Foetal Pain

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6.1 Introduction

We have decided to publish the available evidence on foetal pain, even because several authors have argued that although a preterm baby can feel pain, a foetus of similar gestation age is anaesthetized while in the womb by some endogenous sedatives [1]. This contrasts with the evidence that prenatal life is not entirely spent in sleep and that the foetus is aroused by noxious stimuli; but the main concern with this theory is that foetal endogenous sedative's (adenosine, pregnenolone and prostaglandins) mean level overlap those in common mothers' blood, without provoking anaesthesia in mothers, and, consequently, with no chance of provoking but a middle sedation in the foetus but absolutely no analgesia [2].

The relationship between the mother and the foetus starts immediately through biochemical dialogue, which is fundamental to good implantation: β-HCG induces the production of progesterone by the mother, while many molecules, such as early pregnancy factor (EPF), cause immunological tolerance in the mother [3]. During the foetal period also, the conceptus is a "protagonist", promoting cellular traffic with the mother and to initiating labour. For these reasons, in the field of prenatal medicine, we need to consider the foetus as a patient, and the old concept of foetal well-being must be transformed in the new science of foetal medicine, which includes both treatment and diagnosis.

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In our centre the main approaches to foetal therapy are transplacental, invasive ultrasound-guided and (at present only in experimental animals) open foetal surgery. Many of these procedures require transgression of the foetal body (e.g. thoracentesis, paracentesis, cystocentesis, pyelocentesis, shunt placement and foetal tissue biopsy), so, in our opinion, the important question is "does the foetus feel pain"?

6.2 Foetal Pain Indicators

The definition of pain proposed by the International Association for the Study of Pain ("an unpleasant sensory and emotional experience associated with actual or potential tissue damage, that is described in term of such damage") is not adapted to dealings with the newborn or the foetus, because it assumes recognition and verbal expression of experience. We therefore need to use "indicators" of foetal pain. From the literature we can distinguish different types of indicators:

- Anatomical
- Cytochemical
- Neurophysiological
- Hormonal/haemodynamic
- Behavioural

6.2.1 Anatomical Indicators

Peripheral cutaneous sensory receptors develop early in the foetus. They appear in the perioral cutaneous area at around 7–8 weeks of gestational age and later in the palmar regions (10–10.5 weeks), abdominal wall (15 weeks) and then all over the body (16 weeks). The peripheral sensory neuron synapses on a dorsal horn interneuron, which stimulates the ventral horn motor neuron. These synapses are responsible for motor reflexes, which allow withdrawal of the limb from noxious stimuli (8 weeks) [4].

Many studies have focused on the presence of thalamic fibre synapses to cortical plate to assess whether foetuses feel pain: there are no studies of thalamocortical fibres in relation to foetal pain, so we will analyse studies on other thalamocortical circuits. Kostovic and Rakic have shown that the density of cortical plate synapses increases around 26 weeks of gestational age, but histological analysis of eight foetuses showed that thalamic projection reached the visual cortex at 23–27 weeks of gestational age [5]. Krmpotic-Nemanic et al. showed that the auditory cortex was reached at between 26 and 28 weeks of gestation, and in one case cortical plate penetration was shown at 24 weeks [6]. These data are confirmed by a study of eight foetuses that demonstrated mediodorsal afferents to frontal cortex at 24 weeks [7].

Several studies have shown that before thalamic fibres reach the cortex, they synapse on subplate neurons, that is, a waiting "compartment" before the cortical

plate. Thalamic projections reach the somatosensory subplate at 18 weeks [8]. There is evidence that neurons in the subplate zone initiate excitatory neurotransmission in the cortex, influencing the development of foetal cortical circuits [9]. These neurons may play a role in nociception transmission to the cortex.

6.2.2 Cytochemical Indicators

In the human foetus, substance P appears in the dorsal horn at 8–10 weeks' gestation [10] and enkephalin at 12–14 weeks [11].

6.2.3 Neurophysiological Indicators

EEG is a measure of the electrical activity of cortical neurons. A primitive EEG is present from 19 weeks; from 22 weeks it is possible to recognize a continuous EEG pattern that is typical of the awake state and of REM sleep in the neonate. Somatosensory evoked potentials, which test the activity of the spinal cord, transmitting visceral pain sensation, are measurable from 24 weeks [12, 13].

Positron emission tomography has showed that glucose utilization is maximal in the sensory areas of the foetal cortex, implying high levels of activity [14].

In neurobehavioural studies in drug-addicted patients, the recording of foetal cardiotocographic patterns showed a cerebral involvement (between 27 and 35 weeks of gestation) of these patterns, demonstrating the presence of opiate receptors in these foetuses [15, 16].

6.2.4 Hormonal/Haemodynamic Indicators

Stress hormones, normally released by adults experiencing pain, are released in massive amounts by the foetuses subjected to needle puncture to draw a blood sample [17, 18]. Redistribution of blood flow occurs after acute painful stimuli [19].

In a fundamental study for research into foetal pain, Fisk has shown that after intrahepatic vein (IHV) procedures, foetal plasma cortisol and endorphin increased two to six times, whereas the foetal middle cerebral artery (MCA) pulsatility index (PI) decreased by two standard deviations, consistent with the centralization or "brain-sparing" response. These hormonal and haemodynamic responses can be prevented by the administration of opioid analgesic (fentanyl) in the foetus [20, 21]. In another study, Fisk et al. demonstrated that noradrenaline (norepinephrine) and corticotropin-releasing hormone (CRH) concentrations increase after acute stress and that these events are independent from maternal responses [17, 22, 23].

The presence of opiate receptors in the foetal bladder was demonstrated by Noia et al., who measured the term of foetal micturition in drug-addicted patients by serial ultrasound evaluation until 18th week [16, 24].

6.2.5 Behavioural Indicators

Behavioural indicators of pain include withdrawing from painful stimuli and changes in vital signs and facial movements. Preterm neonates of 26 weeks' gestation exhibit cutaneous withdrawal reflex after acute stress [25], and scalp sampling increases heart rate in some foetuses [26]. Some studies have identified a special set of facial expressions, similar to those of adult pain perception, that is present during invasive procedures in the premature neonate of 30 weeks' gestation [27–30].

6.3 Long-Term *Sequelae*

There is increasing evidence that early painful or stressful events can sensitize an individual to later pain or stress. Many invasive procedures resulting in acute pain, chronic pain and prolonged stress—and also antenatal maternal psychological problems such as complications of past pregnancies or the current one, anxiety before and after invasive karyotyping or mental disorders of the mother—can be dangerous if they happen during a critical window associated with epochal brain development.

Characteristics of the immature pain system in foetuses (such as a low pain threshold, prolonged periods of windup, overlapping receptive fields, immature descending inhibition) predispose them to greater clinical and behavioural sequelae from inadequately treated pain than older age groups [31]. Repetitive pain in neonatal rat pups can lead to an altered development of the pain system associated with decreased pain thresholds during development [32]. Evidence for developmental plasticity in the neonatal brain suggests that repetitive painful experiences during this period may alter neuronal and synaptic organization [19]. It is evident from animal study that prenatal stress can modify adaptive capacities throughout the entire life of animals: the hypothalamic–pituitary–adrenal (HPA) axis mediates the animal's responses to perinatal stressful events and thus serves as a neurobiological substrate of the behavioural consequences of these early events.

In an elegant study, Vallee et al. [33] showed that stress potentiates the age-related increase in circulating glucocorticoid levels in rats. They also demonstrated a reduction of hippocampal glucocorticoid receptors, which could be responsible, at least in part, for this prolonged corticosterone secretion observed after stress in prenatally stressed rats. In addition, they showed that prenatal stress enhances age-related memory impairments; thus, they hypothesized that elevated glucocorticoid levels could cause neuronal loss in the hippocampus, with subsequent impairment of cognition and memory [33].

In the primate model, exposure to a 2-week period of exogenous ACTH is associated with impaired motor coordination and muscle tonicity, reduced attention span and greater irritability [34]. Exposure to stress in utero is associated with higher levels of ACTH and cortisol in stressed newborns and with lower scores for attention and neuromotor maturity after birth [35, 36].

As we know, the HPA and immune systems are mutually regulatory, and their interactions partially determine the effects of stress on immune function. Premature

alteration of the HPA axis can cause alteration of the immune function, and thus prenatal stress could also have long-term implications in respect of infectious and autoimmune diseases.

In primates prenatal stress effects also appear to vary with the stage of pregnancy at which disruption occurs. Disruption during early pregnancy increases cellular immune responses, whereas prenatal stress exposure during mid- to late pregnancy can be immunosuppressive in adult offspring [37].

In rats, Gorczynski observed that stress-related immunosuppression (as measured by antibody responses and skin graft rejection) was most pronounced in offspring born from prenatally stressed dams [38]; prenatal stress accelerates the onset and increases the prevalence of diabetes in the nonobese diabetic (NOD) mouse model of insulin-dependent diabetes [39].

In humans, several studies demonstrated that early pain or stress (both in utero and in the neonatal period) impairs the physiological development of the nervous system, the HPA axis and the immune system, producing long-term altered susceptibility to pain, to inflammatory diseases and to psychiatric disorders in later life.

It is important to understand the concept of "development plasticity", which means that one genotype can become many phenotypes depending on different environmental conditions during development [40]. Preterm neonates who had experienced 4 weeks of neonatal intensive care unit therapy manifested decreased behavioural responses and increased cardiovascular responses to the pain of a heel prick compared with neonates born at 32 weeks [41]. Taddio et al. demonstrated that children undergoing ritual circumcision immediately after birth without any kind of anaesthesia react more vigorously to vaccination at 2 months of age than those who received anaesthesia before surgery [42]. Other studies focused on hypersensitivity and hyperalgesia in the wound area after surgery [43].

The best evidence for an effect of maternal stress on the physical development of the baby comes from a study which has examined the links between prenatal stressors and foetal brain development. Information about stress was obtained from 3021 pregnant women by questionnaire. The 70 most stressed patients were compared with 50 controls. The authors found that antenatal stress is associated with a lower gestational age, lower birth weight, smaller head circumference and worse score on the neonatal neurological examination [44].

Zappitelli et al. showed that the mother's emotional state has a role in abnormal development of the neural dopaminergic system and can lead to attention deficit hyperactivity disorder (ADHD) in early childhood [45].

To test the role of maternal stress during pregnancy in psychiatric and behavioural disorders, a retrospective epidemiological study was conducted. One hundred and sixty-seven persons were identified whose fathers had died before they were born; a control group comprised 168 persons whose fathers had died during their first year of life. The number of diagnosed schizophrenics treated in psychiatric hospitals and the number of persons committing crimes were significantly higher in the index than in the control group. The results suggest that, especially during months 3–5 and 8–9 of pregnancy, maternal stress may increase the risk of psychiatric disorders in the children, perhaps mediated through the inborn temperament of the child [46].

The studies by Bracha et al. of schizophrenia in twins are very interesting. Concordances in subtypes of monozygotic twins can be used to investigate the influence of prenatal development in the aetiology of mental illness. The results of Bracha et al. indicate that simple monozygotic concordance rates may overestimate the heritability of schizophrenia and that prenatal development may also be important in its aetiology. These authors thought that the second prenatal trimester is the critical period of the massive neural cell migration to the cortex and of the migration of fingertip dermal cells to form ridges. By determining differences in the fingertip ridge count of monozygotic twins discordant for schizophrenia, they demonstrated that prenatal stressors may contribute to the aetiology of schizophrenia. They analysed 30 pairs of monozygotic twins, 23 pairs in which the twins were discordant for schizophrenia and 7 pairs in which both twins were normal. In the discordant for schizophrenia pairs, no pair had the same number of digital ridges, despite their homozygosity. The authors concluded that twins, even homozygous ones, can react differently to the same maternal stress during the second trimester of pregnancy [47, 48].

It is our daily experience that invasive procedures can induce the pregnant mother to stop up "the channels" with her baby during the time when she is waiting for the answer on a prenatal diagnosis. Women who have an amniocentesis put their feelings on hold: what happens is a kind of separation of body and mind. The woman alienates herself from her own body and, by implication, from the child growing within her [49]. In our opinion this can be a severe insult to the developing foetus, and psychological support for these women could be an act of future social prevention.

6.4 Discussion

Some authors distinguish nociception from pain: the former is just an activation of anatomical pathway, while the latter requires the presence of consciousness [50, 51]. Recently, Lee and colleagues published a systematic review that caused an interesting debate among scientists [52]. This is the first review about foetal pain. Many states in the USA are considering legislation requiring informed consent regarding analgesia for the foetus during abortion procedures after 20 weeks of gestation. Georgia and Arkansas have already approved such statutes [53, 54], so the authors ask: "Does the fetus have the functional capacity to feel pain?" They undertook a systematic review via PubMed of English language articles on foetal pain. A multidisciplinary team revisited all the articles. They conclude that evidence regarding the foetus's feeling of pain is limited, and anyway it is unlikely that there is pain perception before the third trimester. The authors state that pain is an emotional and psychological experience that requires conscious recognition of a noxious stimulus. The presence of an anatomical pathway and other indicators does not mean that pain perception exists [52]. Derbyshire affirms that pain perception requires the development of representational memory that is acquired only after birth [55]. Other authors

state that studies on pain in preterm infants are not applicable to foetal pain perception, because "the fetus is actively maintained asleep (and unconscious) throughout gestation and cannot be woken by nociceptive stimuli". According to the authors, if the foetus is never awake, it cannot be conscious and thus cannot feel pain. They try to demonstrate that the foetus is always asleep because in utero there are some chemical suppressors of foetal behaviour and cortical activity such as adenosine, allopregnanolone, pregnanolone and prostaglandin D_2. They also point to the warm temperature in the uterus and the presence of amniotic fluid, which induces sleep and protects the foetus from tactile stimulation. All these factors produce inhibition of cortical activity that is responsible, in their opinion, for the differences between foetus and neonate in their responses to stimuli, such as the response to hypoxia, which causes an arousal reaction in the neonate and depression in the foetus. In our opinion, it has been widely shown in the scientific literature that foetuses have access to a great deal of sensation in the uterus: they can perceive sound, the changing taste of the amniotic fluid, touch and pressure stimuli to the mother's abdomen, changes in light and dark and changes in balance [56–58].

The review by Lee and colleagues has many limitations. The first issue to discuss is the question of whether consciousness is a condition necessary for the feeling of pain. According to the Oxford English Dictionary, pain is "a strongly unpleasant bodily sensation such as is produced by illness, injury or other harmful physical contact" [59]. Probably when a pregnant woman asks if her foetus can feel pain, she does not mean a conscious rationalization of pain. This is important for well-informed counselling of the women. Moreover, as Austin suggests [60], some of statements from which the author draws his conclusions must be questioned. The first is a semantic matter: according to the International Association for the Study of Pain, "each individual learns the application of the word [pain] through experiences related to injury in early life". This definition has limited biological and clinical application: in order to experience pain, the individual must first learn what pain is, and in order to learn what pain is, he must first experience it. This is a never-ending circular argument.

The second point is "Derbyshire claims that the perception of pain requires the development of representational memory; but, although memory may be necessary for the interpretation of pain, it is not for its perception. Even if the foetus does not recognize pain, the experience still remains unpleasant [60].

Despite their limited scientific significance, foetal pain indicators must be borne in mind especially because they are clinical signs of pain during surgery in unconscious and anaesthetized adults and paediatric patients [61].

The evidence that early exposure to noxious stimuli has adverse effects on future neural development is increasing [12, 62]. It follows that noxious stimulation may not need the presence of consciousness to alter the course of sensory development.

In our opinion this debate is strongly motivated by the question around voluntary termination. Claiming that abortion can cause foetal pain has important consequences for the personal ethics of both the parents and the clinicians—but this fear must not impede a scientific and honest search for the truth.

Conclusions

The American Academy of Pediatrics, Fetus and Newborn Committee wrote a statement on the prevention and management of pain and stress in the neonate. The objectives of the statement are to:

- Increase awareness that neonates experience pain. Provide a physiological basis for neonatal pain and stress assessment and management by healthcare professionals.
- Make recommendations for reduced exposure of the neonate to noxious stimuli and to minimize associated adverse outcome.
- Recommend effective and safe interventions that relieve pain and stress [63].

Opioid analgesia for minor and major procedures has been shown in randomized trials to reduce metabolic and biophysical stress responses, postoperative morbidity and mortality and abnormal imprinting of subsequent pain responses in infancy [64].

Premature neonates are foetuses out of the intrauterine environment. Prevention or treatment of pain is a basic human right regardless of age, and the humane care given to premature babies needs to be extended to the foetus.

We hope that all foetal medicine units will really take care of the well-being of the foetus, which is to take care of the well-being of the person for his entire life.

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