

Report of the MRC Expert Group on Fetal Pain

28 August 2001

1. Background

1.1 In November 1996, the Royal College of Obstetricians and Gynaecologists (RCOG) set up a Working Party in response to questions raised in Parliament relating to fetal pain and awareness. The findings of the Working Party were published in October 1997 in a Report, which highlighted several areas where further research should be undertaken. The main recommendations resulting from the Working Party's findings were:

- i. that practitioners who undertake diagnostic or therapeutic surgical procedures upon the fetus at or after 24 weeks' gestation consider the requirements for fetal analgesia and sedation;
- ii. that practitioners who undertake termination of pregnancy at 24 weeks or later should consider the requirements for feticide or fetal analgesia and sedation;
- iii. further research be undertaken into the following areas:
 - development of pathways for the transmission of noxious stimuli in the fetus and neonate
 - placental transfer of analgesic drugs in the second trimester
 - effect of analgesic drugs on stress responses in animal and human fetuses
 - potential long term effects of intrauterine procedures, with or without analgesia
 - animal research on the effects of opioids on the development of the fetal brain.

1.2 In 1999 the Department of Health approached Council to ask if the MRC would be willing to organise a scientific meeting to explore the feasibility of research on fetal pain, in particular the research areas recommended by the RCOG Report. Following further discussion with the Department, the Council decided to set up an expert group to advise on the issue.

1.3 The Expert Group met twice, in January and March 2000. Its Report is structured around the four research recommendations in the RCOG Report.

2. Terms of Reference & Membership

2.1 Terms of Reference

To advise the MRC on the feasibility of further research on fetal pain, with particular reference to the recommendations on further research made by the RCOG report: "Fetal Awareness".

2.2 Membership

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3. Introduction: What is pain?

3.1 Although it is generally considered that the sensation of pain is a negative experience, pain is essential for normal life. Acute pain arising from tissue damage causes arousal, focuses attention and leads to anxiety and avoidance behaviour and as such it may promote homeostasis and ultimately survival. The more prolonged the pain, the less obviously 'useful' it becomes and chronic pain frequently leads to change of mood and depression. Despite the fact that we commonly use such terms as 'my hand hurts', pain is not in the body, but in the mind (Merskey et al., 1967). This is clearly demonstrated by the fact that it is possible to feel pain without a discernible stimulus or indeed without the relevant body part, as in phantom pain (Melzack, 1998). More importantly, pain is not restricted to particular parts of the brain. Whereas the direct sensory component is processed by sensory areas of the spinal cord, brain-stem, thalamus and cortex, the affective component i.e. the emotion of pain cannot be localised and involves a wide neural network

3.2 The issue of fetal pain appears to hinge upon two issues. Firstly, when and how key parts of the nervous system become capable of responding to a tissue damaging stimulation. Current research can and will provide information about this by elucidating the development of sensory pathways involved in the sensory component of pain. It can tell us when various pathways connect up, when impulses arrive at various brain centres and what and when bodily reactions (e.g. reflexes and stress hormone release) can be evoked. It can be reasonably argued that each developmental stage of the pain system has a 'completeness in itself' such that it allows the organism to detect and respond to the inherent dangers of tissue injury.

3.3 The main problem comes with the second issue, which is the development of consciousness or awareness of pain. Consciousness or self-awareness cannot be simply localised within the brain, but is commonly accepted to require the cortex. The current view is that the thalamus, a sub-cortical structure, has more of a permissive than instructive role. One thalamic nucleus, the nucleus reticularis thalami (NRt), appears to 'gate' sensory channels to the cortex and another group, the intralaminar nuclei, are important for maintaining a 'state' of consciousness but not the contents of the consciousness itself (Baars, 1999). Connections from the thalamus to the cortex begin to form at about 20 weeks gestation (Glover and Fisk, 1999) and continue to mature along with other cortical connections well into childhood and adolescence.

3.4 At present, it is not possible to pinpoint a brain area that requires maturation before a fetus or infant can feel pain. Brain imaging has shown that pain perception cannot be ascribed to any one area of the human cortex. Complex functions require complex interactions among highly interdependent neuronal systems. Each system probably does not exert any 'executive' function over the rest, but instead subserves a unique function that contributes to the overall perception of the stimulus and its relevance to the current state of the subject. Such function will not 'switch' on at a particular stage of fetal life when one set of neurons connects to another. It will mature over many pre- and post-natal months to produce complete pain awareness.

4. The Development of Pathways for Transmission of Noxious Stimuli in the Fetus and Neonate

4.1 The neuroanatomical and neurophysiological maturation of sensory pathways involved in pain transmission have been extensively reviewed elsewhere (Alvares et al., 1999; Fitzgerald et al., 1999). However, although much is known about the development in the rat, there is little known about the equivalent development of nociceptive and other sensory pathways in the human fetus. Much public concern has arisen because of the possibility that a fetus may 'feel' pain; such a possibility is founded on the existence of reflex movements and neural activity produced by sensory stimulation. Despite the usefulness of such reflexes in understanding spinal cord and brain stem pain processing, it would be a mistake to equate them with true pain experience which must involve the cortex and develop postnatally along with memory, anxiety and other cognitive brain functions. Pain processing can also be measured using behavioural investigations of infant pain such as facial actions, cry characteristics and body movements and posture. Many studies have shown that there are particular facial expressions, body actions and patterns of cry associated with tissue insult. In contrast to spinal cord reflex responses, younger gestational age is associated with less reactivity in facial expression to heel lance. This may be a reflection of the relative immaturity of relevant motor neurones compared with lumbar spinal motor neurones, or alternatively it may show that sensory events at spinal cord level do not always reflect activity at higher brain levels.

4.2 There is no obvious marker for central processing of noxious messages, other than substrates measured in brain scanning techniques such as blood flow or metabolic need. In the adult these studies are bedevilled by the problems of analysis of the changes in different brain areas following painful stimuli – are the responses sensory, affective, anticipatory, motor etc? Two recent studies illustrate some of the problems in the interpretation of single measures that are thought to represent pain.

1. The injection of formalin into the hind paw of rats produces distinct phases of behavioural and autonomic responses: an early nociceptive response followed by a period of quiescence and a later second phase that matches or exceeds the initial response. The delayed reaction of the second phase has been suggested to be a model of changes in neuronal sensitivity associated with more persistent pain. While the first phase is present in the fetal and neonatal rat the onset of the second phase is later maturing. However, recent studies using two different 'pain' measures report that the first phase occurs in 7 day old pups when measured behaviourally, but only in 14 day pups when assessed by increased heart rate. The behavioural response in second phase appears first at 21 days of age, while the biphasic tachycardic response was not noted until even later, at 35 days of age. These data confirm that the neural mechanisms that mediate the secondary behavioural phase in the formalin test are late maturing, that the biphasic cardiovascular response does not occur until substantially later, after weaning, and that the behavioural and cardiovascular responses are dissociated developmentally (Barr, 1998a).

2. Brain function needs precise connections between neurones and these connections are thought to need chemical signals from growing axons to be established. In a mutant mouse with a deletion of a protein, Munc18-1, there is no transmitter secretion. These animals have normal brains, laminated structures, fibre connections and synapses. However, the neurones then die and massive neurodegeneration occurs indicating that initial formation of synaptic connections does not require transmitter release but their maintenance does. This shows that the existence of synapses alone does not mean that they are functional and has major implications for pharmacological and other interventions in the fetal and early neonatal period that may alter transmitter function (Verhage et al., 2000).

3. Opioid receptor affinities have been found to resemble those of the adult from very early stages in life, but the relative numbers of the different receptors declines with time. A comparison of the ontogeny of the mu, delta and kappa receptors in the spinal cord shows that whereas the mu (the receptor for morphine) and kappa receptors are present at early stages the delta receptor only appears in the second postnatal week in the rat. The mu and kappa receptors increase over the first week of life and then start to decline to finally reach the lower adult levels. Opioid receptor function is mature very early in life and morphine is more potent at producing analgesia in young animals compared to the adult. This early functionality of opioid receptors means that there is a substrate present for the production of analgesia by exogenous opioids in early life (Dickenson & Rahman, 1999).

4.3 Topics Requiring More Research

There is a need to increase the understanding of i) the neurophysiological and neuropharmacological aspects of immature sensory pathways, and ii) of the ability of the fetal and neonatal brain to process pain. Further research in this area would lessen the dependence upon reflex or metabolic responses to measure fetal stress. There is also a need to increase understanding of the neuroanatomical development of the neuroanatomical development of the human fetus, especially of the nociceptive and other sensory pathways.

5. Placental Transfer of Analgesic Drugs in the Second Trimester

5.1 Transplacental transfer of several different opiate drugs, anaesthetic agents, local anaesthetics and sedatives has been studied in several different ways.

1. There is a sizeable literature on materno-fetal transport of various drugs in human pregnancy at term, usually at elective Caesarean section (Reynolds, 1984; D'Alession & Ramanathan, 1998). Maternal venous or arterial blood levels have been compared to umbilical cord blood levels (venous and/or arterial). Effects on the neonate have also been examined. Harmful effects have hardly ever been found, as neonatal drug levels have been very low, because the babies have usually been delivered very quickly. It was not the aim of these studies to assess anaesthesia/analgesia in the neonate.

2. Several studies have investigated materno-fetal transport of various drugs in early human pregnancy (late first trimester) at termination of pregnancy. Maternal blood levels have been compared with concentrations in fetal blood, tissues, amniotic fluid and coelomic fluid (Jauniaux et al., 1996; Jauniaux et al., 1998; Cooper et al., 1999). It is not known whether these levels anaesthetise the fetus, but it has often been observed that fetal movements are absent at the start of the termination.

3. In vitro studies on the isolated human placental cotyledon dual perfusion model have measured drug transport under various conditions (Johnston et al., 1997; Johnston et al., 1999; Krishna et al., 1997).

4. In vivo animal studies have examined physiological variables, e.g. in fetal sheep (Santos et al., 1999).

5.2 Topics Requiring More Research

None of these studies has directly addressed fetal pain. Those in group 1 explored other effects in a live neonate and those in group 2 were on early termination of pregnancy. The relevance of in vitro placental work and of placental transfer studies in animal models to fetal pain (groups 3 and 4) is questionable. Very little work has been done in the second trimester of human pregnancy. In the long-term it is not known whether blunting of stress responses in the fetus by the administration of drugs affects survival/development.

Thus, there is a need for; i) studies of placental transfer of analgesic drugs in the second trimester of human pregnancy, ii) correlation of drug levels with anaesthetic/analgesic effects in the fetus. The latter are unlikely to be ethical in humans and animal models would therefore have to be used.

6. The Effect of Analgesic Drugs on Stress Responses in Animal and Human Fetuses/Neonates

6.1 In an attempt to define markers of pain, investigators have used surrogate endpoints including the stress response (Taylor, 2000) while clinicians have relied upon indices based on complex behavioural patterns (Taddio, 1997) evoked by stimuli which are deemed as "threatening" to the organism. Recent work in this field has mostly focussed on three clinical topics, namely, fetal procedural pain, neonatal circumcision and sedation/analgesia in the neonatal intensive care unit. Studies agree that analgesic drugs may reduce the stress responses to noxious stimuli in human fetuses (Fisk et al., 2000) and newborns (Larsson, 1999). However, it is apparent that the efficacy of different analgesics ability to attenuate responsiveness varies; e.g., morphine seems to show similar analgesic effects in newborn rats as those seen in adult animals (Barr, 1999), whereas nitrous oxide, the most commonly used inhalational gas in clinical anaesthesia, lacks analgesic effects in newborn rats (Maze et al., 2000). Although this raises concerns regarding the validity of animal models of pain, research undertaken in animal models may nevertheless be extrapolatable to humans since the behavioural and physiological responses to noxious stimuli appear to be highly conserved in evolutionary terms.

6.2 Topics Requiring Further Research

It is not known to what extent the stress and/or nocifensive responses are reflective of a long-term effect. It will be extremely valuable to identify parameter(s), which may be predictive of the "commitment" of the organism to a long-term adverse consequence after a transient response. Such a parameter may well lie in the realm of molecular genetics and be amenable to DNA micro-array technology.

It is not known which pharmacodynamic mechanisms underlie the differences in analgesic responsiveness, which are seen in the developing neonate. This should be addressed by characterising the development of neural substrate targets (including components of transmembrane signalling, ascending and descending sensory processing pathways) for analgesic action, which may allow the development of optimal methods of pain relief.

7. Potential Long-term Effects of Intrauterine Procedures, with or without Analgesic

7.1 The number of intrauterine surgical procedures involving direct fetal contact performed annually in UK is very small. It is estimated that the number is approximately 250 per year. Studies into in utero pain would be limited in their usefulness, as given the small numbers involved, there would be insufficient statistical power to reach firm conclusions. Also, the procedures that are performed vary in their degree of invasiveness, and so it would be difficult to standardise results.

7.2 It may be more beneficial to study the preterm period, i.e. equivalence to in utero of later gestation. In the UK, approximately 2500 infants per year born less than 1000grams and 6000 less than 1500grams (about 32 weeks' gestation). These infants provide a significant potential investigational base for delineating long term effects, from both pragmatic studies, and possibly mechanistic studies. Preterm infants are probably similar to the third trimester fetus with regard to stage of brain development and the potential effects of both pain and powerful analgesic medications. There is evidence that multiple painful procedures experienced by preterm neonates may affect their pain-related behaviours later in life.

7.3 Follow up studies of ex-preterm neonates almost all show an increased prevalence of clinical and subclinical neurological deficits, neurobehavioural disorders, and psychosocial problems. Males seem more vulnerable (Verloove-Vanhorick et al., 1994). These sequelae include mental retardation (Grunau et al., 1994b; Hack et al., 1994; Pharoah et al., 1994a), poor motor performance (Marlow et al., 1993; Mouradian and Als, 1994; Pharoah et al., 1994a), visual and auditory deficits (Hack et al., 1994), and learning disorders (Marlow et al., 1993; Lya den Ouden et al., 1993). Other problems include impaired language processing, hyperactivity and attention deficit disorder (Hack et al 1994, Pharoah et al 1994b), problems with impulsivity and social control, inability to cope with novel situations, poor adaptive behaviour, and specific learning deficits as compared to matched controls (Teplin et al., 1991; Marlow et al., 1993). Very few of these problems can be linked directly with pain, stress or intensive care, rather than with the process of preterm birth and the pathologies related to immaturity. However, neurobehavioural outcomes during infancy are correlated with the severity of medical complications and these in turn, are highly correlated with the number of invasive procedures performed (Barker and Rutter 1995).

7.4 Of direct importance for the issue of whether behavioural outcomes can be causally related to repeated pain/stress in preterm neonates is a study by Johnston and Stevens. They compared 4-week-old preterm neonates who were born at 28 weeks gestation (i.e., they were 32 weeks post-conception) with neonates 4 days old born at 32 weeks gestation. They noted decreased behavioral responses but increased cardiovascular responses in the 4 week old infants compared to the newly born (born at 32 weeks). Differences in these response patterns were correlated with the total number of invasive procedures experienced since birth, rather than other clinical factors (e.g., age, Apgar score, birth weight, severity of illness, or body weight) (Johnston and Stevens 1996). In addition, increased somatization has been reported in 4-5 year old ex preterm neonates, the strongest predictor of which was the duration of Neonatal Intensive Care Unit (NICU) stay (rather than length of gestation per se, or later factors such as family relations and maternal sensitivity to the child's cues) (Grunau et al., 1994b). Additional studies have reported a neuro-psychological complex of altered pain thresholds and abnormal pain-related behaviours during early childhood (Herzog 1983; Grunau et al 1994a).

7.5 This evidence suggests that repetitive painful experiences can alter the psycho-physiological

responses to subsequent pain in preterm neonates. Taddio's data (1995, 1997) suggest this is still possible in the fullterm infant. It is likely that these long-term effects are mediated by altered neurobiological mechanisms at all levels of the pain system. Local mechanisms probably include the marked hyper-innervation and lowered pain thresholds noted following skin wounds applied in the neonatal period as compared with similar wounds applied at older ages during development or adult life (Reynolds and Fitzgerald 1995). It is a value judgement whether any long-term effects are a good or a bad thing.

7.6 If it is accepted that the pain system is highly developed and preterm neonates (particularly) have low thresholds for pain and that there are substantial data that clinical, behavioural, physiological and psychological sequelae may result from inadequately treated pain, it is logical to investigate therapeutic approaches to analgesia and sedation in this group. This needs to be done carefully as it is at least possible that the immature brain may be more affected by powerful analgesics than by the pain itself.

7.7 Topics Requiring More Research

There are many problems associated in determining whether perinatal pain causes long-term effects. The complexity of neonatal care required for immature and sick infants, compounded by the fact that there is a preponderance of psychosocial disturbance in the families that have such infants, means that only large experimental (intervention) studies randomising such infants to different arms of care are likely to succeed.

A current study, the multicentre NEOPAIN study, will randomise infants less than 32 weeks gestation to morphine or placebo (dextrose) blind while receiving intensive care (pilot study, Anand et al, 1999). The immediate outcome measures are death, severe degrees of brain haemorrhage or periventricular white matter abnormality at neonatal discharge. This study addresses the fairly short term effects of stress/pain associated with intensive care, but after intensive care (ventilation) has finished there may be many painful procedures in the period before discharge which confound longer term behavioural follow-up studies.

Many preterm infants do not require intensive care and yet their close monitoring necessitates multiple painful procedures such as heel pricks, venepunctures, cannulations, lumbar punctures etc. In most UK units, very little is done to minimise the distress of these events. These infants form a large group within a neonatal unit. It would be a logical group to involve in studies to determine whether procedural pain rather than operative pain (comparatively uncommon) or prolonged stress (being addressed by the Neopain study) is of long term consequence. The active intervention group would probably need to be a mix of behavioural manoeuvres and oral suckling and sucrose. This could probably not be done blind or randomly within a unit so would probably need to be set up as a clustered randomised controlled trial involving units using different therapeutic means.

8. Animal Research on the Effects of Analgesics on the Development of the Fetal Brain

8.1 A number of papers have been published which represent significant developments in the area since the RCOG Report was published. Papers have continued to appear which extend previous work on the effects of opioids upon postnatal development of behaviour, neuroanatomy and neurochemistry (Barr et al., 1997; Barr et al., 1998b; Van den Berg et al., 1999a; Van den Berg et al., 1999b). The primary driver for these studies relates to chronic administration of opioids (mostly morphine or methadone) based on the need to address the issue of maternal opioid abuse and its adverse effects on the neonate. In addition, fetal expression of mRNA encoding for the mu, delta and kappa opioid receptors has now been comprehensively mapped in both the mouse (Zhu et al., 1998) and the rat (Leslie et al., 1998) and confirms a very differential and widespread expression of receptor subtypes with earlier appearance in neural and non-neural tissue than has previously been postulated from ligand binding experiments.

8.2 In addition, two other important scientific developments in the opioid field have occurred since the RCOG Report which impact the potential for relevant future research in the area. Firstly, gene knock-out mice deficient in all three opioid receptor subtypes have been generated (Matthes et al., 1996; Simonin et al., 1998; Zhu et al., 1997) as well as gene knockouts deficient in the opioid peptide transmitters that act at these sites (see Kitchen, 1999). These novel genetic tools provide the opportunity to address the importance of each opioid receptor and peptide upon fetal and postnatal brain development. Secondly, recently Zagon et al., (1999) reported the cloning of a novel receptor (called an opioid growth factor receptor) which appears to mediate cell proliferation activated by the opioid peptide Met-enkephalin.

8.3 Topics requiring more research

Although there is clearly a concern over the potential acute effects of opioid use upon the fetus, the greater concern is that therapeutic intervention with opioids might have deleterious effects on development, which persisted postnatally and had a bearing on adult behaviour and neuronal circuitry. The primary driver for research is thus the possibility of long-term damage from fetal toxic insult by opioids. Much of the previous research in the field has been driven by opioid abuse concerns and mostly addressed the effect of chronic morphine treatment upon subsequent receptor expression and behavioural deficits in offspring. The focus of future research should relate to acute fetal exposure to opioids at concentrations that are relevant to therapeutic doses used in man. In addition, because of the early developmental expression of opioid receptors in the fetus, studies addressing acute effects at several gestational time points would be necessary to determine whether there are critical ages where toxic insult causes long-term changes in receptor expression, transmitter release, stress responsiveness or behaviour. The driver to animal experimental design should rest firmly with the prevalent clinical usage of analgesics in the fetus. Although other analgesics used for fetal and neonatal pain relief should not be ignored, it was recognised that currently morphine is still the primary drug for pain relief in the majority of instances.

To date, virtually all of the work on gene knockout animals has been directed to phenotypic characterisation of adult mice. Developmental studies of gene knockout mice (both homozygote and heterozygote animals, deficient in 50% of opioid receptors) should provide additional information on the importance of opioid receptor subtypes on developmental processes.

9. Conclusions

Although there have been some developments in research into fetal pain since the publication of the RCOG report, there is still a great need for further research in many areas. The basic molecular and cellular mechanisms of fetal and neonatal pain are still poorly understood, as are the effects of anaesthetics or analgesics. The development of transgenic mice will allow more detailed studies to be carried out. A major concern is the long-term effects of pain and analgesics on the behavioural and physiological development of neonates. Although some studies have been carried out (see section 7), further research in this area would be important.

10. References

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