



New insights into fetal pain

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ABSTRACT

Fetal pain is difficult to assess, because the main feature needed to spot pain, is the subject's capability of declaring it. Nonetheless, much can be affirmed about this issue. In this review we first report the epochs of the development of human nociceptive pathways; then we review since when they are functioning. We also review the latest data about the new topic of analgesia and prenatal surgery and about the scarce effect on fetal pain sentience of the natural sedatives fetuses produce. It appears that pain is a neuroadaptive phenomenon that emerges in the middle of pregnancy, at about 20–22 weeks of gestation, and becomes more and more evident for bystanders and significant for the fetus, throughout the rest of the pregnancy.

1. Introduction

Fetal pain is one of the most debated issues in medicine: in fact, it is very difficult to determine if a subject who cannot express its own feelings is actually experiencing pain after a potentially noxious stimulus. The international definition of the word 'pain', made by the International Association for the Study of pain (IASP) is not of help in this case: in fact it says that pain is "an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage" [1]. This definition has been criticized because it does not include those subjects who are not aware of their own body or cannot describe it, such as mentally challenged people or babies. In short, pain has wider borders than those of standard definitions. Nonetheless, to feel pain, some basic requisites should be present [2]. They are, in order from the periphery to the center of the nervous system: a) nociceptors, b) pain neurotransmitters, c) centripetal fibers that lead the stimulus to the brain, d) the thalamus, e) connection with the cortex. Some authors argue that the thalamo-cortical connections are essential to feel pain [3], while others say that the connections from the spinal cord to the thalamus are enough, even though they allow pain to be felt only at a subconscious level. In the fetus, the cortex is relatively underdeveloped, but it is rudimentally present from the 20th week of gestation; meanwhile, a transitory structure takes the place of the cortex: the subplate. Here we review if these structures are present and active in the fetus and then analyze when their functions start.

1.1. Setting and development of nociceptive pathways in the fetus

Nociceptors are extensively present in the fetus' skin, at least at the

same density than in adults. Their axons reach the skin between 11 and 15 weeks of gestational age (WGA) and the mucosae at 20 WGA [4] after having formed synapses with the ascendancy pathways in the dorsal horn of the spine at 6 WGA [5]. Most of these nerves will be precociously myelinated, starting between 12 and 14 WGA, guaranteeing a higher conduction speed of the impulse they carry to the brain [6]. Even pain neuromediators like substance P and enkephalins appear early, at 8–10 and 12–14 WGA respectively [7]. The production of endogenous opioids starts in the brain around the middle of pregnancy [8].

The spinothalamic tract is a major ascending pathway required for the normal processing of pain, temperature and itch. It is well established in fetal life, with little differences throughout the life of mammals [9]. The mesodiencephalon [brain stem, insula and thalamus] in intact fetuses shows signs of sufficient maturation starting from the 15th week of gestation [10]. Another important structure is also present in fetal life: the amygdala. The amygdala is the center of fear and anxiety in mammals, and its early appearance [11] could be a sign that even these sensations, albeit rudimentary, can be felt in utero.

Direct thalamocortical fibers appear at the beginning of the second half of the pregnancy (23–30 WGA), reaching in large numbers the subplate – which they had started to colonize at 12 WGA - at 24 WGA [12]. The subplate is an important fetal structure; it is an active though transient layer of the human brain cortex between 10 and 35 WGA, capable of processing thalamic information and of contributing to transient cortical circuits [13]. It has a pivotal role in the development of the mature cortex, appearing as an intermediate station for the neurons which are colonizing the grey matter, the first cortical neurons to respond to sensory stimuli [14]. Between 24 and 32 WGA,

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thalamocortical fibers converge on various areas of the mature cortex, completing this process after 34 WGA [15].

The process of cortex formation starts in the first trimester of pregnancy, with the migration of the neurons from the depth of the brain up to the periphery, and the appearance of characteristic folds on the brain surface. The first folds can be seen at 13–15 WGA, and among them the fold which gives birth to the insula, one of the main sites for pain perception, is visible [16]. The cortex is supposed to be the center of conscious activity, and its absence would rule out any conscious pain sensation; nonetheless, it seems that some conscious sensation may be possible even with an immature cortex [17], and consequently even pain at a more or less conscious level can be felt. If even hydranencephaly, with the almost total absence of the cortex, does not preclude infants the ability to discriminate stimuli, receiving even visual information, and feeling fear, then the cortex is not so essential in elaborating, at some level of consciousness, the information it receives [18,19]

1.2. Efficiency of the nociceptive pathways in the fetus

Since the fetus has a sufficiently developed nociceptive system, it is important to assess if this system is active and operational. The answers to this question arrive from behavioral observation, and from either electrophysiological or endocrine responses to potentially nociceptive stimuli. Three main signs show the possibility that at a certain point of the pregnancy, the fetus may feel pain, and we will describe them in this paragraph. Firstly, its extensive reaction to external stimuli, that can make them suddenly change their behavioral state, even waking them up from sleep. Second, the changes in behavioral patterns and specific EEG pain-related features. Third, the rise in fetal blood stress hormones, after a painful stimulus to the fetus.

Fetuses can respond to external stimuli, showing sensitivity to noise, light or tactile impulses [20]. After 26 WGA their generalized movements are replaced by more coordinated responses of the head and limbs. Fetal expressions of actual crying have been registered [21], such as the blink-startle responses to sudden noises, at 30 WGA [22], as well

as an avoidance reaction from 8 WGA. Ultrasound is a useful tool to detect differentiated behavioral states and even pain signs [23]. Fetuses show, at the end of pregnancy, well-established sleep-wake cycles [24]; they spend 9–21% of the time at term in active wake [25] and they can be awoken after being stimulated. States F3 (calm wake), F4 (active wake) and the state F5 (crying) are described in fetuses [26], and at 30 WGA a frank wake EEG can be recorded in prenatally born fetuses [27]. The environment within the womb is supposed to have some sedative property, because of some neuroinhibiting substance present there. These substances are adenosine, progesterone, allopregnenolone, pregnenolone and prostaglandin D2. Adenosine is a purinergic messenger, regulating many physiological processes in excitable tissues, namely in the brain. Prostaglandin D2 is a sleep-inducing hormone that induces adenosine release and the consequent GABAergic inhibition of wake-inducing neurons. Pregnenolone and allopregnenolone have an analgesic effect as well: they also increase the activity of GABA inhibitory pathways in the central nervous system. Progesterone, and its pregnane metabolites, are strongly implicated as inhibitory modulators of fetal EEG activity and behavioral state. The blood levels of allopregnenolone are similar in mothers' and fetal blood [28], while pregnenolone sulfate values are far higher in fetal blood in one study [28], but its isomers appear at similar levels in maternal and fetal blood [29]. Adenosine levels are higher in normal fetuses than in non-complicated pregnant women's blood [30], but in women with hyperemesis gravidarum it is far higher than in fetal blood [31] (Fig. 1). PGD2 synthase concentration in human amniotic fluid appears to increase during gestational weeks 12–25 but it declines slowly until term [32]. Average progesterone is twice as high in fetuses than in mothers [33], but also in preeclamptic mothers progesterone is twice the base level [34]. Neural inhibitor effects of both adenosine and PGD2, have been recorded when they are artificially administered into the brain of test animals and, even in this case, the effect of these substances was not analgesic but just sedative [35]. The anesthetic effect of pregnenolone is observed only if injected in high doses, attaining high blood concentrations (2–2,5 µg/ml) [36].

Brain electrical activity is still rudimentary in immature fetuses: the

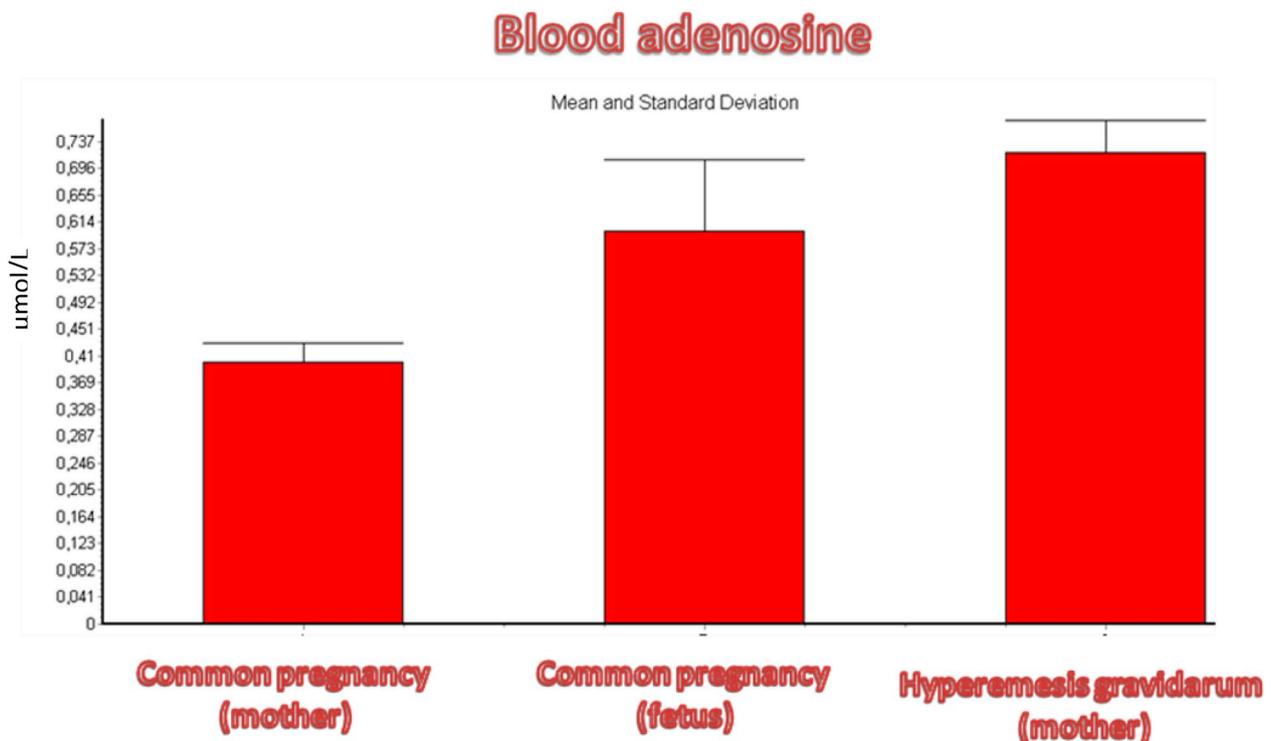


Fig. 1. Data are obtained from reference #30 and #31.

first signs of cortical EEG activity are recorded in prematurely born fetuses at 23 WGA, showing very long flat unreactive periods, interrupted by very high voltage bursts, with no sign of behavioral states. Anyway, fetal magnetoencephalography gives positive responses from 27 WGA [37], and fetal brain activation to sounds has been demonstrated using functional magnetic resonance imaging in fetuses of 33 WGA [38]. Using the information we have from premature babies, we know that at 26–28 weeks GA, evoked potentials may be recorded from somatosensory, visual, auditory and frontal cortex [39]. Near infrared spectroscopy in preterm infants has demonstrated localized somatosensory cortical responses from 24 weeks, following painful heel lance and venepuncture [40]. More recently, EEG has demonstrated evident nociceptive-evoked potentials in newborns of 35–39 postmenstrual weeks following heel lance [41].

An increase in stress hormones is seen after a painful intervention in 16–25 WGA fetuses: in a group of fetuses, an in utero blood transfusion was performed using the intrahepatic vein the process of which activates nociceptors, while a control group received the transfusion using the umbilical vein without activating the nociceptors [42]; the result was that in the former group, a dramatic increase of cortisol, adrenalin and beta-endorphins was seen, while in the latter, these hormones showed no changes in their blood level. In another study [43], the same procedure of intrahepatic transfusion was performed, but with prior administration of fentanyl to the fetus: the result was that the increase of stress hormones was much lower, compared with that of the first experiment.

1.3. Fetal pain and fetal surgery

Fetal pain and fetal surgery are highly correlated, because if a fetus can feel pain after a certain gestational age, then providing appropriate analgesia is important for three main reasons: medical ethics, the risk of long-term consequences of pain on the development of the brain and the possibility of sudden movements induced by pain that can jeopardize the surgeon's work [44].

Some researchers recommend administering 20 µg/kg of intramuscular fentanyl to the fetus prior to the procedure [45], while others recommend the administration to the mother of a continuous infusion rate of remifentanyl 0.1 µg kg⁻¹ min⁻¹, to achieve fetal immobilization and maternal sedation, though they do not exclude directly administering analgesics to the fetus [46]. Some researchers utilized intra-amniotic opioids for fetal analgesia on lamb fetuses [47]: they showed that greater plasma concentrations were obtained in the fetal lamb as compared with the ewe, suggesting that this route might be utilizable for humans. In several studies, surgeons have directly administered opioids to the fetus, while others have considered maternally administered analgesics to be sufficient. A review of the literature to assess the state of the art of fetal analgesia during surgery retrieved 34 papers [48]. In three papers, surgery did not hurt the fetus, being performed on fetal placenta; in two papers, it was performed in the first half of pregnancy, when pain perception is unlikely and therefore analgesia is unnecessary. In 10 of the 29 remaining papers, fetal surgery was performed using direct fetal analgesia, while in 19, analgesia was administered only to the mother. In most cases, fetal direct analgesia was obtained using intramuscular opioids, and muscle relaxant. Adverse effects on either fetuses or mothers due to fetal analgesia were rarely reported [49]. Recently it has been showed that fetuses during fetal surgery can respond to pain with bradycardia [50]; nonetheless, more research is needed to find out actual fetal pain markers. However, the anesthetic that pregnant women receive is not enough to anesthetize the fetus; in fact, fetuses born through cesarean section performed with maternal general anesthesia are born awake. Administering opioids and not only neuromuscular blockers to the fetus is also necessary because maternal laparocentesis, necessary to perform fetal surgery, does not necessarily require general maternal analgesia, but only local spinal analgesia.

2. Discussion

As we stated at the beginning of this review, determining if a fetus can feel pain is an important challenge, with two major limitations: the fetus cannot speak and we have no specific markers of pain, but only marker which measure both pain and stress. Anyway, if we rely on the hints and indications given by scientific observation, we can draw a series of 'pros and cons' about fetal pain. We report them in Table 1. It emerges from this review that pain, a progressive adaptive process that includes sensations and reactions, progressively appears throughout fetal life [51]. This may be due to the fact that in early stages of development, mammals do not have the need to defend themselves from external threats. To clearly understand when pain appears in a fetus, we should understand the sense of pain. It is a potent process aimed to make the organism react to threats recalling all its forces, and aimed to send a unambiguous alarm and a dramatic request for external help. Thus, it is why, from an evolutionistic point of view, it appears when life can be saved by use of these forces and by the external helps that cries summon, namely when the organism is mature enough. This interestingly corresponds to the observations reported in this text, that describe pain as a phenomenon that emerges in the middle of gestation – when a fetus acquires the possibility of surviving outside the womb, and that becomes more and more evident and significant with increasing gestational age. We report in Fig. 2 the most relevant steps in the development of the prenatal nociceptive system.

One frequently raised objection is that, since the fetus seems constantly in a sleep state, it cannot feel pain. This is contradicted by several observations we have reported: the fetus is not constantly in a sleep state, and above all, it can be awakened by external stimuli. Moreover, the substances that are supposed to shield it from pain, the neuroinhibitors, are at a level in the fetus' blood non significantly different from that in the pregnant mother's blood (allopregnenolone), or from that of pregnant mothers in particular states such as preeclampsia or hyperemesis gravidarum (adenosine a progesterone), while mothers are not anesthetized by these substances at these levels. Only pregnanolone is significantly higher in fetuses than in mothers, though its isomers do not differ in either. Anyway, neuroinhibitors are not anesthetics, but sedatives, and no sedation can eliminate or prevent pain. One evidence of fetal non-sedation is birth: all fetuses cry at birth, if they were anesthetized or deeply sedated, this would not be possible.

In conclusion, we should acknowledge that pain in infants was a debated matter until the end of the last century, and this exposed thousands of babies to untreated pain. Nowadays no physician is permitted to expose babies to a potentially painful treatment without providing due analgesia; but denying pain in foetuses would jeopardize these advances in care, because it would question the use of analgesia in neonates of similar WGA. Another negative consequence of denying fetal pain is that fetuses who go through surgery may not receive anesthetics, with the possible negative consequences we reported in the text. Nonetheless, the advances in this field are ongoing and we believe that, in the future, pain scales will be developed and validated for fetal pain, drugs will be refined to overcome it, and fetal analgesic treatments will eventually be available.

Table 1
Pros and cons for the likelihood of pain in the second half of pregnancy.

CONS	PROS
Immature cortex	Presence of thalamus and subplate
Scarce myelination	Adequate nociceptive pathways
Continuous sleep state	Periods of wake
Presence of neuroinhibitors	Arousability
Fetal non-verbality	Hormonal and behavioral signs of pain

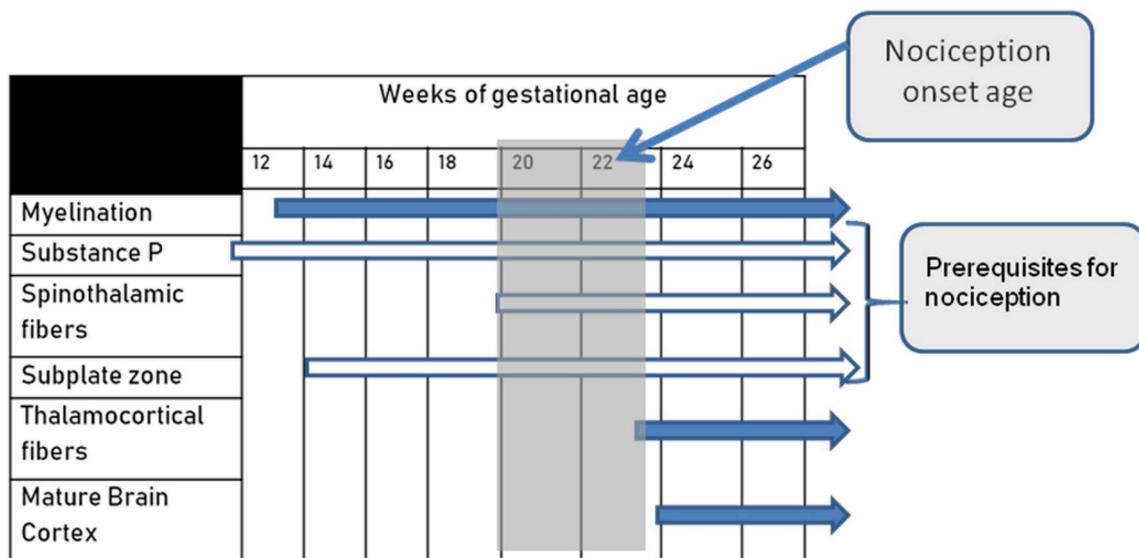


Fig. 2. The onset of nociception. The structures actually necessary for nociception are indicated by white arrows. The most likely age for fetal nociception onset is 20–22 weeks of postnatal age.

Conflicts of interest

I declare no conflict of interests.

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