, growing and developing organs and their function, training the body for birth (behaviour), and being attached to an organ (the placenta) which delivers life, and a healthy dose of sedatives and analgesics on a constant basis.

The psychological component of pain perception: fetal consciousness

A few years ago, researchers, rather disturbingly, repeatedly exposed human fetuses to the theme tune to the Australian TV soap-opera "Neighbours" in an attempt to evaluate fetal memory (Hepper 1988; Hepper 1997). The study showed that at the start of the programme the fetuses would adopt a "quiet, alert behavioural state" and 3-5 days after birth more babies who had been exposed to the tune adopted a similar state, slowed their heart rate and stopped crying, than those who had not been exposed. This was taken as recognition and memory of sorts. The data are consistent with the age-old knowledge that babies respond differently to the sound of their mothers voice, the voice they hear most and closest during fetal life (DeCasper & Fifer 1980). Numerous studies have demonstrated that the fetus can apparently form memory *in utero* from around 30 weeks of gestation, and can retain this information for up to 6 weeks after birth (van Heteren et al. 2000; Gonzalez-Gonzalez et al. 2006; Granier-Deferre et al. 2011). From such observations, it has been suggested that this means that the fetus must be conscious or awake. Otherwise, how could it learn?

What is being described here, of course, is auditory memory and the neural entrainment of sound. Fetuses progressively develop hearing in the late gestation period, and numerous studies have shown that they can discriminate variations in both frequency and amplitude of complex sounds (Granier-Deferre et al. 2011). Learning is defined by habituation to the stimuli (e.g., noise). First exposure to noise produces a startled response and increased cardiovascular responses such as heart rate. However these responses attenuate with repeated exposure as the fetus apparently becomes "used to" the sound. When the fetuses are tested later in life, or after birth this attenuation remains when compared to a fetus or baby who has never heard the noise (Hepper 1997; van Heteren et al. 2000; Gonzalez-Gonzalez et al. 2006; Granier-Deferre et al. 2011). This is a form of implicit memory, but such memory does not require conscious thought, and indeed, neural entrainment does not require consciousness (Wang & Orser 2011). Interestingly, the attenuation to stimuli was reported in the first studies of fetal conditioning in the 1920s and '30s, where authors noted that after the fetus is stimulated, time must elapse before it can be stimulated again. This was considered problematic when testing learning and senses in fetuses (Forbes & Forbes 1927; Ray 1932).

Defining whether a fetus is conscious is difficult, as any definition must encompass sensory awareness and cognitive integration of experiences usually with reference to a concept of self (Mashour 2008). The

fetus cannot tell us about self-awareness, but we can in many respects use sleep as a surrogate measure for consciousness, as you can be awake and conscious, but not asleep and conscious. So is the fetus ever awake? For the most part, physiologists and clinicians alike consider that the fetus is asleep (Mellor et al. 2005). However, it is suggested by some, that in late gestation, the fetus may experience periods of wakefulness (Mellor et al. 2005).

In preterm fetuses fetal brain activity is disorganised, and associated with the constant simultaneous expression of numerous behaviours, and erratic cardiorespiratory function (Davidson et al. 2011). Over time, fetal brain activity evolves into two specific states similar to rapid eye movement (REM) and non-REM sleep states. Fetal behaviour becomes episodic and groups of behaviours become associated with specific states. Generally breathing, swallowing, licking and eye movements, and atonia occur in REM sleep, whereas apnea, absence of eye movements and tonic muscle activity occur in NREM sleep. These states account for 95% of fetal activity. The remaining 5% is characterised by mixed brain activity, erratic heart rate, and the vigorous occurrence of all behaviours simultaneously. Such constellations of behaviours occurring together are seen when newborn infants are awake (and at other times, as discussed below), and on this basis this grouping of fetal behaviours has been interpreted as evidence that the late gestation fetus is sometimes awake (Mellor et al. 2005).

Curiously, this behaviour is described as wakefulness only in term fetuses, despite the same simultaneous occurrence of behaviours in mixed brain activity states earlier in gestation. Further, these behaviours do not describe the purposeful, directed, "aware" nature of wakefulness, and most importantly such behaviours can also occur during sleep. As we know, complicated behavioural activity can be undertaken when we are asleep; witness sleep walking where sleepwalkers can play musical instruments, make meals, drive cars etc. The warning here is that complex behaviours do not in themselves mean wakefulness. Sleep is also more complicated than just the states of REM and NREM. The behavioural constellation described as evidence of wakefulness, can also describe transitional or indeterminate sleep. This is a common sleep state seen in infants, which we tend to experience less with age, and is characterised by mixed brain and cardiorespiratory activity, open eyes, and startle-like jerking and limb thrashing (McNamara et al. 2002; Gottesmann 2004). This phase of sleep is frequently seen at the end of NREM and REM periods and allows cardiorespiratory exercise while maintaining sleep, which is vitally important to the developing brain, particularly the state of REM sleep (Kisley et al. 2003). REM sleep, and indeed periods of arousal with large movements, may in large part substitute for wakefulness in the development of neural network organisation, providing intense sensory input not otherwise available *in utero* (Blumberg 2010). Importantly, this transitional sleep-state does not represent wakefulness; it is not, for example, drowsiness (Gottesmann 2004).

Thus it may be hypothesised that so-called wakefulness *in utero* is likely to represent transitional sleep in view of the behaviours described, its occurrence during transition from one sleep state to another, and its similarity to post-natal sleep-arousal (McNamara et al. 2002; Mellor et al. 2005). In support of this concept Rigatto and colleagues watched unanaesthetised sheep fetuses via a plexiglass window and observed no evidence of fetal wakefulness or purposeful, directed awareness for being watched, and they did not interact with the watchers (Rigatto et al. 1986). The evidence, as reviewed by Mellor and colleagues (Mellor et al. 2005), is that the fetus is likely kept in a state of unconsciousness or unarousable sleep. A considerable body of evidence exists to show that there are several suppressors *in utero* which act to inhibit neural activity in the fetus to a far greater degree than is seen post-natally in the infant. For example, cerebral adenosine levels are 3-4 times higher in the fetus than seen post-natally. It must also be appreciated that the fetus is influenced by the placenta, which plays a key role in secreting additional chemical factors such as progesterone, and a potent sleep-inducing hormone (prostaglandin D2). Substance P, which is a key neuromodulator of pain processing, is suppressed in the fetus. All of these factors, acting together with the effects of low oxygen tensions and the warmth of amniotic fluid provide powerful neuro-inhibition. A fascinating demonstration of the impact of temperature upon the developing brain was made by Eales and Small in newborn lambs (Eales & Small 1980). Immersing aroused, physically active and conscious newborn lambs within 4 hours of birth in

water at maternal body temperature induced a sleep-like, non-aroused, unconscious state, and cooling the water restored their prior aroused, conscious and physically active state.

Pain wakes the adult up, so can the fetus be woken?

If we accept that the fetus is kept actively asleep, the logical next question is: can pain wake the fetus up? When we are asleep, we will wake to cutaneous nociceptive stimuli, and to other noxious stimuli such as hypoxia or elevated CO_2. The question has not been directly tested in fetuses, but one can assess the likely answer as being no from a number of studies. During hypoxia the response of the fetus is to switch into a deeper (NREM) or more suppressed form of brain activity (isoelectric state). These states require less energy, and the fetus will further reduce energy expenditure by stopping all behavioural activity including breathing movements (Bennet et al. 2009). Fetuses do not breathe for air of course, but rather breathing movements occur to exercise the respiratory musculature needed at birth and to promote movement in the lungs to facilitate lung growth. Apnea is mediated by areas of the lateral pons which lose their input at birth (Johnston & Gluckman 1989). The apneic response to hypoxia (versus the adult response of hyperventilation) is thus a good example of the unique nature of fetal behaviour, and its adaptation to the *in utero* environment.

Similarly, while elevated CO_2 tensions can elicit an increase in stimulated fetal breathing movements if started in REM sleep, this response is inhibited when the fetus transitions into NREM sleep; there is thus no consistent sleep-state response, and wakefulness was never seen as part of the response (Rigatto et al. 1988). In response to vibroacoustic stimulation, which induces a brainstem dependent startle reflex and heart rate increase, cortical activation is similar to sleep state transitional activity as described above (Bauer et al. 1997), or no change in state occurs if the fetus is in NREM sleep (Abrams et al. 1993). Similar mixed brain activity responses (response and no response) are seen using functional magnetic resonance imaging (fMRI) (Fulford et al. 2004). Further work to test the hypothesis is necessary. However, collectively these data suggest that the fetus does not wake-up or become conscious when faced with noxious stimuli.

If in doubt treat?

One may readily argue that there are data for and against the concept of fetal wakefulness, and the potential for the fetus to cognitively perceive pain, and therefore "feel" pain. Thus ethically we should consider treatment in the face of simply not knowing either way. This is a reasonable point of view, but the development of potential treatment strategies must assess the appropriate analgesic to use, dose and route of administration, the efficacy of selected agents, and above all whether selected agents may have the capacity to do harm. Several studies have demonstrated that analgesics do not necessarily have the same effects on the fetus and indeed newborn, demonstrating the very different neurobiology that must be considered when administering analgesics. An intriguingly titled paper on the subject of analgesia in neonates encapsulates the issue: "Anaesthetic effects on the developing nervous system: if you aren't concerned, you haven't been paying attention" (Drasner 2010). Currently, a significant lack of evidence has led to a lack of consensus about what to give, but the data show that the risks are potentially very high (Mellon et al. 2007).

A variety of studies have shown that analgesics can have adverse effects on the fetus, and do not elicit the same responses as the adult. Morphine given to fetal sheep is not a cardiorespiratory depressant for example, as it is in adults, but rather stimulates cardiorespiratory activity, and can induce acidosis, seizures and fetal death (Bennet et al. 1986). It can also stimulate hypothalamic-pituitary adrenal (HPA) function and cortisol and adrenocortiotrophic hormone (ACTH) release; cortisol being a one factor used determine the presence of pain (Taylor et al. 1997). The synthetic opiate, Finadyne, did not markedly alter fetal sheep nociceptive stress responses to cutaneous electrical stimulation, and induced marked acidosis (Smith et al. 2004), and blunted the defence responses to hypoxia (Boekkooi et al. 1995). In humans, maternally administered morphine caused reduced placental perfusion by acting as a vasoconstrictor (Kopecky et al. 2000). Similar observations are made for other agents such as ketamine during development and exposure can lead to persistent changes in maternal and fetal perfusion, and blood gases and fetal wellbeing (Strumper et al. 2004; Jonker et al. 2008; Walker et al. 2010). Of significant

interest in recent years is the observation that opiates can increase neural apoptosis in both fetal humans and animals leading to impaired neurodevelopment (Hu et al. 2002; Liu et al. 2011). It can also affect other organs such as the heart; in rats, for example, opiates alter production and potentially release of natriuretic peptides from the fetal heart which regulate cardiac function (Ernest et al. 1998).

Non-steroidal anti-inflammatory drugs (NSAIDS) such as indomethacin, ibuprofen, and nimesulide have also been shown to have deleterious effects, such as premature closure of the ductus arteriosus (thus impairment of fetal cardiovascular function) (Weichert et al. 2010), and impairment of renal function and development (Loudon et al. 2003; Kent et al. 2007). Our own laboratory experience with indomethacin in normoxic fetal sheep is that it can cause significant fetal acidosis and the death of some fetuses. Others have observed that indomethacin significantly impairs fetal metabolism during hypoxia, causing severe metabolic acidosis (Hooper et al. 1992). The potential side-effects of maternal analgesia during labour have recently been extensively reviewed (Reynolds 2011). Remifentanil is proposed as a good agent for fetal immobilisation and analgesia during and after fetal surgery (Fink et al. 2011). However, significant work has yet to be carried out on this short-acting opioid to determine good and bad effects. It clearly can reduce fetal movement, one measurement of fetal pain. It is not known if it alters HPA function as morphine does and therefore cortisol or catecholamine release, or other indices of fetal pain processing.

Clearly caution is needed when considering the development of any analgesic treatment strategy for the fetus or newborn, and simply extrapolating from neonatal therapies is insufficient, in the same way as extrapolating from therapies devised for adults and children is deleterious for newborns (Fitzgerald & Walker 2009). Of course the evidence suggests that we do not need to treat the fetus because the fetus is never conscious, and thus not psychologically aware of painful stimuli as painful. However, some would argue that the experience of pain, even if only physiologically, can itself cause long-term harm. Findings in newborns, are extrapolated back to the fetus, with the suggestion that age-equivalent fetuses are likely to feel pain if their newborn counterparts do, and thus analgesia is necessary for the fetus to stop acute pain (Vanhatalo & van Nieuwenhuizen 2000; Van de Velde et al. 2006), and to prevent long-term harm (Bhutta & Anand 2002). Certainly, newborns have the capacity to feel pain, and repeated exposure to painful stimuli can induce increased sensitivity to pain (hyperalgesia), and the experience of pain in response to non-noxious stimuli (allodynia) (Fitzgerald & Walker 2009). These changes in the response to noxious stimuli arise in part from changing the control of membrane excitability, with an increase in the input from excitatory inputs and reduced inhibitory control (Sandkuhler 2009). However, as discussed above, the fetus lives in a very different environment, one in which neuro-inhibition predominates (Mellor et al. 2005). It may be readily argued that the presence of significant levels of neuro-inhibitors would serve to prevent the development of hypersensitivity to stimuli through inhibiting upregulation of neuronal excitability.

To date, the concept of hypersensitivity has not been examined in the fetus. However, limited data suggest that hypersensitivity does not occur to repeated exposure to the noxious stimuli of vibroacoustic stimulation. Repeated exposure leads to rapid attenuation not exacerbation of the fetal responses (van Heteren et al. 2000). The greater neuro-inhibition the fetus experiences is also likely to prevent the development of hypersensitivity. For example, the fetus experiences much higher levels of prostaglandins and adenosine, both of which can act as an analgesic which in turn can prevent the development of allodynia and hyperalgesia (Minami et al. 1997; Sawynok & Liu 2003; Sandkuhler 2009). In the fetal sheep, adenosine levels are high in the fetal brain after fetal surgery, and decline with recovery suggesting that nociception associated with surgical procedures stimulates an increase in circulating levels of neuroinhibitors (Watson et al. 1999). Similarly, neurosteroids which are potent sedatives and analgesics are significantly upregulated in the fetus, after the noxious stimulus of asphyxia (Nguyen et al. 2004).

Complete functionality of the physiological pathways may also be necessary and there remains, of course, the key issue of the role of consciousness (Sandkuhler 2009). Hypersensitivity to pain is known to have an emotional content. Anticipation of pain can, for example, make the experience more painful

(Sandkuhler 2009). Further, functional imaging of the brain in response to pain demonstrates that hypersensitivity in adults incorporates sensory, cognitive and behavioural processing (Peyron et al. 2000). These data strongly suggest consciousness is a necessary part of the development of hypersensitivity to pain, and that awareness of the stimuli may play an important positive feedback role in the development of the necessary changes in neuronal excitation.

Conclusions and perspectives

In conclusion, this brief review highlights the complex issue of pain assessment and management in the fetus. Collectively, the data discussed in this review demonstrate that the fetus from around mid-gestation may have the rudimentary capacity to process nociceptive stimuli physically, but that the peripheral and neural pathways function quite differently to the adult. However, at all ages, the data demonstrate that the fetus is likely maintained in a sleep-like unconscious state by high levels of circulating neuro-inhibitors of placental and fetal origin. Without conscious awareness the fetus cannot experience the meaning of nociceptive stimuli in a psychological manner and thus will not feel pain in the way that we as adults understand the concept emotionally.

The review also discusses the concept "if in doubt treat". Considerable evidence exists to show that analgesics may be deleterious to developing organs. Conversely, unlike the newborn and adult, there is little or no data to show that the experience of pain itself results in adverse effects. Thus considerable work must be done to establish the impact of analgesics on the fetus before we can embrace this concept, and one must truly consider the data which suggest that treatment is not actually necessary. Ultimately, the key message of this review is that if we are to understand fetal pain, we must not evaluate the fetus by comparing it to the newborn or adult. Rather we must assess the fetus, as a fetus, a being who is regulated by and adapted to its unique *in utero* environment, an environment which significantly modulates the physiological sensations of pain, and prevents the totality of that adverse experience by preventing conscious awareness.

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