



Royal College of Obstetricians and Gynaecologists

Fetal Awareness

Review of Research
and Recommendations
for Practice

March 2010

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REPORT OF A WORKING PARTY

March 2010



Royal College of Obstetricians
and Gynaecologists

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Glossary

4-D (four-dimensional) images	Three-dimensional images that move in real time (time being the fourth dimension)
anencephalic fetus	A fetus with the major part of the brain missing
anoxic stress	Physiological stress through lack of sufficient oxygen
anterior cingulate	A higher cortical (brain) structure responsible for processing the unpleasantness of pain
arborisation	Branching – in this case of nerve fibres growing into a brain region; this is required before all the correct connections can be formed
auditory cortex	The part of the brain responsible for processing sound
axons	‘cables’ or nerve fibres connecting different parts of the brain
brainstem	A lower brain structure, lying between the spinal cord and the thalamus which is responsible for many reflex actions such as breathing
catecholamines	A chemical typically released during stress
cerebral cortex	A sheet of densely packed neuronal cells which form the outer, folded part of the brain associated with higher functions
cognition/cognitive	Thinking, knowing, sensing and perceiving
cortical plate	Develops before the cerebral cortex proper
EEG (electroencephalogram)	Measures electrical discharges in the brain. Electrodes are placed on the scalp of a subject and the activity of the neurons in the underlying cortex is recorded
electrophysiological	Techniques used to directly record the electrical activity of the peripheral or central nervous system in the body
endocrine	Hormone circulating in the body
endorphins	A neurochemical released naturally in the body that, in adults, suppresses pain
endoscopic laser ablation	A technique for destroying tissues directed by a small telescope inserted into the body
<i>ex utero</i> intrapartum treatment	Delivery of the head and shoulders at caesarean section so that surgery can be performed while the baby is still receiving oxygen from the placenta
fetal magnetoencephalography	A technique to measure brain activity in fetus
haemodynamic	The movement of blood
hypoxaemia	Decreased blood oxygen

hysterotomy	Surgical incision in the uterus, usually to remove the fetus
insular cortex	Part of the cerebral cortex believed to be responsible for integrating sensory information
fMRI (functional magnetic resonance imaging)	A technique for measuring blood flow in the brain, which is indirectly related to neuronal activity
neurobiological	A generic term relating to the biological functions of the central nervous system
neuronal connection	A communicative contact between two neurons
neuropsychological	A psychological function associated with a part of the brain
nociceptor activity	Passage of electrical signals through a nerve fibre that detects noxious stimuli
noxious stimuli	Stimuli that do or could cause damage to the body
opiate/opioid	A neurochemical that suppresses pain, of which endorphins are an example
sensory cortex	Part of the cortex responsible for processing sensory stimuli from the body, such as touch
sentience	The ability to detect and experience a sensory stimulus
somatosensory	The senses that are detected on the surface or deep within the body, such as touch, temperature, pressure
spinothalamic pathways	Major pathway transmitting noxious information through the spinal cord
stress/stress response	Typically the release of catecholamines following an adverse event but may also include other chemical and behavioural responses
subcortical sensory nucleus	A part of the brain between the spinal cord and cortex that processes sensory information, such as the thalamus
subplate zone	A developmental structure that holds and guides neurons to their correct place in the cortex
synapse	A communication juncture between two neurons
thalamic	Pertaining to the thalamus
thalamus afferents	Fibres carrying information into the thalamus
transient tachypnoea	Rapid breathing observed shortly after birth indicating a temporary difficulty with respiration
venepuncture	Penetrating a vein for injection or for withdrawal of blood
viability	Ability to survive
visual cortex	Part of the cortex responsible for processing vision

Attention is also drawn to the glossary entitled *Medical Terms Explained* available on the RCOG website:

www.rcog.org.uk/womens-health/patient-information/medical-terms-explained.

Summary

The need to review the 1997 RCOG Working Party Report on Fetal Awareness arose following discussion during the House of Commons Science and Technology Committee Report on Scientific Developments relating to the Abortion Act 1967. In accepting the findings and conclusions of the House of Commons report, the Minister of State for Public Health recommended that ‘the College review their 1997 report into fetal pain’. Accordingly, this Working Party was established with the remit and membership described. The intention was to review the relevant science and clinical practice relevant to the issue of fetal awareness and, in particular, evidence published since 1997. In so doing, the report was completely rewritten, not only to take account of recent literature but also the evidence presented to the House of Commons Committee.

In reviewing the neuroanatomical and physiological evidence in the fetus, it was apparent that connections from the periphery to the cortex are not intact before 24 weeks of gestation and, as most neuroscientists believe that the cortex is necessary for pain perception, it can be concluded that the fetus cannot experience pain in any sense prior to this gestation. After 24 weeks there is continuing development and elaboration of intracortical networks such that noxious stimuli in newborn preterm infants produce cortical responses. Such connections to the cortex are necessary for pain experience but not sufficient, as experience of external stimuli requires consciousness. Furthermore, there is increasing evidence that the fetus never experiences a state of true wakefulness *in utero* and is kept, by the presence of its chemical environment, in a continuous sleep-like unconsciousness or sedation. This state can suppress higher cortical activation in the presence of intrusive external stimuli. This observation highlights the important differences between fetal and neonatal life and the difficulties of extrapolating from observations made in newborn preterm infants to the fetus.

The implications of these scientific observations for clinical practice are such that the need for analgesia prior to intrauterine intervention, for diagnostic or therapeutic reasons, becomes much less compelling. Indeed, in the light of current evidence, the Working Party concluded that the use of analgesia provided no clear benefit to the fetus. Furthermore, because of possible risks and difficulties in administration, fetal analgesia should not be employed where the only consideration is concern about fetal awareness or pain. Similarly, there appeared to be no clear benefit in considering the need for fetal analgesia prior to termination of pregnancy, even after 24 weeks, in cases of fetal abnormality. However, this did not obviate the need to consider feticide in these circumstances and, in this respect, further recommendations of relevance are included in the parallel report on *Termination of Pregnancy for Fetal Abnormality*.

Background

Remit

The Working Party was established in May 2008 with the following remit:

1. To review the RCOG Working Party Report *Fetal Awareness*, published in October 1997.
2. To review all evidence submitted to the Science and Technology Committee relating to the Abortion Act 1967.
3. To review all other evidence of relevance to fetal awareness and pain.
4. To publish a report based on the Working Party's findings.

The Working Party met on four occasions between July 2008 and July 2009 and reported to Council in November.

Membership

The Membership of the Working Party was:

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1. Introduction

Following concerns generated by the debate on fetal awareness and, particularly, the controversy around whether the fetus could feel pain, the RCOG published, in October 1997, a working party report.¹ A guiding principle in that report was concern that the fetus should be protected from any potentially harmful or painful procedure but, at the same time, the assessment of the capacity to be harmed should be based on established scientific evidence. A major and important conclusion of the report was that the human fetus did not have the necessary structural integration of the nervous system to experience awareness or pain before 26 weeks of gestation. In addition, the report recommended that those carrying out diagnostic or therapeutic procedures on the fetus *in utero* at or after 24 weeks should consider the need for fetal analgesia.

This guidance was welcomed by the clinical and scientific communities, although, in recent years, the report has from time to time come under criticism in some quarters for being out of date and perhaps not having assessed all the known scientific evidence. This criticism has been most evident in discussing the age of viability (at present taken as 24 weeks of gestation in the UK) and the upper gestational limit in the context of induced abortion. The House of Commons Science and Technology Committee, in its report on *Scientific Developments Relating to the Abortion Act 1967* (published in October 2007),² made a number of important conclusions and recommendations, including some of direct relevance to this issue: ‘We conclude that, while the evidence suggests that foetuses have physiological reactions to noxious stimuli, it does not indicate that pain is consciously felt, especially not below the current upper gestational limit of abortion. We further conclude that these factors may be relevant to clinical practice but do not appear to be relevant to the question of abortion’.²

A minority report, however, recorded in the minutes of the Committee on 29 October 2007 said, ‘We are deeply concerned that the RCOG failed to give full information to the House of Commons Select Committee...since 1997 the RCOG has consistently denied that foetuses can feel pain earlier than 26 weeks, without acknowledging that amongst experts in this field there is no consensus. Professor Anand is a world authority in the management of neonatal pain and has put forward a cogent argument suggesting that the RCOG position is based on a number of false or uncertain presuppositions’.¹

In the Government response to the House of Commons report (released November 2007) the Minister of State for Health welcomed the report and its conclusions and recommendations but importantly also indicated that ‘we note the Committee’s findings and are in agreement that the consensus of scientific evidence with regard to fetal pain at gestations below 26 weeks and we will be commissioning the College to review their 1997 working party report into fetal pain which will re-examine the latest evidence, much of which has been considered by the Committee, and any new research currently underway’.³

Accordingly, a Working Party was formed to review the 1997 report. At its first meeting it decided to review not only the evidence in the original report but also, more importantly, any relevant evidence published since, including particularly the literature referred to in the minority report. As with the original report, it was decided not to reconsider the ethical situation

surrounding viability and abortion, not least because many of the relevant issues had been addressed in the Nuffield Council publication *Critical Care Decisions in Fetal and Neonatal Medicine: Ethical Issues* (2006).⁴ Their terms of reference centred on the ethical, social, economic and legal issues arising from recent developments in fetal and neonatal medicine relating to prolonging life, as well as issues raised by advances in research and practice. This discussion very much revolved around 24 weeks as the age at which survival without impairment becomes more likely and, with the acceptance that survival without serious impairment or disability is highly unusual at 22 weeks of gestation, this led to the conclusion that there was no obligation to attempt resuscitation at gestational age of 23 weeks or lower. Importantly, the report recommended that a group of specialists and interested parties should develop a definition of 'born alive', with consideration to incorporating such a definition in statute. The RCOG has now considered this issue and intends to pursue further discussion with the Department of Health in relation to the clinical and legal consequences.

Furthermore, the Working Party agreed that, in reviewing past and current evidence, the report would need to be completely rewritten and that, while it should retain its relevance for practitioners and those with a professional interest in the area, it should also contain advice of relevance to women and parents. At the same time, the Working Party was aware of a parallel piece of work, also arising from the Government response to the House of Commons Science and Technology Report on termination of pregnancy for fetal abnormality.⁵ Much of that Working Party's report and, in particular, the conclusions and recommendations are of relevance to the issue of fetal awareness and, in this respect, the reports complement each other.

Particular acknowledgement is paid to those who took the lead in drafting the various chapters but responded constructively to discussion and modification, such that the report is one in which all of the participants contributed significantly. It is hoped that most will find the report helpful and that it goes some way to answering some of the criticisms of recent times, as well as offering sound advice to practitioners and consumers.

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2. Neurobiological developments relevant to pain

This section examines current knowledge of central nervous system function during fetal and neonatal periods of human development. The aim is to provide a description of key events and changes to inform whether the fetus can reasonably be said to experience pain. To do this, we reviewed all new evidence related to the neurobiology of fetal pain that has been published in peer-reviewed journals listed on PubMed.

We begin by considering the scientific evidence for the presence of specific anatomical and physiological connections in the brain that are responsible for signalling noxious events to the central nervous system. Noxious stimuli are those that damage the tissues of the body or threaten to do so, such as surgical incision or physical trauma of the skin. In this context, we define pain as ‘the unpleasant sensory or emotional response to such tissue damage’ and trace the development of those responses through fetal development. We follow the path of the signals produced by tissue damage at sensory detectors in the skin and other organs, through to sensory circuits in the spinal cord, brainstem and thalamus and finally to the cerebral cortex, the site of higher level sensory processing. At each stage, we consider the scientific evidence for functional development and how this evidence may be interpreted. This section includes details derived from over 50 papers identified as relevant. Most were published since the last Working Party report¹ but this current report also considers the older material included in the previous report.

In addition to understanding the anatomical and physiological connections, it is also important to consider the psychological aspects of pain. Broadly accepted definitions of pain refer to pain as a subjective experience involving cognition, sensation and affective processes.² These psychological concepts are inevitably harder to address in a fetus but should not be ignored. A discussion of the importance of psychological processes in pain can be found in Box 1.

Development of neural pathways related to pain

The neural regions and pathways that are responsible for pain experience remain under debate but it is generally accepted that pain from physical trauma requires an intact pathway from the periphery, through the spinal cord, into the thalamus and on to regions of the cerebral cortex including the primary sensory cortex (S1), the insular cortex and the anterior cingulate cortex.^{3,4} Fetal pain is not possible before these necessary neural pathways and structures (figure 1) have developed.

The generation of nerve signals from damaged tissue

For the fetus to respond to surgical damage, receptors in the affected tissue, such as skin and muscle, must signal the noxious stimulus or damage to the central nervous system. Nociceptors are sensory nerve terminals found in the skin and internal organs that convert tissue

damage into electrical signals. The pattern and strength of these nociceptor signals is the first determining step in generating pain. If nociceptor activity is prevented, such as following local anaesthesia, then pain is blocked. Deep tissue damage, for example, that cuts through nerve bundles causes a brief burst of electrical activity in some of the cut nerve endings known as an injury discharge.⁵ The injured tissue, however, is now isolated from the central nervous system and, within a few minutes, the isolated tissue becomes ‘numb’ and pain free. Similarly, rare genetic defects that prevent all nociceptive signals result in a complete inability to sense pain.⁶

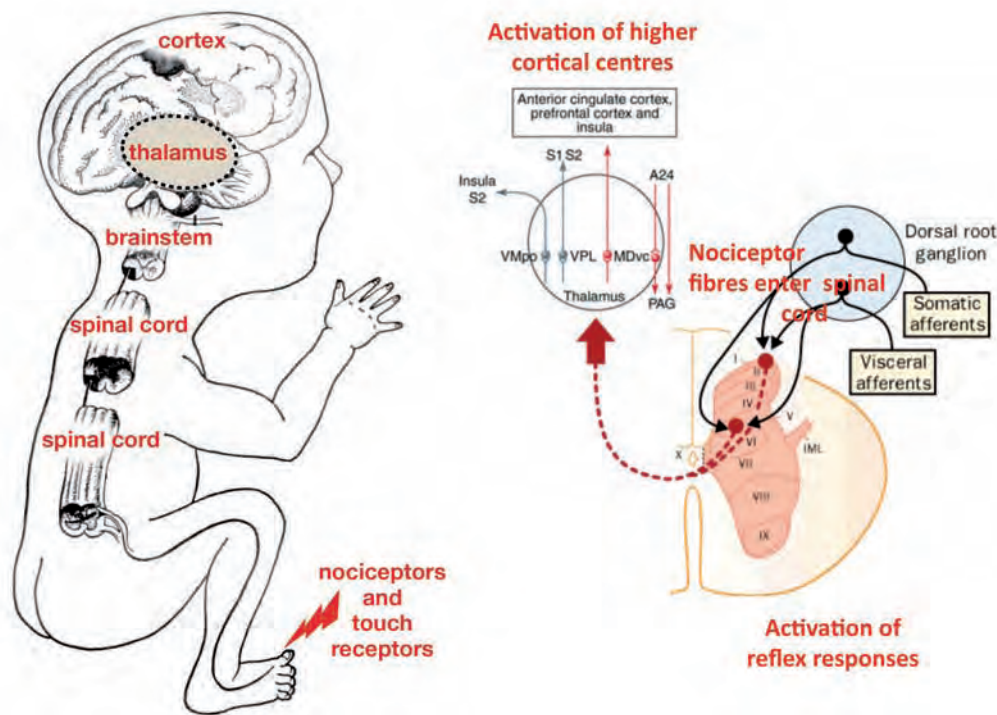


Figure 1. Pathways from the periphery through the spinal cord and into the thalamus and to the cortex. Nociceptor activity evoked by tissue damage reaches the spinal cord and can activate reflex responses through spinal cord connections. Pathways projecting to the thalamus and cortex may also be activated. Higher-level pain processing is thought to occur through a medial system (red lines) which has both ascending and descending components and a lateral system (blue lines) from the ventroposterior lateral (VPL) and ventromedial posterior (VMpo) nuclei. MDvc = mediadorsal ventral caudal nuclei; PAG = periaqueductal gray; S2 = secondary somatosensory cortex; S1 = primary somatosensory cortex; A24 = area 24, anterior cingulate cortex (adapted from Cervero and Laird,⁵⁵ Derbyshire⁵⁶ and Fitzgerald & Walker⁵⁷)

Anatomical studies of human fetal skin shows the presence of nerve terminals and fibres deep in the skin from 6 weeks of gestational age. These terminals are not nociceptors and are specialised for the processing of non-damaging sensations such as touch, vibration and temperature, rather than pain. From 10 weeks, nerve terminals become more numerous and extend towards the outer surface of the skin.^{7,8} The terminals closer to the surface are likely to be immature nociceptors, necessary for pain experience following tissue damage, but they are not unequivocally present until 17 weeks.⁸ In other mammals, newly formed fetal nociceptors are able to signal tissue damage but the intensity of their signals is weaker than in adults.⁹ The internal organs develop nerve terminals later than the skin, beginning to appear from 13 weeks and then increasing and spreading with age, so that the pancreas, for example, is innervated by 20 weeks.¹⁰

Interpreting these data

Specialised nerve terminals, nociceptors, are likely to detect surgical tissue damage from early in fetal life (around 10 weeks for the skin and 13 weeks for the internal organs). These nociceptors gradually mature over the next 6–8 weeks and the strength of their signals increases over fetal life. The presence of nociceptors is necessary for perception of acute surgical pain and so pain is clearly not possible before the nociceptors first appear at 10 weeks. The presence of nociceptors alone, however, is not a sufficient condition for pain experience. The electrical activity that is generated at nociceptor terminals by tissue damage must also be conducted along nerve fibres from the skin and into the spinal cord and brain. It is only when the brain receives information about the damage that the fetus can have any potential of awareness of it.

The transmission of signals from damaged tissue to the lower levels of the central nervous system

Before any information about a noxious or tissue damaging stimulus can reach the brain, it has to be transmitted through the spinal cord (for the body) or the brainstem (for the head and neck). This transmission requires the growth of nerve fibres from the skin to the spinal cord or brainstem and then further growth of nerve fibres along the spinal cord or brainstem and into the brain. Staining of postmortem tissue reveals that nerve fibres grow into the fetal spinal cord from 8 weeks. These fibres, however, are specialised for the control of movement and some aspects of touching or prodding the body or positioning a limb.

The growth of nerve fibres connecting nociceptive terminals to the spinal cord lags behind that of other sensory inputs in non-human mammals. Similar connections in the human are also likely to lag but the specific timings remain unknown. Preliminary studies have failed to demonstrate nerve fibres from nociceptive terminals in the fetal post-mortem spinal cord before 19 weeks.¹¹

The growth of sensory nerve fibres into the spinal cord is required for the fetus to display reflex movements in response to external stimuli. Sensory reflex responses are relatively simple, central nervous reactions to external events, some of which provide simple protection against damage. Examples of these reflexes include blinking in response to an air puff to the eye or the withdrawal of a limb in response to prodding the skin. The presence or absence of these reflexes at various stages of fetal life can provide information about the first functional sensory connections. In mammals these reflexes are mediated by the spinal cord and brainstem (Figure 1).

During the first 8 weeks of pregnancy, the human fetus displays a range of spontaneous movements, which are not actually reflexes, as they arise from random muscle actions rather than as reactions to a sensory stimulus. However, when sensory nerves have reached the skin, mechanical stimulation of the body can produce reflex movements. This confirms that these nerve fibres are carrying information about touch and have connected to the spinal cord and activated nerve fibres controlling motor actions. The fetal spinal cord and brainstem develop well before the cerebral cortex. This means that these reflex movements occur without any possibility of fetal awareness.

The exact timing of the first nociceptive reflex responses to more traumatic mechanical stimulation is not known but they are unlikely to occur before the second trimester, somewhat later than responses to touch. It is known that the fetus withdraws from a needle from about 18 weeks and also launches a stress response following needle puncture.¹² This stress response includes the release of hormones and neurotransmitters dependent on activity in areas of the midbrain. These findings confirm that signals about tissue damage are transmitted from the spinal cord and brainstem to the midbrain from at least 18 weeks.

Box 1. A discussion of the nature of pain

The word 'pain' is used in different ways. The most frequent use, especially with respect to subjects that cannot communicate verbally, is in describing the behavioural response to noxious stimulation. However, if we accept this use, we are presented with the difficulty of distinguishing between the responses of simple versus complex organisms. Fruit fly larvae, for example, have been demonstrated to bend and roll away when approached with a naked flame but most people would agree that larvae do not feel pain in the way that we do.

Ruling out the responses of larvae and similarly simple organisms as indicating pain is possible if we suggest that responses must include more than mere reflex responses to be labelled as a pain response. When someone reaches out and accidentally touches something very hot, there is an immediate tendency to drop the object. That reaction is entirely regulated by a simple loop of sensory neurons speaking to motor neurons in the spinal cord. Typically, the person will drop the object before there is any conscious appreciation of pain. The action of dropping the object indicates the presence of something noxious but does not necessarily indicate the presence of pain.

Most pain researchers adopt a definition of pain that emphasises the sensory, cognitive and affective response to a noxious event. This understanding of pain is supported by the International Association of Pain (IASP) which defines pain as 'an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage...pain is always subjective. Each individual learns the application of the word through experiences related to injury in early life'.¹ By this definition, pain does not have primacy over subjectivity, existing before and in addition to subjectivity, but is experienced through subjectivity. It suggests that pain is a part of knowledge and requires the existence of a conceptual apparatus that can marshal all its dimensions into a coherent experience.

Although there is considerable merit in the IASP definition of pain, it does tend towards a view of pain as being a constituent part of higher cognitive function. There is disquiet in denying a rawer, more primitive, form of pain or suffering that the fetus, neonate and many animals might experience.²⁻⁴ One possible solution is to recognise that the newborn infant might be said to feel pain, whereas only the older infant can experience that they are in pain and explicitly share their condition with others as an acknowledged fact of being.⁵

Currently there is no immediately obvious way of resolving these arguments empirically. It is possible, however, to argue that even a raw sense of pain involves more than reflex activity and will, therefore, require the higher regions of the cortex to be connected and functional. The age when this minimum requirement is fulfilled is explored in the rest of this chapter.

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Interpreting these data

Observations of fetal movements in response to sensory stimulation show us that information about tissue stimulation has reached the spinal cord from 8 weeks. The demonstration of a hormonal stress response at 18 weeks following needle puncture shows us that information about tissue damage has reached the midbrain. A connection from the skin to the spinal cord and brain is a basic requirement for the fetus to feel or be aware of pain. Again, it is important to emphasise that, while such input to the spinal cord and brain is necessary for perception of acute surgical pain, it is not sufficient. Activity in the spinal cord, brainstem and subcortical midbrain structures are sufficient to generate reflexive behaviours and hormonal responses but are not sufficient to support pain awareness. At 18 weeks of gestational age, local spinal cord or brainstem reflexes control movement and, even as movement becomes more coordinated from 24 weeks, it does not require the involvement of higher brain centres. Extremely preterm infants of 24–30 weeks of gestation show the same motor responses to a noxious heel lance (required for clinical blood sampling) even when there is severe damage of the pathways connecting the spinal cord and brainstem to higher brain centres.¹³ Also, such reactions to noxious stimuli, even those involving changes in facial expression, do not always correlate with cortical activity¹⁴ when the nervous system is intact, showing that they cannot be assumed to reflect higher brain function.

Hormonal responses to needling show that there are functional brainstem and midbrain mediated reactions to noxious events but they, too, do not require higher brain processing to take place and can occur independently of sensory awareness. The specific relationship between pain and the release of hormones and neurotransmitters is unclear. In a prospective crossover study on 50 extremely low gestational age infants (less than 28 weeks of gestation), no difference in hormonal response was observed after heel lance¹⁵ and, in adult mice, it is difficult to distinguish changes in levels of naturally occurring opioids due to stressful handling from those due to tissue damage.¹⁶

The transmission of signals from damaged tissue to cortical regions of the brain

Reflex movements and hormonal stress responses provide information about sensory connections at lower levels of the nervous system and cannot be assumed to indicate perception or awareness. For perception or awareness, the sensory information needs to be transmitted to the thalamus, the major subcortical sensory nucleus and then to the cortex, the highest region of the brain.

Anatomical evidence

At 8 weeks, the fetal brain is profoundly immature and its surface layer, the cerebral cortex, is smooth, with no indication of the folds (sulci and gyri) that are so prominent later.¹⁷ There is also no internal cellular organisation in either the thalamus, which is the main source of sensory input to the cortex, or the cortex itself.^{18,19} The limbic system, an evolutionary older part of the brain, consisting of interconnected deep brain structures involved in various fundamental drives and regulatory functions, is already discernable and has begun to form interconnections.²⁰ The external surface of the brain is about 1 mm thick and consists of an inner and outer layer with no cortical plate, the structure that will gradually develop into the layers of the cortex proper.²¹ At 13 weeks, a furrow or groove appears on each side of the brain,¹⁷ which becomes part of the insular cortex around 15 weeks, a key region involved in the experience of external stimuli, including pain.²² In spite of this, the fetal brain is still largely

smooth at 26 weeks. Massive growth of the brain after 34 weeks rapidly results in the characteristic folds and surface features of the more mature brain.

An important stage of cortical development is the formation of the subplate zone, a prominent, transient layer of the human fetal cerebral wall which develops around 13 weeks and gradually disappears after 32–34 weeks. The subplate is composed of newly arrived neurons and their connections together with other brain cells and cellular components and a large amount of extracellular material. All this makes the subplate very clearly distinguishable in fetal and neonatal brain scans (magnetic resonance images) and in postmortem brains. The subplate is thought to be the main synaptic or neuronal connection zone in the human fetal cortex where incoming fibres from the thalamus, the main sensory (and pain) relay centre, and other regions of the cortex gather during the crucial phase of cortical target area selection. Recent neurobiological evidence from other mammals shows that subplate is a site of spontaneous electrical activity and that this activity is required to build a framework for the precise organisation of cortical connections. The subplate is a focus of interest of paediatric neurology because damage to this area may lead to cognitive impairment in later life.²³

The first projections to the subplate from the thalamus arrive between 12 and 18 weeks^{21,24,25} and wait for the overlying cortical plate to mature and facilitate the invasion of neurons from the subplate.²⁶ Electrical activity arising from synaptic connections has been recorded in subplate neurons in isolated slices of mammalian brain but it is not known whether that activity can be selectively produced by thalamic connections or by noxious stimulation of body tissues in intact animals. It is known that this synaptic activity in the subplate performs a maturational function. In non-human mammals, synaptic activity in the subplate facilitates connections between thalamus and cortex and refines the early, initially crude, connections between the thalamus and cortex.²⁷

By 24 weeks, substantial thalamocortical fibres have accumulated at the superficial edge of the subplate, which is the stepping-off point for axons growing towards their final cortical targets.²¹ Between 24 and 32 weeks, there is substantial ingrowth of thalamocortical axons in the cortical plate of the frontal, somatosensory, visual and auditory cortex, and formation of the first synapses in the deep cortical plate. This is consistent with observations in neonates with rare brain malformations, such as lissencephaly, where the brain resembles that of a fetus before 23–24 weeks of gestation, and which shows a lack of connections between the cortex and subcortical nuclei and an abnormal limbic system.²⁸

At the same time, the relocation of neurons from the subplate to the cortical plate also begins around 24 weeks, thus coinciding with the invasion of thalamic afferents. This relocation is extremely rapid from about 34 weeks, leading to the dissolution of the subplate as the extracellular matrix and other growth-related and guidance molecules disappear.²¹ The subplate has been observed to thin in the insula and in areas where cortical folding occurs rather earlier than the rest of the cortex, from at least 20 weeks.²⁹ It is currently uncertain whether this thinning is due to earlier maturation and potentially earlier synaptic activity in these regions, some of which are key areas in the experience of pain in adults,³ or attributable to incidental morphological changes.

The arrival of thalamic fibres and formation of thalamocortical synapses in the newly formed cortex from 24 weeks onwards provides the minimum connection required for cortical processing of sensory events in the body. However, completion of the major pathways from the periphery to the cortex, at around 24 weeks, does not signal the end of cortical development but the beginning of a further maturational process. As spinothalamic pathways complete their connections with the cortex, they increasingly stimulate the development of intracortical pathways, which is the next major phase of neuronal maturation. Furthermore, the cortex sends

connections down to the brainstem and spinal cord; the motor centres of the brain have begun to form connections with the spinal cord and brainstem by 26–28 weeks.³⁰ This phase involves elaboration and refinement of neuron processes and connections, including selective elimination of some cell populations and corresponds to the cortical maturation described by Goldman-Rakic³¹ in primates and by Chugani³² in humans. McKinstry *et al.*³³ illustrated the effects of this development using diffusion tensor imaging in neonates born at 26 and 35 weeks. The proliferation of cortical neurons and the overgrowth of arborisation and synaptic contacts begins prenatally³² but continues postnatally, together with synaptic elimination, pruning and programmed cell death.^{31,32,34,35}

Physiological evidence

While the study of anatomical connections between brain regions provides important information about developing pain processes, the existence of a connection is not evidence of its function. Connections viewed under the microscope between the thalamus and the cortical plate at 24 weeks, for example, may or may not transmit information from nociceptors upon tissue damage. Fetal magnetoencephalography has been used to effectively record fetal auditory and visual evoked responses and spontaneous brain activity of cortical origin from 28 weeks and fetal brain activation to sound has been demonstrated using functional magnetic resonance imaging (fMRI) from 33 weeks. It has not been possible to record directly from human fetal cortex to establish when cortical neurons first begin to respond to tissue damaging inputs. Near infrared spectroscopy with preterm infants in intensive care, however, has demonstrated localised somatosensory cortical responses in premature newborn infants (from 24 weeks) following noxious heel lance³⁶ and venepuncture.³⁷ More recently, EEG has demonstrated a clear, time-locked, nociceptive-evoked potential in preterm infants following heel lance.³⁸ Thus, there is direct evidence of neural activity in primary sensory cortex following tissue damage in very premature infants equivalent to 24 weeks of gestational age.

Behavioural evidence

Fetal behavioural responses have also been used as indicators of stress or pain.^{22,39} Shortly after the development of skin sensitivity, around 10 weeks, repeated stimulation results in hyperexcitability and a generalised movement of all limbs. After 26 weeks, this generalised movement gradually gives way to more coordinated behavioural responses that indicate improved organisation within the nervous system. Infants delivered at 26–31 weeks, for example, show coordinated facial expressions in response to heel prick,²³ although these are immature compared to older infants.⁴⁰ Four-D images of the fetus have also been reported to show fetuses ‘scratching’, ‘smiling’, ‘crying’ and ‘sucking’ at 26 weeks of gestational age.

Although these later behavioural responses are not spinal cord reflexes, the responses are still unlikely to involve higher cortical centres. An anencephalic fetus withdraws from noxious stimulation, demonstrating that this response is mediated at a subcortical level.⁴¹ Similarly, infants with significant neonatal neurological injury due to a parenchymal brain injury respond to noxious stimulation with a pattern of behavioural reactions similar to infants without brain injury.¹³

Interpreting these data

The cortex is required for both the discriminative and emotional aspects of the processing of noxious stimuli and both anatomical and functional studies show that cortical neurons begin to receive input about sensory events in the body and the external environment from 24 weeks.

Long axonal tracts now course through the brain to the cortex and evoked responses in the primary sensory cortex indicate the presence of a spinothalamic connection and the ability of somatosensory cortical neurons to generate specific activity in response to tissue damaging stimulation. The primary sensory cortex is an important area in pain processing but it is only one of many areas that are active during pain experience.⁴ Other important areas include the secondary somatosensory, the anterior cingulate and the insular cortices. Although we may speculate that these regions will also be functionally active from 24 weeks, similar to primary sensory cortex, there is no evidence for this at the moment.

It has been suggested that subcortical regions, including the brainstem, and transient brain structures, including the subplate, organise responses to noxious information at each stage of development and provide for a pain experience complete within itself at each stage.⁴²⁻⁴⁴ There is, however, no evidence or rationale for subcortical and transient brain regions supporting mature function. Although developing brain circuits often display spontaneous neuronal activity this activity is a fundamental developmental process and not evidence of mature function.

The fact that the cortex can receive and process sensory inputs from 24 weeks is only the beginning of the story and does not necessarily mean that the fetus is aware of pain or knows that it is in pain. It is only after birth, when the development, organisation and reorganisation of the cortex occurs in relation to the action and reaction of the neonate and infant to a world of meaning and symbols, that the cortex can be assumed to have mature features. The cortex is an important step beyond the spinal cord and brainstem because it facilitates pain experience by enabling the higher functions of cognition, emotion and self-awareness that are realised in the postnatal environment. Thus, there is good evidence for claiming that the cortex is **necessary** for pain experience but not **sufficient**.

The interpretation of 4-D ultrasound images as evidence for emotional or sentient experience in the fetus is similarly problematic. While 4-D ultrasound provides better-quality images that can be useful to diagnose problems in fetal growth or structure, they provide no new evidence relevant to fetal sentience. As noted above, behavioural reactions can be mediated at a very low level in the brain and are not, therefore, evidence for experienced emotion or sentience. It is also important to recognise that 'labelling' a set of movements with a functional or emotional purpose can import too much certainty. Yawning, for example, is most likely a protective lung reflex that maintains proper lung inflation and prevents the developing alveoli (a kind of sponge-like material) from collapsing. While this protective reflex is unnecessary in the womb where oxygen is delivered by the umbilicus, it will be necessary soon after birth and therefore the neural connections that mediate it need to be fully functional well in advance of birth.

Sleep and wakefulness in the womb

It has been proposed that arguments around fetal pain can be resolved by the fact that the fetus never enters a state of wakefulness *in utero*.⁴⁵ This evidence is derived largely from observations of fetal lambs. Rigatto *et al.*,⁴⁶ for example, directly observed an unanaesthetised sheep fetus, *in utero*, through a Plexiglas window, for 5000 hours without observing signs of wakefulness such as eyes opening or coordinated movement of the head. Several factors explain this lack of wakefulness, including the environment of the womb, which is warm, buoyant and cushioned, and the presence of a chemical environment (most notably adenosine) that preserves a continuous sleep-like unconsciousness or sedation and suppresses higher cortical activation in the presence of intrusive external stimulation. Mellor *et al.*⁴⁵ also propose that the fetus is unconscious based on the presence of sleep-like EEG patterns observed in the lamb fetus, which enter a more quiescent state together with lack of movement, during hypoxic stress,^{46,47} although it should be emphasised that this is quite different from the kind of nox-

ious stress generated by surgery discussed here. Mellor *et al.*⁴⁵ report that the general pattern of EEG during gestation is equivalent to a sleep-like state analogous to non-rapid eye movement and rapid eye movement sleep.

Interpreting these data

Although these data are derived from sheep, this species has been a useful investigative model of human pregnancy and the extrapolation of these data to the human fetus is plausible. Being asleep or awake is not as easy to distinguish in the fetus and newborn as it is in adults⁴⁸ but the broad categories can still be classified on the basis of EEG recordings. On this basis, sleep state differentiation appears in humans as early as 25 weeks in preterm infants and is complete at 30 weeks.⁴⁹ EEG recordings in late fetal baboons support these observations and define only two physiological states from EEG analysis, quiet sleep and active sleep.⁵⁰

While the lack of fetal movement during anoxic stress in sheep may not be the same as the response to acute surgical tissue damage in humans, this work does highlight the important differences between fetal and neonatal life and the potential pitfalls of extrapolating from observations of newborn preterm infants to observations of the fetus. Sedation of the fetus and suppression of cortical arousal in times of stress imply that the cortex *in utero* responds differently from the neonatal cortex and that it is only after birth, with the separation of the baby from the uterus and the umbilical cord, that wakefulness truly begins. This conclusion is not inconsistent with reports of fetal conditioning and habituation to repeated exposure of sounds and smells in late pregnancy which are often referred to as fetal learning. Such responses do not require a cortex in a state of wakefulness and can be induced in simple circuits in lower organisms.⁵¹

Summary

Connections from the periphery to the cortex are not intact before 24 weeks of gestation. Most pain neuroscientists believe that the cortex is necessary for pain perception; cortical activation correlates strongly with pain experience and an absence of cortical activity generally indicates an absence of pain experience.^{52–54} The lack of cortical connections before 24 weeks, therefore, implies that pain is not possible until after 24 weeks. Even after 24 weeks, there is continuing development and elaboration of intracortical networks. Furthermore, there is good evidence that the fetus is sedated by the physical environment of the womb and usually does not awaken before birth.

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3. Current clinical practice

Introduction

In the previous section we discussed the neurobiological basis and neuropsychological arguments around the possibility of fetal awareness of pain. Here, we focus upon the clinical perspective of fetal sensitivity to external stimuli *in utero* and the complex nature of the fetal stress response. Concerns have been raised that fetal medical procedures during pregnancy may lead not only to an immediate fetal stress response but also have long-term consequences. This section reviews all recent clinical developments to assess the validity of these concerns when balanced against the uncertain nature of the evidence for long-term harm, which has been based on postnatal rather than fetal studies, and the ubiquity of the fetal stress response, particularly during the normal process of vaginal birth.

Normal responses to vaginal delivery

Vaginal delivery may be considered a stress-inducing event to which most fetuses are subject. Fetuses born vaginally have higher levels of catecholamines, cortisol and endorphins than those born by elective caesarean section.^{1,2} It is unclear whether this stress response is related to the painful stimulus of head compression or to other factors, such as mild hypoxaemia or maternal stress. In normal labour, this evidence of fetal stress would be considered a normal fetal physiological response and the stress is thought to have benefits for fetal survival. The labour-related surge in steroids and catecholamines is an important factor in activating sodium channels and promoting the clearance of lung fluid. Babies born by caesarean section before the onset of labour have an increased incidence of respiratory complications, such as transient tachypnoea of the newborn.³ In addition, recent data show that elements of the stress response, perhaps noradrenaline or endorphins, have a short-term analgesic effect, so that babies born vaginally have an attenuated physiological and behavioural response to a painful stimulus compared with those born by elective caesarean section.⁴ Evidence of endogenous fetal analgesia during vaginal birth, as well as the role of catecholamines in promoting lung fluid reabsorption and the respiratory depressant actions of fetal opiate exposure, all suggest that the current approach to intrapartum analgesia, centred around maternal, rather than fetal, requirements for pain relief, is the correct one. The evidence that stress responses during normal vaginal delivery have benefits cannot, however, be readily extrapolated to stress responses during pregnancy.

Fetal stress response

The fetal response to noxious stimuli, described in detail in section 2, comprises two elements, both of which need to be present for the fetus to feel pain. The first of these involves nociception and a physiological stress response to it, while the second requires cortical processing of the nociceptive stimulus to produce a negative emotional perception. The evidence clearly sug-

gests that the autonomic and endocrine pathways are in place for the fetus to mount a stress response as early as 18 weeks of gestation, with increases in cerebral blood flow, catecholamines and cortisol observed following invasive procedures.^{5,6} These responses can be attenuated by administration of fetal analgesia at the start of the procedure.⁷ It is worth noting that the fetal stress response can be elicited by a number of non-painful stimuli; the most extensively described is the response to acute hypoxia, where many of the components, such as increased cerebral blood flow, are part of a coordinated fetal response to minimise damage to organs such as the brain and heart. Increased cerebral blood flow, catecholamines and cortisol cannot therefore be interpreted as evidence that the fetus is feeling pain.

Data gathered from premature babies on intensive care units suggest that exposure to repeated, strong stimuli can alter cardiovascular responses to a painful stimulus later in infancy and that fetuses born with higher cortisol levels in cord blood, owing to vaginal delivery, have an altered stress response to vaccination. These data suggest that fetal exposure to ‘stress’ *in utero* can modulate the later function of the hypothalamic–pituitary axis. From this, it has been suggested that reducing the magnitude of the initial stress response, for example by using fetal analgesia, will have a beneficial effect. However, the degree to which these effects can be observed following fetal exposure to a painful stimulus remains uncertain, as the majority of studies to date are postnatal and refer to intense, repetitive stimuli that are not normally experienced *in utero*. The uncertain benefit of attenuating the fetal stress response to a noxious stimulus *in utero* by administering analgesia needs to be balanced against the practical difficulties to the administration of effective fetal analgesia, as well as the possibility of adverse effects.

Gestational age and fetal pain perception

In contrast to the endocrine and haemodynamic responses to a noxious stimulus, which are easily quantified, it has not been possible to directly measure the cortical response to such a stimulus. Assessments about the gestation at which a fetus could feel pain are therefore made on the basis of the existence of the necessary neural pathways for pain perception, particularly the nature of thalamocortical connections (see section 2), as well as indirect evidence for functionality based on evoked responses and evidence for a sleep–wake cycle of EEG activity. Interpretation of existing data indicates that cortical processing of pain perception, and therefore the ability of the fetus to feel pain, cannot occur before 24 weeks of gestation and that the nature of cortical activity becomes more complex as gestation advances from this point. It is reasonable to infer from this that the fetus does not require analgesia for interventions occurring before 24 weeks of gestation. Furthermore, and importantly, the evidence that analgesia confers any benefit on the fetus at any gestation is lacking.

Fetal exposure to noxious stimuli in utero

The fetus may be exposed to a variety of noxious stimuli *in utero*. The majority of fetuses will experience head compression owing to uterine contractions during labour, while a small number will have a needle placed in a blood vessel or organ. In addition, there is the vexed question as to whether the process of abortion represents a noxious stimulus to the fetus. In general, a noxious stimulus is considered to include forms of tissue damage related to physical interventions, such as head compression or needling, rather than fetal hypoxia or hypoglycaemia. A number of invasive procedures can be performed, as follows.

Most diagnostic procedures, including amniocentesis, chorion villus sampling and fetal blood sampling from the umbilical cord do not involve fetal contact. However, on occasion it is necessary to take a sample from the fetus itself, normally using a small gauge needle; for example, when fetal blood sampling from the umbilical vein in the fetal liver, when withdrawing fluid from a cyst or cystic organ or when carrying out a biopsy of fetal skin, liver, muscle, tumour or other tissue.

Again, the majority of therapeutic procedures, including fetal -ell or platelet transfusion via the umbilical cord and endoscopic laser ablation of twin–twin anastomoses on the placental surface, do not involve fetal contact. Some procedures, however, are performed directly on the fetus, including transfusion of donor red cells into the fetal intrahepatic umbilical vein or the peritoneal cavity. Also, drainage of abnormal fluid collections (for example, a dilated bladder or hydrothorax) can be achieved by a single aspiration using a needle or the percutaneous insertion of an indwelling shunt to the amniotic cavity. Similarly, endoscopic placement of a balloon that is inflated in the fetal trachea can be used to improve outcome in cases of congenital diaphragmatic hernia.

As mentioned previously, there is evidence that fetal needling results in a stress response and that this can be attenuated by administration of analgesia given directly to the fetus. In practice, maternal infusion of opiates has been used to sedate the fetus, to achieve immobilisation, rather than analgesia, just as muscle relaxants have been given directly to the fetus.

Open uterine surgery on the fetus is extremely unusual but has been described where surgical access to the fetus has been obtained during the second and third trimesters by performing a maternal hysterotomy. Fetal conditions treated via this approach include congenital diaphragmatic hernia and spina bifida. Use of these techniques is currently confined to a small number of specialist centres in the USA.

An *ex utero* intrapartum treatment can be performed if it is predicted that the fetal airway will be compromised at birth, normally as a result of a cervical tumour or laryngeal atresia. The fetus is partially delivered at the time of caesarean section and access obtained to the airway while the placental circulation maintains adequate oxygenation. As these procedures are performed under maternal general anaesthesia, the fetus is also anaesthetised as a result of transplacental passage of the high concentrations of volatile agents given to the mother.⁸

Administration of fetal analgesia

Lack of access to the fetus *in utero* limits ability to provide fetal analgesia. Two routes are available, either injection directly into the fetus or cord, or transplacental, following administration to the woman:

- direct fetal injection
- transplacental analgesia.

Direct fetal injection

Although it is possible to give an intramuscular or intravenous injection into the fetus under ultrasound guidance, there are a number of practical challenges to doing so:

- Fetal analgesia is not considered a sufficient indication to expose a pregnancy to the increased risk of miscarriage associated with insertion of a possible additional needle into the amniotic cavity. This means that the injection would have to be given as part of another diagnostic or therapeutic procedure involving the insertion of a needle.

- Giving an intramuscular injection before a diagnostic or therapeutic procedure will make the fetus move, with the potential of making the subsequent procedure more complicated.
- The majority of procedures involving percutaneous fetal needling are rapid, involving placing the needle appropriately, taking fluid or blood and then withdrawing the needle. There is normally insufficient time for the analgesic to work. It is important to minimise the time of intervention both for safety and to minimise exposure to the procedural stimulus.
- The needle and the trochar used for shunt placement is large (13 gauge) and not designed for intravascular access.

These considerations mean that the only procedure currently performed for which analgesia might be practical and appropriate is transfusion into the intrahepatic umbilical vein. This requires vascular access and the procedure can last for sufficient time (approximately 5–30 minutes) to allow analgesia time to have an effect.

Transplacental analgesia

Given to the woman, intravenously or via epidural, opiates such as morphine and fentanyl and benzodiazepines have all been shown to cross the placenta and have been associated with changes in fetal heart rate and neonatal respiratory depression.⁶ Similarly, inhaled volatile anaesthetic gases such as isoflurane can cross the placenta. Indeed, when a woman is under general anaesthesia it is believed that the fetus is also anaesthetised. The fetus is more sensitive to the effects of anaesthetic agents and so fetal anaesthesia will normally be achieved.⁸ In pregnant ewes, the dose of inhalational anaesthesia necessary to achieve maternal anaesthesia is sufficient for fetal anaesthesia.⁹ However, in current obstetric practice maternal analgesia and anaesthesia is titrated against maternal requirements and physiological status rather than the status of the fetus. Lower concentrations in fetal compared with maternal blood mean that to achieve high fetal levels of an analgesic, such as morphine, the mother would be exposed to the risks of opiate overdose, including respiratory depression. These certainties outweigh uncertainty about the fetal need for analgesia.

Termination of pregnancy

A comprehensive evidence-based review of current UK practice is provided by the RCOG guideline, *The Care of Women Requesting Induced Abortion*.¹⁰ A brief summary is provided here.

Surgical termination may be performed between 7 and 24 weeks of pregnancy, although procedures after 12 weeks should only be performed by a very experienced surgeon. In the UK, most centres perform surgical termination under general anaesthesia although at earlier gestations local anaesthesia with or without sedation is increasingly used. The procedure is often preceded by medical preparation of the cervix with prostaglandin administered around 3–6 hours earlier. This allows easier dilatation of the cervix in both parous and primigravid women and reduces blood loss, although in some cases the administration of prostaglandin 6 hours before evacuation will induce significant uterine activity, with associated pain and bleeding requiring the surgical procedure to be expedited. The pregnancy is removed by suction through a cannula and fetal death is very rapid. After 14 weeks, termination can be performed by dilatation and evacuation. For surgical termination in the UK, general anaesthesia is usually administered for dilatation and this will result in transfer of anaesthetic agents to the fetus. Al-

though fetal transfer occurs more slowly than maternal transfer, the amount of anaesthetic required is lower for the fetus and so fetal anaesthesia will normally be achieved.⁸ However, as current evidence indicates the inability of the fetus to experience pain, certainly before the end of the second trimester, it should not be necessary to consider the need for fetal analgesia.

Hysterotomy (incision of the uterus) is rarely carried out, except where vaginal delivery is contraindicated because of placenta praevia or pelvic tumour or because of a fetal abnormality such as conjoined twins. This procedure is carried out under general anaesthesia with administration of substantially greater doses of anaesthetic and analgesic agents than is required for transcervical surgical termination of pregnancy, with consequently greater doses reaching the fetus.

Medical termination is induced by the administration of a prostaglandin, usually preceded by the administration of the antiprogestone mifepristone. The regimen and dose vary according to gestation. At up to 9 weeks of amenorrhoea, the currently recommended regimen is oral mifepristone followed 24–48 hours later by misoprostol administered vaginally. Misoprostol can also be administered orally, sublingually or buccally, although the oral route is less effective and these routes are associated with more adverse effects. Between 9 and 12 weeks of gestation, a second dose of prostaglandin may be administered and occasionally further doses may be required. In the second trimester, a similar regimen of mifepristone followed by misoprostol, repeated as required, is used. The fetus is not directly manipulated during a medical termination of pregnancy. It will, however, be subjected to the compressive forces of uterine contractions. The likelihood of fetal death occurring during contractions or delivery, as a result of contraction related hypoxaemia, is higher at low gestations. Although women often receive analgesia and/or sedation during the procedure, this is for maternal benefit rather than fetal analgesia.

Feticide

When termination of pregnancy is performed after 22 weeks of gestation, it is recommended practice that feticide is performed before delivery, unless the fetal abnormality is lethal and will cause the death of the fetus during or immediately after delivery.¹¹ Although the rationale is to ensure fetal death at delivery, some parents may find it reassuring that the fetus will not experience any noxious stimuli during labour. Feticide can be used prior to medical termination of pregnancy for fetal abnormality after 22 weeks of gestation or for selective reduction of multiple pregnancies, either where one fetus has an abnormality or where the number of fetuses increases the risk of maternal morbidity or pregnancy complications to unacceptable levels.

The most common method of feticide is to place a small-gauge needle into the fetal heart under ultrasound guidance and inject 1–5 ml of strong potassium chloride (15%). This causes rapid asystole. Consideration can be also given to stopping fetal movements by the instillation of anaesthetic and/or muscle relaxant agents immediately before potassium chloride administration. The injection of digoxin into the amniotic fluid or into the fetus has also been used to bring about asystole.

Alternatively, if there is a possibility of vascular connection between twins (monochorionic and acardiac twins) and where it is necessary to achieve vascular isolation of the dead twin, feticide can be performed by occluding the umbilical circulation using diathermy applied by either bipolar diathermy forceps or unipolar diathermy at the fetal cord insertion. Multifetal reduction is usually performed in the late first or early second trimester, before 14 weeks of gestation, by injection of potassium chloride into the chest cavity or heart.

Summary

The implications for clinical practice of the neurobiological evidence presented in section 2 have been considered. Interpretation of existing data suggests that cortical processing and therefore fetal perception of pain cannot occur before 24 weeks of gestation. It is reasonable to infer from this that the fetus does not require analgesia for interventions occurring before 24 weeks of gestation. Diagnostic or therapeutic procedures that involve the fetus directly are very uncommon but do occur and can be associated with a stress response. However, this does not indicate that the fetus is aware or can feel pain. The case for administering analgesia before an invasive procedure (in addition to maternal general anaesthesia) after 24 weeks when the neuroanatomical connections are in place, needs to be considered together with the practicalities and risks of administration of fetal analgesia in continuing pregnancies and the uncertainties over long-term effects. Evidence that analgesia confers any benefit on the fetus at any gestation is lacking but should be a focus of future research that will need to include medium and longer-term as well as immediate outcomes. However, the need for maternal sedation before fetal interventions such as transfusion or feticide is still recognised, as it provides both maternal and procedural benefits.

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4. Information for women and parents

These questions and answers have been written to support women. They specifically relate to questions some women ask when having a termination of pregnancy, undergoing an invasive diagnostic procedure and about feticide. The questions below address issues to do with fetal awareness and pain only.

Note that each question and answer has been written to be as self-contained as possible unless specific sign-posting has been given. This is because women wanting information may not read all questions and answers.

Questions some women ask when having an abortion before 24 weeks

Will the fetus/baby feel pain?

No, the fetus does not experience pain. Pain relates to an unpleasant sensory or emotional response to tissue damage. To be aware of something or have pain, the body has to have developed special sensory structures and a joined-up nerve system between the brain and the rest of the body to communicate such a feeling. Although the framework for the nervous system in the growing fetus occurs early, it actually develops very slowly. Current research shows that the sensory structures are not developed or specialised enough to experience pain in a fetus less than 24 weeks.

After 24 weeks, it is difficult to say that the fetus experiences pain because this, like all other experiences, develops postnatally along with memory and other learned behaviours. In addition, increasing evidence suggests that the fetus never enters a state of wakefulness inside the womb. The placenta produces chemicals that suppress nervous system activity and awareness.

Will the process hurt the baby?

No. To be hurt, you need to feel pain. Current research shows that the sensory structures are not developed or specialised enough for a fetus to experience pain less than 24 weeks. Pain experience after 24 weeks depends upon a psychological development that is restricted before birth. See the question ‘Will the fetus/baby feel pain?’

Will the fetus/baby be born alive?

The fetus will almost always die during the abortion process. This is always true for surgical termination. A fetus born before 22 weeks is not capable of surviving. If a medical abortion is carried out after 21 weeks and 6 days feticide will always be offered. To ensure that the baby is not born alive, the heart of the fetus will be stopped before the termination is carried out.

This involves an injection of a solution of potassium chloride directly into the fetal heart. A specially trained doctor carries out feticide. Before anything else is done, the fetal heart will be checked to ensure it has stopped.

When a late medical abortion is carried out and feticide is not performed, the fetus may show signs of life when delivered. This may involve body and limb movements. These movements are a reflex action. They cannot be avoided and can occur after death. This can be very distressing for both the woman and the clinical team looking after her, particularly if it is unexpected. Women undergoing late abortion should always be counselled about what might happen and should be aware of this possibility.

How does the fetus/baby die?

There are different methods of abortion. Which type of abortion you have depends on how many weeks pregnant you are. The different methods are:

- medical abortion – used most commonly in early and late abortions, this uses specific drugs to end the pregnancy
- Vacuum aspiration – used in early abortions where the contents of the womb are removed by suction
- Surgical dilatation and evacuation – used in later abortions where the fetus is removed in fragments.

Most abortions are carried out before the fetus has any chance of surviving outside the womb. In medical abortions, the fetus will usually die during the process and before delivery. Current research shows that the sensory structures are not developed or specialised enough to experience pain in a fetus of less than 24 weeks. If the abortion is carried out over 21 weeks and 6 days, feticide will be offered. This is where a specially trained doctor injects a solution of potassium chloride directly into the fetal heart to ensure it is not born alive. Fetal death is extremely quick.

Questions some women ask when undergoing an invasive diagnostic procedure

What harm could the procedure cause the baby?

To help to find out what problem the baby has, a practitioner has to carry out an invasive diagnostic procedure. This will involve inserting a needle into the uterus (womb) to take either a sample of fluid or tissue from the placenta or very occasionally from the umbilical cord. To ensure that the needle is inserted in the correct place, ultrasound guidance (a special device that uses sound waves to show the inside of the body to see organs and tissue) is used. All invasive procedures carry a small risk of miscarriage. Fewer than one woman in 100 (0.5–1%) will have a miscarriage because of the procedure.

Will the needle hurt the baby?

No. The procedure involves only the placenta or umbilical cord, which do not contain the nerves that are necessary to signal pain.

Does an anaesthetic or the pain relief I receive affect the baby?

If you are given a general anaesthetic for a diagnostic procedure, the substances used in this will cross the placenta to the baby. The effect will happen more slowly to the baby and will not cause any harm to the baby.

If you are given other forms of pain relief, there is evidence that they will cross the placenta to the baby, but the doses are not large enough to cause any harm.

Can the baby be given pain relief?

No. Current research shows that the sensory structures are not developed enough or specialised enough to respond to pain in a fetus of less than 24 weeks. See question on ‘Will the fetus/baby feel pain?’ In later pregnancy, when the fetus/baby is over 24 weeks, we do not yet have enough knowledge to know if providing pain relief would be beneficial. This means that it is extremely difficult to know what kind of pain relief should be used, how any pain relief should be given and whether it would be safe and effective. If pain relief was to reach the baby inside the womb, this would mean giving the mother larger and potentially dangerous doses to try and make sure enough crossed the placenta to the baby. This may cause more harm than benefit. Injecting pain relief drugs directly into the baby would increase the risk of miscarriage.

Questions some women ask when undergoing feticide

Will the baby suffer/feel pain?

No, the fetus does not experience pain. In addition, increasing evidence suggests that the fetus never enters a state of wakefulness inside the womb and that the placenta produces chemicals that suppress nervous system activity and awareness. Feticide is always offered when an abortion is carried out after 21 weeks and 6 days, unless the fetal abnormality is lethal and will cause death of the fetus during or immediately after delivery. A doctor who is specially trained in fetal medicine carries out feticide. To ensure the baby is not born alive, the doctor will inject a solution of potassium chloride directly into the fetal heart. Before anything else is done, the fetal heart will be checked to ensure it has stopped. Death is extremely quick after feticide.

How quickly will the baby die?

When feticide has been carried out, death is extremely quick.

A question some women ask when carrying a baby with a serious abnormality

Will the baby be in pain in the womb because of the condition that has been diagnosed?

This is very unlikely. Current research shows that the sensory structures are not developed or specialised enough to respond to pain in a fetus of less than 24 weeks. Even after 24 weeks it is difficult to say that the fetus experiences pain, because this, like all other experiences, develops postnatally along with memory and other learned behaviours. Moreover, the environment of the womb is usually protective with the fetus floating in the warm amniotic fluid.

5. Conclusions

The primary purpose of this report was to review current knowledge of the central nervous system to assess the likelihood that the fetus *in utero* could experience or be aware of pain. The experience of pain needs cognitive, sensory and affective components, as well as the necessary anatomical and physiological neural connections.

Nociceptors first appear at 10 weeks of gestation in the fetus but they are not sufficient for the experience of pain in themselves. That requires that electrical activity is conducted from the receptors into the spinal cord and to the brain. Fibres to nociceptor terminals in the spinal cord have not been demonstrated before 19 weeks of gestation, although it is known that the fetus withdraws from a needle and may exhibit a stress response from about 18 weeks. At this stage, it is apparent that activity in the spinal cord, brain stem and mid-brain structures are sufficient to generate reflex and humoral responses but not sufficient to support pain awareness. At the same time, completion of the major neural pathways from the periphery to the cortex, at around 24 weeks of gestation, heralds the beginning of a further neuronal maturation. The proliferation of cortical neurons and synaptic contacts begins prenatally but continues postnatally. Magnetic imaging techniques have recorded fetal auditory and visual responses from 28 weeks but it has not been possible to record directly when cortical neurons first begin to respond to tissue damaging inputs, although there is evidence of neural activity in primary sensory cortex in premature infants (around 24 weeks). It has been suggested that subcortical regions can organise responses to noxious stimuli and provide for the pain experience complete within itself but there is no evidence (or rationale) that the subcortical and transient brain regions support mature function.

Thus, although the cortex can process sensory input from 24 weeks, it does not mean that the fetus is aware of pain. There is sound evidence for claiming the cortex is necessary for pain experience but this is not to say that it is sufficient. Similarly, the interpretation of ultrasound images is problematic. It is important that ‘labelling’ a set of movements, such as ‘yawning’, with a functional or emotional purpose that is not possible does not imply such a purpose.

A further important feature is the suggestion, supported by increasing evidence, that the fetus never enters a state of wakefulness *in utero* and is bathed in a chemical environment that induces a sleep-like unconsciousness, suppressing higher cortical activation. Although this cannot be known with certainty, the observation highlights important differences between fetal and neonatal life and the potential pitfalls of extrapolating observations in newborn preterm infants to a fetus of the same gestational age.

From the clinical perspective, there is increasing awareness of the complex nature of the fetal response to stimuli *in utero* and a better understanding of the nature and circumstances of the stress response, including the likelihood of any short or long term consequences. These issues become particularly relevant when placed in the context of the normal processes involved in vaginal, or indeed caesarean, birth. Infants born vaginally demonstrate a chemical response to the birth processes that can be characterised as a stress response. This response can be provoked by a number of non-painful stimuli, such as hypoxia, but it is not clear that the response is merely that, rather than a physiological preparation for extra uterine life. Indeed, there is

even the possibility of a short-term analgesic effect during the birth process. What is clear, however, is that none of us has any memory of the pain of being born, which is not to say that birth, from the fetus' point of view, could not still have been a painful process.

A number of invasive procedures are required in the practice of fetal medicine, for both diagnostic and therapeutic purposes. Most involve needling of the cord or placenta, not the fetus itself. In some circumstances, a needle or catheter is inserted into the fetus or a biopsy is taken from the fetus. In these situations, it is likely that the procedure will be associated with a stress response in the fetus and the need for analgesia has been considered. Indeed, in the previous report, it was recommended that the use of analgesia be considered where the fetus was over 24 weeks of gestational age. However, this more recent review has concluded that the evidence that the fetus can and does experience pain is less compelling and accordingly the benefit of administering analgesia is less evident, while the risks and practicalities of so doing remain. So on the basis of 'first do no harm', prior to the procedures described in this report, analgesia is no longer considered necessary, from the perspective of fetal pain or awareness. However, it is recognised that maternal sedation confers both maternal and procedural benefits. Similarly, the need for analgesia before termination of pregnancy at advanced gestations, whether medical or surgical, is no longer considered necessary, although the need for feticide at viable or immediately pre-viable gestations should still be considered.

These and related issues are considered in the revised Working Party report, *Termination of Pregnancy for Fetal Abnormality*, whose findings and recommendations supplement this report. Furthermore, consideration needs to be given to the education and support of clinical staff working in this difficult area.

Finally, an important addition in this report is the section on information for women and parents and it is hoped that this will provide helpful guidance as well as extending the relevance and usefulness of the report to a wider audience.

Additional reading

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