# RCOG Fetal Awareness Evidence Review, December 2022

## Background

The Royal College of Obstetricians and Gynaecologists (RCOG) has on two previous occasions reviewed the evidence surrounding fetal awareness. A Working Party report in 1997 was followed by extensive review of the scientific and clinical practice relevant to the issue, with a second Working Party Report published in 2010. That report concluded, based on scientific evidence, that the cortex is necessary for pain perception, that connections from the periphery to the cortex are not intact before 24 weeks of gestation, and thus it was reasonable to conclude that the fetus cannot experience pain in any sense prior to this gestation.

Since then, there have been considerable developments in in utero surgery, and in the neuroscientific study of pain perception. In the light of ongoing scientific developments and interest in fetal awareness, including from the Department of Health and Social Care in England, the RCOG agreed it would be timely to review the 2010 Working Party report.

The RCOG has therefore undertaken a further review of the literature since 2010 to assess whether developments in the understanding of fetal awareness and pain might impact clinical practice. This document also considers whether and potentially how this new knowledge might be used to ensure the highest standards of care for women and birthing people during pregnancy.

## 1. Fetal neurobiology relevant to pain

### 1.1 Introduction

The aim of this section is to examine central nervous system function in the fetal and neonatal periods of human development with relation to pain experience, and to update our knowledge of fetal neurobiology relevant to pain since the last Working Party report.

Since the information provided in the last Working Party report on the development of neural pathways related to pain remains unchanged, the focus here is on more recent technical and scientific advances that have added to our understanding of the developing human brain and of the neural pathways that underlie human pain experience. To do this, relevant scientific evidence published in peer-reviewed scientific papers and listed in PubMed since 2010 have been reviewed.

### 1.2 A new definition of pain

In 1979, the International Association for the Study of Pain (IASP) defined pain as “An unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage”. A further note on the definition stated, “Pain is always subjective. Each individual learns the application of the word through experiences related to injury in early life”. Thus the 1979 definition emphasised that pain is multidimensional, rather than a unitary sensation, and is a conscious subjective experience. The definition also placed an emphasis on language to communicate pain and possibly to understand or feel pain.

The IASP revised its definition of pain in 2020 as "An unpleasant sensory and emotional experience associated with, or resembling that associated with, actual or potential tissue damage", with a key distinction that it no longer includes the term "described". The revised definition is also accompanied by a series of notes, which are:

(i) pain is always a personal experience that is influenced to varying degrees by biological, psychological, and social factors;
(ii) pain and nociception are different phenomena; pain cannot be inferred solely from activity in sensory neurons;
(iii) through their life experiences, individuals learn the concept of pain;
(iv) a person's report of an experience as pain should be respected;
(v) although pain usually serves an adaptive role, it may have adverse effects on function and social and psychological well-being, and
(vi) verbal description is only one of several behaviours to express pain; inability to communicate does not negate the possibility that a human or a nonhuman animal experiences pain (Raja et al., 2020).

Thus, the statement that "pain is always subjective" has been replaced with "pain is always a personal experience", and instead of individuals learning "the application of the word [pain]" the revised notes state that "through their life experiences, individuals learn the concept of pain". This revision infers that pain is not dependent on language, thus making it possible to ascribe pain to adult individuals who are unable to communicate verbally, but that in early life, the concept of pain may not yet be understood.

### 1.3 What is meant by pain in the fetus

In the light of this definition, more recent scientific evidence that can inform us about any pain sensation, albeit immediate or limited, following tissue damage in the human fetus has been reviewed. In its simplest form, pain may be viewed as an alarm system, warning an organism of danger in the environment (Tracey et al., 2019). To be effective, such 'protective' pain should trigger immediate attention, action and adaptive learning. To experience pain requires consciousness, but conceptually consciousness means various things and the word is used in many ways. Importantly, 'sensing' or 'detecting' a noxious event does not require consciousness and does not mean that pain is necessarily 'perceived', in the form of a representation or image in the mind (Damasio, 2021). In this report, the focus is on the basic characteristics or qualities that determine the nature of a pain sensation and make it distinguishable from, for example, a sense of touch. Broadly, this document summarises any new biological evidence of when the most immediate and limited feeling of pain might emerge in the fetus following tissue damage.

It is important to note that pain is fundamentally a subjective sensory experience that cannot be directly measured or quantified, only reported, or inferred. It is essential to avoid the term "pain stimuli" because pain is an experience and not a stimulus. Similarly, the terms "pain behaviour" or "emotional behaviour" are not used in this report to avoid assumptions of a subjective experience from body movements alone (Apkarian, 2018).

## 2. Fetal behaviour following tissue injury

Under many circumstances, observation of an apparently protective behaviour in response to a noxious stimulus or injury indicates that an organism might be experiencing pain. In the absence of self-report (i.e. no verbal communication), this behaviour, if interpreted as a 'pain' response, should be clearly distinct from any other sensory evoked or 'startle' response, such as to a non-noxious touch or a loud sound. It should also be distinguished from randomly generated 'spontaneous' movement occurring in the absence of any stimulus.

### 2.1 Spontaneous fetal motor behaviour

Advances in ultrasound recording, including three-dimensional rendering, and dynamic magnetic resonance imaging (MRI) have provided new insights into the onset and maturation of fetal movements (Einspieler et al., 2021) from as early as 7.5 weeks of gestation. Evidence from animal models suggests that these early large scale muscle movements are spontaneously generated by neurons in the spinal cord and do not require a sensory stimulus to trigger them. These movements rapidly become more complex and 2–3 weeks later, identifiable patterns emerge through induced contractions of specific muscle groups, such as isolated limb and head movements, hiccups, and breathing movements. Some (e.g. movements similar to yawning, smiling) appear to have no obvious purpose in the fetal environment, while others have important intrauterine functions, such as breathing movements for lung development, or eye movements for retinal development (Einspieler et al., 2021).

Complex spontaneous movements of the hands towards the eyes, mouth and other regions have been observed from 18 weeks of gestation. Those movements vary according to the target. Movements towards the eye are slow and delicate, and involve a prolonged deceleration phase, compared with movement towards the uterine wall. From 18 weeks, differential use and control of one hand versus the other can accurately predict postnatal handedness (Parma et al., 2017). Opening of the mouth before the hand arrives has been demonstrated to increase after 24 weeks of gestation, suggesting maturation of sensory driven anticipatory behaviour over this period, perhaps in preparation for feeding (Reissland et al., 2014).

### 2.2 Behavioural responses to benign sensory stimulation

In addition to spontaneous movements, fetal movements can be evoked by sensory stimulation. These are called reflex movements because, at the minimum, they require functional neuronal connections between sensory and motor neurons through synapses (junctions) in the spinal cord and/or in the brainstem, indicating the formation of a reflex circuit within the fetal central nervous system. Reflex movements can be a simple withdrawal of a limb from a stimulus (a spinal reflex) or a more complex set of head and body movements, such as a grimace (a brainstem reflex). Behavioural studies using quantitative recording techniques following auditory and tactile sensory stimulation have been undertaken in utero (Einspieler et al., 2021). Distinguishing between sensory evoked and spontaneous movements is an important consideration if they are to be interpreted as sensory responses; sonographic assessment of auditory evoked reflexes between 16 and 40 weeks of gestation reveals their onset at 28 weeks, as the incidence of spontaneous movements declines (Das et al., 2020). Other studies using two-, three- and four-dimensional ultrasound images have reported more fetal activity and facial movements in response to vaginally applied music compared to vibration after 16 weeks of gestation (López-Teijón et al., 2015), observations of increased fetal mouth opening when the mother sang part of a nursery rhyme compared with her chewing noises from 19 weeks of gestation (Ferrari et al., 2016), and an apparent increase in tendency of the fetus to touch the uterine wall in response to someone touching the abdominal wall after 27 weeks of gestation (Marx and Nagy, 2017).

Taken together, the observations of fetal movements in response to non-noxious stimuli, such as touch and sound, show that initial simple reflex responses become increasingly complex, with evidence of regulation according to body area, the target of the movement and, importantly, the nature of the stimulus. By the final trimester, fetal behaviour suggests engagement of neural circuitry beyond that of local spinal cord or brainstem reflex connections and the emergence of a sense of touch, taste and of sound (Einspieler et al., 2021, Ustun et al., 2022).

### 2.3 Behavioural responses to tissue damaging stimulation

Nociceptive behaviour is distinct from that of general sensory behaviour and nociceptive reflexes are so-called because they are specifically evoked by a noxious stimulus. Their presence is evidence that peripheral nociceptive fibres in the skin and underlying tissues have formed functional connections with specific groups of spinal or brainstem motorneurons that activate groups of muscles and cause a protective movement. In the context of this report, they are evidence that the basic qualia, or qualities, that determine the nature of a pain sensation and make it distinguishable from, for example touch, are present in the fetus (see Introduction ).

Evidence for the developmental age of onset of distinct nociceptive reflexes in healthy human fetuses in utero is lacking. An example of a reflex behaviour in the context of pain is the pattern of facial movements or grimaces that are used as one measure of pain in newborn infants and in laboratory animals (Chambers and Mogil, 2015; Mogil et al., 2020). Alongside other spontaneous movements, healthy fetuses display increasingly complex spontaneous facial movements, similar to these grimaces, from 24 to 36 weeks of gestation (Reissland et al., 2013). It has been reported that such facial grimaces are also observed in third trimester fetuses following needle injection of anaesthetic into the thigh before uterine surgery (Bernardes et al., 2021), with one case report describing a needle-evoked reflex grimace at 23 weeks of gestation (Bernardes et al., 2022). These responses might reasonably be described as early nociceptive reflexes, but it should be noted that these behaviours also occur spontaneously, so their existence alone is not evidence of nociception. Furthermore, a study of newborn infants aged 28 and 42 weeks' postmenstrual age (equivalent to gestation) shows that at 28 weeks, the facial movements following a noxious, clinically required, heel lance are indistinguishable from those following an innocuous touch stimulus (Green et al., 2019). This study reported that facial discrimination between noxious and innocuous stimulation is first seen from approximately 33 weeks of gestation and is significantly related to brain response maturity. A similar lack of distinction between touch and noxious evoked spinal limb withdrawal reflexes is reported in early preterm infants (Cornelissen et al., 2013). This highlights the need for care in interpreting fetal behaviour as evidence of pain experience (Fitzgerald, 2015; Green et al., 2019).

## 3. Pain and the fetal brain

The capacity to experience any sensory stimulation depends upon neural connections from specific peripheral receptors to processing regions in the brain. Therefore, the onset of fetal pain experience depends upon the formation and maturation of connections between functional nociceptive inputs ascending from the spinal cord to higher, supraspinal brain regions.

### 3.1 How is pain experience generated in the brain?

The biological investigation of when and how the fetus might feel pain is complicated by the fact that there is no single identifiable brain area that is sufficient or necessary to generate pain. Research in adults has revealed that the experience of pain arises from highly distributed processes in the brain, including both serial and parallel processing of nociceptive input that ascends to the cerebral cortex via multiple pathways (Coghill, 2020). In contrast to other sensory modalities where processing can be typically mapped to a distinct anatomical brain region (i.e. visual processing in the occipital lobe), there is a "dynamic pain connectome" that represents a spatiotemporal physiological signature of pain, which occurs sequentially over areas distributed throughout the brain (Kucyi and Davis, 2015). Viewing a set of brain regions as one fixed core pain system or matrix (as suggested by earlier studies) is now understood to be an oversimplification. Neural activity in brain areas previously associated with pain carry information related to both painfulness and intensity/saliency, and the features that distinguish these two aspects are spatially distributed across the brain and cannot be ascribed to specific brain structures (Liang et al., 2019; Tracey et al., 2019). Thus, information is coded in the

brain at multiple anatomical scales: locally, distributed across regions and networks, and globally. Multi-study analyses show that distributed, multisystem models predict pain intensity 20% more accurately than any individual region or network and are more specific to pain. Thus, multiple cortical and subcortical systems are needed to decode pain intensity, and representation of pain experience may not be circumscribed by any elementary region or canonical network (Petre et al., 2022). Within this representation, 21 regions have been identified as important pain predictors, some showing great interindividual variability and others, such as ventromedial and ventrolateral prefrontal cortices, showing larger individual variability, whereas regions such as somatomotor cortices show more stable pain representations across individuals (Kohoutová et al., 2022).

In the face of the rapidly moving field of the neural basis of human pain experience, discussion of fetal brain development related to pain must therefore encompass a network approach, rather than simply focussing upon the connections in individual brain regions. To this end, the evidence can be divided into three parts:

- Neuroanatomy: mapping the physical existence and maturation of anatomical brain regions, neuronal populations and synapses which are likely to contribute to (but not necessarily be sufficient for) pain experience.
- Neurophysiology: measuring the onset and maturation of brain activity that reflects the transmission and processing of nociceptive information.
- Networks: analysis of the development of interconnected activity in time and space across multiple regions or structures in the brain. Mapping the maturation of the integrated and interdependent functional brain network that generates pain experience.

### 3.2 Neuroanatomy of the fetal brain in relation to pain

(a) Subcortical regions

Increasing evidence that the nociceptive system is distributed across the brain means that subcortical structures including the brainstem deserve more attention with respect to understanding pain (Coghill, 2020). The survival advantages of a functional and protective nociceptive system suggests that the neural circuitry represented in phylogenetically older parts of the brain which also contain nociceptive neurons, such as the brainstem, should be investigated further (Henderson and Keay, 2018). Pain-predictive regions in the healthy adult brain include the brainstem, as well as non-cortical brain areas such as the basal ganglia and the phylogenetically oldest part of the cortex, the insula (Kohoutová et al., 2022). Sensory connections from the spinal cord to these regions could form earlier than thalamocortical connections (see below), but little is known about their fetal development. Human fetal diffusion MR tractography reveals migration pathways to the insula (which has a somatosensory role in pain, itch, and temperature) at 15 weeks of gestation and discernible fibre tracts to the posterior insular cortex at 20 weeks (Das and Takahashi, 2018). Fetal MRI and ultrasonographic methodology have also provided increasing volumetric information about developing brainstem structures, but no details of their connections (Dovjak et al., 2021). The role of the brainstem in pain is hard to dissect in isolation; its importance lies in its connections to multiple brain networks involved in both fundamental homeostatic (cardiovascular, respiratory, endocrine) and cortical areas thought to be involved in higher cognitive functions, with such integration argued to be the key to consciousness (Damasio, 2021). Another such multifunctional node in the brain, the claustrum, which has been shown to have roles in pain, sleep, perception and salience (Atilgan et al., 2022) develops later than the adjacent cortical plate in rodent models (Hoerder-Suabedissen et al., 2022).

(b) Cerebral Cortex

Knowledge of the developing microstructural organisation and neural circuitry of human fetal and early postnatal cerebral hemispheres has been extensively reviewed, with a focus upon the onset of sensory processing in the fetal brain (Kostović et al., 2019).

The formation of the cortex is a relatively protracted process across gestation, characterised by the proliferation and tangential/radial migration of neural progenitor cells from the ventricular and outer-subventricular zones along a scaffolding of radial glial cells. They reach their final location on the superficial surface of the brain from 12 weeks of gestation, with this process largely complete by approximately 30 weeks, but in specific areas continues even up to 2 years of age (Cadwell et al., 2019). Migration occurs earlier in the dorsal side of the brain (peaking at 20 weeks of gestation in the occipital lobe) compared with the frontal regions (where it peaks at 26 weeks) (Paredes et al., 2016). It is maximal around 23 weeks in the parietal lobes where the primary somato-motor cortices are located (Trivedi et al., 2009). Across this time period, neuronal differentiation proceeds via genetic mechanisms and signalling pathways, including thalamocortical inputs, and gradually acquires organisational features seen in the mature cortex such as lamination (Cadwell et al., 2019). Lamination is present first in the primary sensory and motor cortices at 25 weeks of gestation, with the full adult complement of distinct lamina seen by 32 weeks (Kostović et al., 2019).

Since the thalamus is a primary hub for sensory connections arriving from the spinal cord and, in turn, sends connections to the somatosensory cortex, a key area of focus and progress has been in understanding the development of human fetal thalamocortical connections. These have been analysed using histological sections from post-mortem fetal brain (7–34 weeks) and additional postmortem diffusion tensor imaging (DTI)-based fibre tractography, mapping the fetal age for each of the key stages of fibre outgrowth from the thalamus (beginning at 8–9.5 weeks), path-finding (9–14 weeks), "waiting" in the cortical subplate region (14–22 weeks), (2 weeks earlier in somatosensory cortex than visual and other cortices) and ingrowth in the cortical plate (23–24 weeks) (Krsnik et al., 2017). Laboratory studies indicate that synaptic connections between thalamic afferents and early-generated, largely transient, subplate neurons are formed during the waiting period (Wess et al., 2017). These synapses are not able to provide a basis for sensory experience as they are not yet part of the cortex, but they play a key role in forming a functional template for developing thalamocortical networks and cortical architecture (Molnár et al., 2020). Their role is instructional, rather than sensory, directing the future cortical neurons in their final migration to form the cortex (Ohtaka-Maruyama et al., 2018). Spontaneous activity is a fundamental feature of developing neural circuits well before the establishment of cortical layers and subplate neurons are the first originators of this activity (Luhmann et al., 2022), which can be recorded in the preterm human brain as delta brush events at 32–36 weeks (Arichi et al., 2017). These findings are consistent with laboratory rodent studies demonstrating that selective surgical ablation of the subplate below the somatosensory cortex abolishes its spontaneous cortical activity and permanently disrupts the development of normal cortical organisation (Tolner et al., 2012).

Neuroimaging has become a ubiquitous tool in basic research and clinical studies of the human brain. MRI scans of postmortem samples have detailed the regional development, growth, and differentiation of brain structures during the early fetal phase (Takakuwa et al., 2021), while three-dimensional reconstructed fetal MRI in utero has revealed structural information about the living developing cortex: such as the evolution of the subplate in the human cortex during the ‘waiting’ period of thalamocortical afferents from 15–24 weeks. Changes in subplate volume, thickness, and contrast are observed from 18–24 weeks, with a linear increase in subplate thickness under the developing somatosensory/motor cortex through the duration of the waiting period (Corbett-Detig et al., 2011). State-of-the-art high-resolution motion-corrected diffusion-weighted MRI (dMRI) has characterised the maturation of white matter (fibre tracts) microstructure in 113 fetuses in utero aged 22–37 weeks of gestation, revealing unique maturational trends in thalamocortical fibers compared with other tracts (Wilson et al., 2021, 2022). Diffusion MRI of the preterm infant brain suggests a predominant increase in dendritic arborisation and neurite growth in cortical grey matter, indicating increased neuronal connections between 25 and 38 weeks of gestation (Batalle et al., 2019). The introduction of interactive open resources to benchmark developing brain morphology derived from multiple sources of MRI data will prove invaluable in the future (http://www.brainchart.io/). To date, neuroimaging data from over 100 000

participants, aged from 17 weeks post-conception to 100 years of age, reveals a striking increase in grey matter (neuronal regions) and white matter (fibre tracts) volume from mid-gestation through to early childhood (Bethlehem et al., 2022).

### 3.3 Neurophysiology of the fetal brain in relation to pain

Real-time recording of brain activity in preterm infants undergoing clinically required tissue damaging procedures have provided considerable insight into the development of nociceptive processing in the immature human brain (Gursul et al., 2019). Near-infrared spectroscopy (NIRS), which measures regional changes in cerebral oxygenation, reveals nociceptive cortical activity evoked by clinically required heel lances from 24 weeks of gestation (Ranger et al., 2011; Verriotis et al., 2016), but even at term, the nociceptive somatosensory cortical map, an essential framework for spatial localisation of sensory stimuli, is poorly defined across the somatosensory cortex (Jones et al., 2022). Electroencephalography (EEG) has also been used to record specific nociceptive activity (evoked potentials and oscillatory activity) evoked by noxious stimulation (Slater et al., 2010; Fabrizi et al., 2011, 2016). Importantly, the distinction between touch and noxious evoked cortical activity, an important indicator of a sense of pain distinct from innocuous or benign stimulation is not clear until 32–33 weeks (Fabrizi et al., 2011; Green et al., 2019), and even at term differs from that seen in adults (Fabrizi et al., 2016). Such studies have emphasised that while present, cortical nociceptive activity does not begin to mature until the third trimester.

Although the somatosensory system already has a somatotopic organisation (body map for touch) by 34 weeks' postmenstrual age (Dall'Orso et al., 2018), its hierarchical organisation ('reporting structure' for touch) develops sequentially over the last trimester. Functional MRI (fMRI) responses of touch stimuli increase in complexity from the contralateral primary sensory cortex alone to engagement of the bilateral association cortices and supplementary motor area by full term (Allievi et al., 2016). In the same period, somatosensory-evoked potentials recorded with scalp EEG not only show increasing spatial complexity but also sequential engagement of the ipsilateral and associate regions with increasing age, such that development of the full hierarchy of somatosensory processing including higher tiers is complete only just before the time of normal birth (Whitehead et al., 2019). In fMRI scans using experimental pin prick, the regions of the full-term infant brain that are active resemble those in adults (Goksan et al., 2015), but there are substantial differences in infant and adult higher cerebral processing of nociceptive information, which are thought to reflect an absence of expectation, motivation and contextualisation associated with infant pain (Duff et al., 2020). Cortical activation in response to tissue injury is poorly located across the newborn somatosensory cortex compared with touch activation from the same body area, reflecting the less precise nociceptive, compared to tactile, information processing in the brain at this age (Jones et al., 2022).

### 3.4 Networks in the fetal brain in relation to pain

It is now recognised that the perception of pain requires a wiring diagram or comprehensive network spatiotemporal brain relationships (with substantial redundancy) that underpin the processing in the brain, rather than the presence or absence of a specific region or set of connections. This has been termed the human pain connectome.

The architecture of the human connectome changes with brain maturation. Advances in MRI have made it possible to characterise distributed spatial patterns of correlated fluctuations in spontaneous brain activity known as resting state networks (van den Heuvel and Sporns, 2013). These networks can be readily identified in preterm infants from 28 weeks postmenstrual age and show a maturational pattern consistent with the emergence of long-range patterns of connectivity, with increasing inter-hemispheric and anterior-posterior correlations seen with increasing age (Doria et al., 2010; Smyser et al., 2011). By full-term, resting

state networks particularly in the primary motor and sensory cortices have an adult-like bilateral spatial distribution (Eyre et al., 2021). Advances in fetal MRI have now also made it possible to also identify resting state networks in utero (Thomason et al., 2013, 2015; Ferrazzi et al., 2014). These methods can be used to evaluate the topology of normative functional network development during connectome genesis in utero (Rajagopalan et al., 2021). As seen in preterm infants, these studies show that fetal resting state networks first consist largely of local patterns of connectivity at the start of the third trimester, with long range (inter-hemispheric) functional connectivity only emerging later and gradually increasing after 30 weeks of gestation (Thomason et al., 2013, 2015). Studies indicate that key features of the functional connectome such as densely connected "hub" regions are present in the second and third trimesters of pregnancy (van den Heuvel et al., 2018; Turk et al., 2019) and that 30–31 weeks is a key time of change for all metrics, coinciding with a shift from endogenous neuronal activity to sensory-driven cortical patterns (De Asis-Cruz et al., 2021).

Specific changes in the sensorimotor network have been studied in 400 preterm and term infants aged across the equivalent period to the third trimester of gestation (32–45 weeks postmenstrual age). The early presence of crude but spatially organised functional connectivity was observed, with rapid maturation across the preterm period to achieve an adult-like configuration by the normal time of birth with increased connectivity between homologue limb processing regions and decreased connectivity between spatially distant (i.e. left arm and right leg) regions (Dall'Orso et al., 2022). An analysis of EEG activity following noxious clinically required stimulation in terms of microstates has been carried out in final trimester equivalent preterm infants. Microstates are global patterns of scalp potential topographies that remain stable for around 60–120 milliseconds before changing to a different topography that remains stable again, suggesting simultaneous activity of large-scale brain networks. The results show a distinct pattern of network activity following tissue damage that changes with increasing age, in keeping with increasing network engagement of distributed cortical regions (Rupuwala et al., 2022). Future studies of fetal and preterm functional connectome and microstate studies promise important insights into early maturing networks in the brain (Krontira and Cruceanu, 2020). Together with an increased understanding of the detailed patterns of neuronal activity that code for brain states in animals (Abbott, 2020), these will enable a better understanding of the developmental emergence of pain representation in the fetal brain.

## 4. Summary of recent developments in fetal neurobiology

- Pain research to date indicates that the perception of pain requires a comprehensive network of neural connections in the brain rather than the presence or absence of a specific region or set of connections.
- While the cerebral cortex is critical for the perception of all senses including pain, subcortical areas such as the brain stem deserve more attention with respect to understanding how a sense of pain is generated.
- Advances in neuroimaging have revealed the maturation of fetal brain resting state networks, which consist largely of local patterns of connectivity from approximately 28 weeks of gestation, with long range functional connectivity emerging and gradually increasing after 30 weeks of gestation.
- Key features of the functional connectome, such as densely connected "hub" regions, are present after approximately 28 weeks of gestation and 30–31 weeks is a key time of change for all metrics, coinciding with a shift from endogenous neuronal activity to sensory-driven cortical patterns.
- Advances in ultrasound imaging and dynamic MRI have increased the quality of recordings of fetal behaviour. While these early movements are spontaneously generated and do not require a sensory

stimulus to trigger them, distinct reflex responses to innocuous sensory stimuli, such as auditory events, can be measured at 28 weeks of gestation, as spontaneous movements decline.

- The developmental age of onset of nociceptive reflexes in healthy human fetuses in utero, distinct from those evoked by innocuous touch, is not known.
- Healthy fetuses display increasing complex spontaneous facial movements from 24 weeks of gestation. Such facial grimaces are observed in fetuses from 28 weeks of gestation, (and in one case at 23 weeks of gestation), following needle injection of anaesthetic into the thigh before uterine surgery. While these responses might be early nociceptive reflexes, at 28 weeks of gestation the facial movements following a noxious heel lance are indistinguishable from those following an innocuous touch stimulus.
- A measurable difference between the facial responses to a noxious and an innocuous stimulation is first seen from approximately 33 weeks of gestation. At the same stage, brain activity distinguishes between the two types of stimulation.
- A similar lack of distinction between innocuous touch and noxious evoked spinal limb withdrawal reflexes is observed in early preterm infants.
- These studies highlight the need for care in interpreting fetal behaviour as evidence of pain experience.

## 5. Invasive fetal medicine procedures

A number of invasive procedures are performed in fetal medicine units and/or by fetal medicine specialists in the UK at present. Abortion may be necessary at any gestation, although only 1% of abortions occur over 19 weeks of gestation (Abortion statistics, England and Wales: 2021). These procedures, with a brief description, are listed in Appendix I.

The use of analgesia in neonatal and paediatric surgery (including in premature babies) is now well-established to be beneficial. Extending the use of analgesia to therapeutic fetal procedures in the third trimester has become common practice, although direct evidence for benefit during in utero surgery is lacking.

All centres performing fetoscopic endoluminal tracheal occlusion, fetoscopic repair of spina bifida and open fetal surgery administer analgesia (fentanyl) directly to the fetus along with other medications during the procedure. This is because of the protocols for these surgeries originating from trials in Europe and the USA that included fetal analgesia.

There appears to be mixed practice regarding the use of fetal analgesia for feticide, selective reduction, radiofrequency ablation, shunts and in utero transfusion. Some units in the UK use fentanyl in these procedures and some do not.

## 6. Conclusions and implications for clinical practice

- To date, evidence indicates that the possibility of pain perception before 28 weeks of gestation is unlikely.
- At present, there is no basis for considering the administration of analgesia or anaesthesia to a fetus before termination of pregnancy in the first or second trimester to prevent fetal perception of pain.
- While direct evidence for benefit during in utero surgery is lacking, this does not preclude the potential for benefit over risk in administering fetal analgesia for some therapeutic fetal procedures. However, the risk to both mother and fetus need to be considered on an individual case-by-case basis.
- It is not routine practice to administer fetal analgesia in obstetric procedures (e.g. operative birth) or during birth, even though fetal tissue damage is likely. This will usually occur when the fetus is fully developed and will shortly gain awareness of external environmental stimuli after birth. The use of fetal

analgesia during labour and birth would require good evidence to define benefit and risk before any change in practice could be considered.

- It is not routine practice to administer fetal analgesia in obstetric procedures (e.g. operative deliveries) or during delivery, even though fetal tissue damage is likely. This will usually occur when the fetus is fully developed and will shortly gain awareness of external environmental stimuli after birth. The use of fetal analgesia during labour and delivery would require good evidence to define benefit and risk before any change in practice could be considered.

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**Appendix: list of invasive fetal procedures**

- *Abortion*: a medical or surgical intervention to end a pregnancy. The recommended surgical methods are: up to 14 weeks' gestation - vacuum aspiration; 14 to 24-26 weeks' gestation - dilatation and evacuation (D & E). These procedures are performed under general anaesthesia, local anaesthesia or sedation, with general anaesthesia being more common as gestational age advances. Hysterotomy or gravid hysterectomy are reserved for circumstances when a transcervical procedure is not feasible and also involve general anaesthesia. Medical abortion may be carried out at any gestational age, most commonly using the anti-progestogen mifepristone followed by one or more doses of the prostaglandin analogue misoprostol. Feticide (see below) is commonly performed at later gestations to reduce the potential for distress in the neonate and to prevent legal complications if the neonate is born alive.

- *Amniocentesis:* a test which is undertaken to obtain amniotic fluid for genetic analysis. It is performed by inserting a needle through the maternal abdomen and uterus into the amniotic cavity under ultrasound guidance. The fetus is not touched.

- *Amniodrainage:* a procedure which is undertaken to remove excess amniotic fluid for maternal symptomatic relief and/or to reduce the risk of preterm labour. It is performed by inserting a needle through the maternal abdomen and uterus into the amniotic cavity under ultrasound guidance. The fetus is not touched.

- *Chorionic villus sampling (CVS):* a test which is undertaken to obtain placental material for genetic analysis. It is performed by inserting a needle through the maternal abdomen and uterus into the placenta under ultrasound guidance. The fetus is not touched.

- *Fetoscopic endoluminal tracheal occlusion (FETO):* a procedure which is undertaken to introduce a balloon into the fetal trachea where the fetus has a congenital diaphragmatic hernia. It is performed by inserting a fetoscope through the maternal abdomen and uterus into the fetal trachea through its mouth. Fetal analgesia by intramuscular injection of fentanyl is usually administered prior to insertion of the balloon.

- *Fetoscopic repair of spina bifida:* a procedure which is undertaken to repair a spinal lesion in the fetus. Multiple techniques exist, including the introduction of fetoscopes and instruments directly via the maternal abdomen and uterus or a maternal laparotomy and insertion of instruments into the exposed uterus. Fetal analgesia by intramuscular injection of fentanyl is usually administered before the repair.

- *Intracardiac Feticide:* a procedure which is undertaken to stop the fetal heartbeat prior to uterine evacuation. It is performed by inserting a needle through the maternal abdomen and uterus into the fetal heart under ultrasound guidance, and then injecting medication to induce asystole. Fetal analgesia by intramuscular injection of fentanyl is used in some centres prior to intracardiac feticide. This is not a universal practice as the fetus will still require a needling procedure to administer the analgesic. Also, such a procedure may cause the fetus to move to an unfavourable position increasing the difficulty of the feticide. Feticide by intra-amniotic injection of digoxin and fetidice by placental cord injection of medication to induce asystole do not touch the fetus but are associated with higher failure rates and the time of fetal demise is variable.

- *Laser vascular ablation:* a procedure which is undertaken to separate connections between the circulations of monochorionic twins. It is performed by inserting a fetoscope through the maternal

abdomen and uterus into the amniotic cavity under ultrasound guidance, then using laser energy to ablate placental anastomoses. The fetus is not touched.

- *In-utero transfusion (IUT):* a procedure which is undertaken to transfuse red blood cells into an anaemic fetus. It is performed by inserting a needle through the maternal abdomen and uterus into the umbilical cord under ultrasound guidance. The umbilical cord is commonly entered within the fetal abdomen (intrahepatic vein); alternatively, it can be entered at the placental insertion (in which case the fetus is not touched). Fetal analgesia by intramuscular injection of fentanyl is used in some centres prior to transfusion through the abdominal course of the umbilical vein.

- *Open fetal surgery:* a procedure which is undertaken most commonly for spina bifida repair, but also for other indications such as resection of a sacrococcygeal teratoma. It is performed by opening the maternal abdomen and uterus, then operating on the fetus directly. Fetal analgesia by intramuscular injection of fentanyl is usually administered before the repair.

- *Selective reduction in monochorionic pregnancies:* a group of different procedures which are undertaken to selectively terminate one or more fetuses in multiple pregnancies where there is monochorionic placentation (the placenta is shared by more than one fetus). The commonest of these are bipolar cord coagulation (BCC) and radiofrequency ablation (RFA). BCC is performed by inserting a bipolar instrument through the maternal abdomen and uterus into the amniotic cavity under ultrasound guidance, then using bipolar energy to stop blood flow in the umbilical cord. The fetus is not touched. RFA is performed by inserting an RFA needle through the maternal abdomen and uterus into the fetal umbilical vein within the fetal abdomen under ultrasound guidance, then using radiofrequency energy to stop blood flow in the umbilical cord. Fetal analgesia by intramuscular injection of fentanyl prior to RFA is used in some centres. These procedures are usually performed in the first or second trimester.

- *Shunts:* these are a group of procedures which are undertaken to drain fluid from a fetal compartment to the amniotic cavity. Common examples of these are pleural shunts and urinary shunts. They are performed by using an introducer and/or guidewire through the maternal abdomen and uterus into the fetus using ultrasound guidance. Fetal analgesia by intramuscular injection of fentanyl prior to shunt insertion is used in some centres.