Int. J. Prenatal and Perinatal Psychology and Medicine Vol. 20 (2008) No. 3/4, pp. 167–178

Fetal Pain

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Abstract: The fetus reacts to nociceptive stimulations through different motor, autonomic, vegetative, hormonal, and metabolic changes relatively early in the gestation period. With respect to the fact that the modulatory system does not yet exist, the first reactions are purely reflexive and without connection to the type of stimulus. While the fetal nervous system is able to react through protective reflexes to potentially harmful stimuli, there is no accurate evidence concerning pain sensations in this early period. Cortical processes occur only after thalamocortical connections and pathways have been completed at the 26th gestational week. Harmful (painful) stimuli, especially in fetuses have an adverse effect on the development of humans regardless of the processes in brain. Moreover, pain activates a number of subcortical mechanisms and a wide spectrum of stress responses influence the maturation of thalamocortical pathways and other cortical activation which are very important in pain processing.

Zusammenfassung: Der Fötus reagiert relativ früh in der Schwangerschaft durch verschiedene motorische, vegetative, hormonale und metabolische Veränderungen auf Schmerzreize. Weil höhere Verarbeitungssysteme noch nicht bestehen, sind die ersten Reaktionen ganz reflexhaft und ohne Abstimmung auf den auslösenden Reiz. Weil das fötale Nervensystem mit einfachen Schutzreflexen auf potentiell bedrohliche Reize reagiert, gibt es keine eindeutige Evidenz für ein Schmerzerleben in dieser frühen Zeit. Kortikale Verarbeitungsmöglichkeiten funktionieren erst, nachdem die thalamokortikalen Bahnen in der 26. Woche ausgebildet sind. Schädliche und schmerzvolle Reize haben insbesondere bei Föten eine negative Wirkung auf die Entwicklung ungeachtet der Auswirkungen auf die Prozesse im Gehirn. Darüber hinaus aktiviert der Schmerz ein Reihe von subkortikalen Mechanismen und ein weites Spektrum von Stressreaktionen beeinflusst die Reifung der thalamokortikalen Bahnen und andere kortikale Aktivierungsvorgänge, die für die Schmerzverarbeitung sehr wichtig sind.

Keywords: fetal pain and nociception, development of pain perception, fetal analgesia.

Introduction

Are we entitled to speak about fetal pain?

In agreement with IASP and World Health Organization, pain is defined to not only include a sensory discriminative component but also emotional-affective, vegetative, and motor components.

Does pain exist in a fetus? Is it pain or only nociception? Is the fetus able to feel pain [2, 4, 5, 6, 18, 26, 28, 29, 45]?

We know very well that pain is a subjective experience; however a fetus is not able to tell us what they are feeling. This means that we do not know if the concept of a conscious and subjective feeling of pain is an integral part of the pain sensation, and whether it's present in fetal life [3]. Therefore instead of pain, a

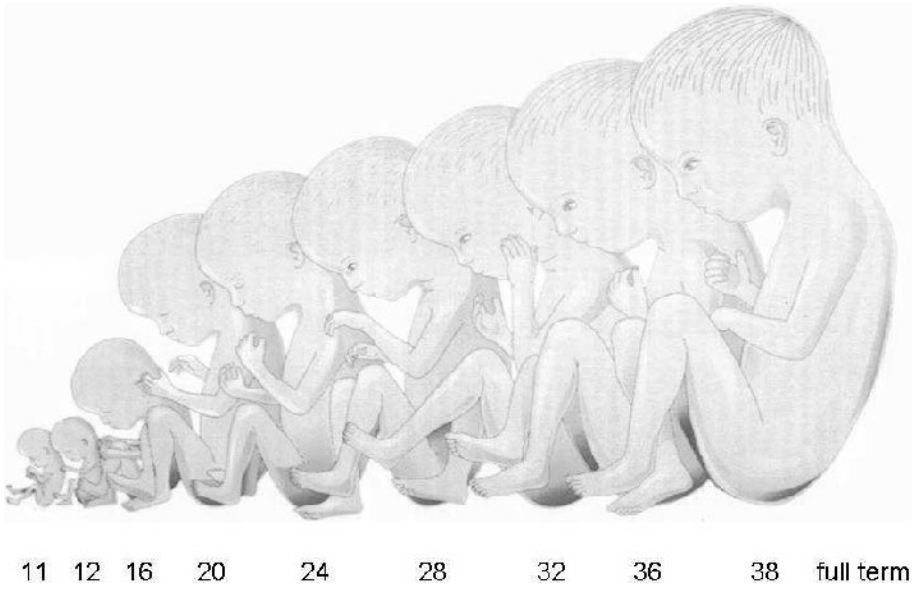


Fig. 1. Transition from embryo to fetus. The embryonic period ends at the end of the 8th week, when frameworks for all main structures have been established. The fetal period starts with the 9th week and is characterized by growth and development of structures established during the embryonic period. It is possible to determine the sex of the fetus starting at the 12th week. Fetuses are viable from the 22nd week after conception; each additional week of gestation dramatically increases survival chances for a prematurely born child. The images of the fetuses from 11–38 weeks in this figure are approximately the half of their actual size (arranged up to the book Zrození člověka – ISV Prague, 2002).

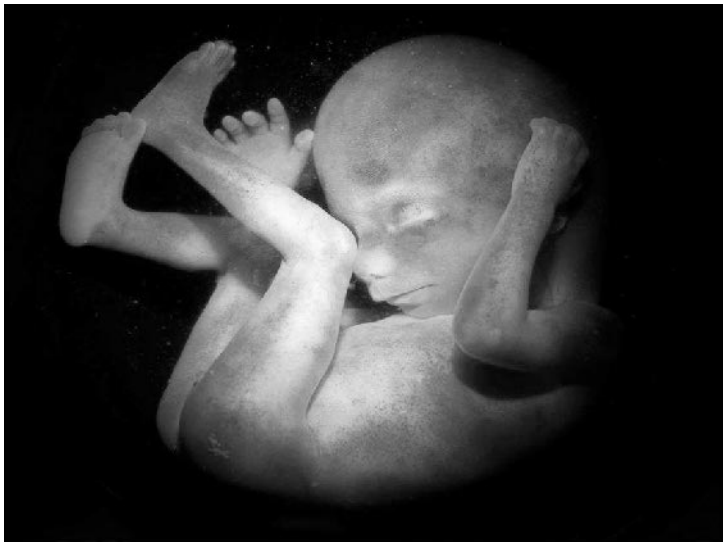


Fig. 2. Image of fetus From the collection of Prof. Jan Evangelista Jirásek (The Institute for Mother and Child in Prague-Podolí).

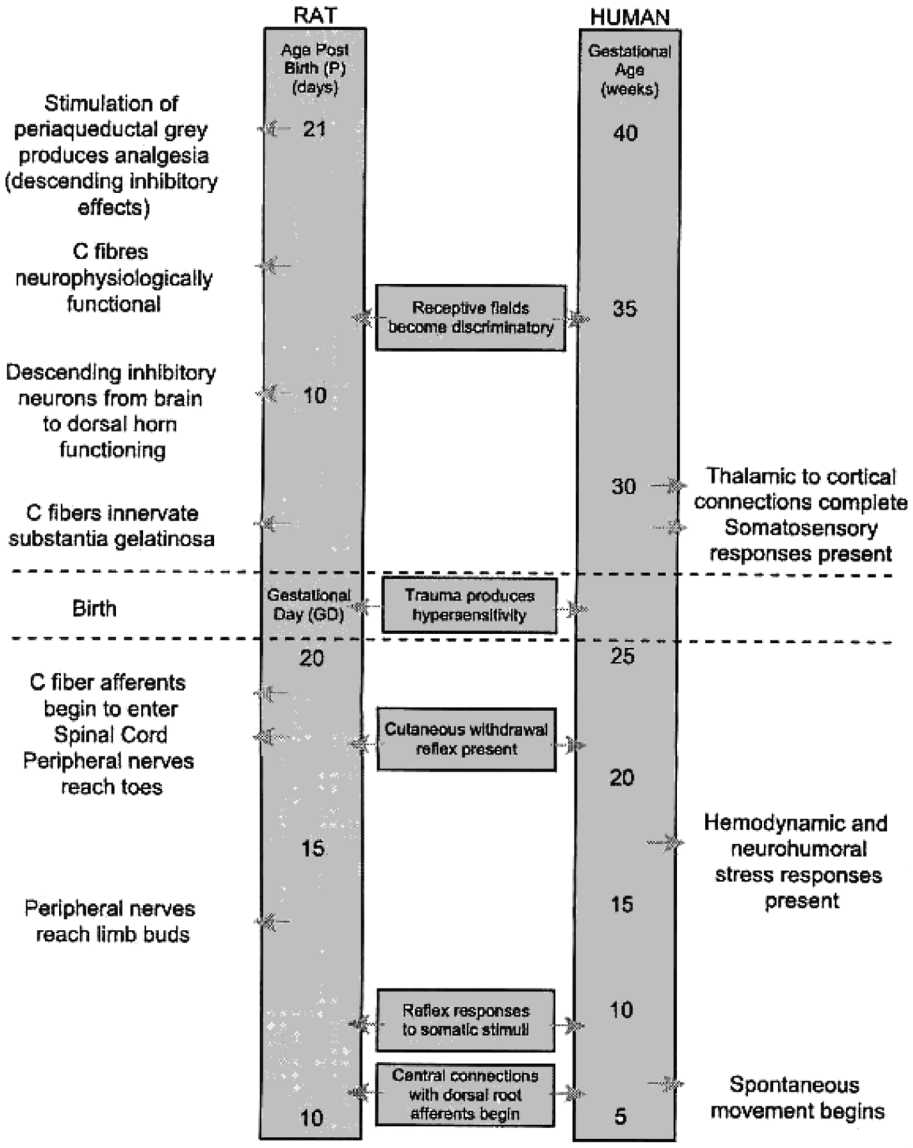


Fig. 3. Development of nociception in rats and humans. Taken from White and Wolf (2004).

better expression is nociception which refers to the anatomical and physiological responses to harmful stimuli. Therefore, it is more precise to use this expression, which is also used in animals, even if we are sure that animals are capable of feeling pain [7, 8, 9, 10, 11].

The receptive field the fetus during development is much greater than in the adult. However, fetal systems are less able to differentiate pain stimuli from other somatosensorical stimuli. Many different types of stimulation induce holistic and

Table 1. Appearance of different parts of the nociceptive system.

The different parts of nociceptive system	**The appearance of anatomical backgrounds and physiological functions**	**The appearance is weeks**
Nocisensors	The appearance of nocisensors (on mouth, on the whole body)	7-20 weeks
Peripheral afferent fibers	The appearance of synapses in spinal cord	10-30 weeks
Spinal cord	The stimulation provokes the motor movement spinothalamic connections myelinization of nociceptive pathways the appearance of descending pathways	7.5 week 20 weeks 22 weeks postnatally
Thalamocortical pathways	First axons appear in the cortical plate formation of functional synapses in thalamocortical connections	20-22 weeks 26-34 weeks
Brain cortex	Migration of brain neurons (brain cortex is developed) first EEG spindles are detected Appearance of symmetric and synchronized EEG activity distinguishing of consciousness and sleep in EEG detection of evoked potentials	8-20 weeks 20 weeks 26 weeks 30 weeks 29 weeks

nonspecific reactions which later in development become more restrictive and functionally more precise [36, 37].

Behavioral reactions during the fetal period. Pain stimuli induce motor movements, such as the defensive flexor reflex, body movements, or vocalization are often taken to be an indication of pain perception in neonates. The first motor reflexive head movements appear about 7.5 weeks into gestation, hands become sensitive about 10.5 weeks into gestation and at 14 weeks the legs began to show reflex movements. These reactions are spinal cord reflexes. During this period of development we can not speculate about perception on levels higher than the spinal cord [24, 38, 46, 49, 50].

Presence of an immature pain modulatory system. The reflex threshold is remarkably low and the reflexes are extensive, e. g. pricking the heel provokes movement of the whole body. There is no obvious correlation between noxious intensity and reflex strength. Strong reflexes to strong noxious stimuli more likely represent an

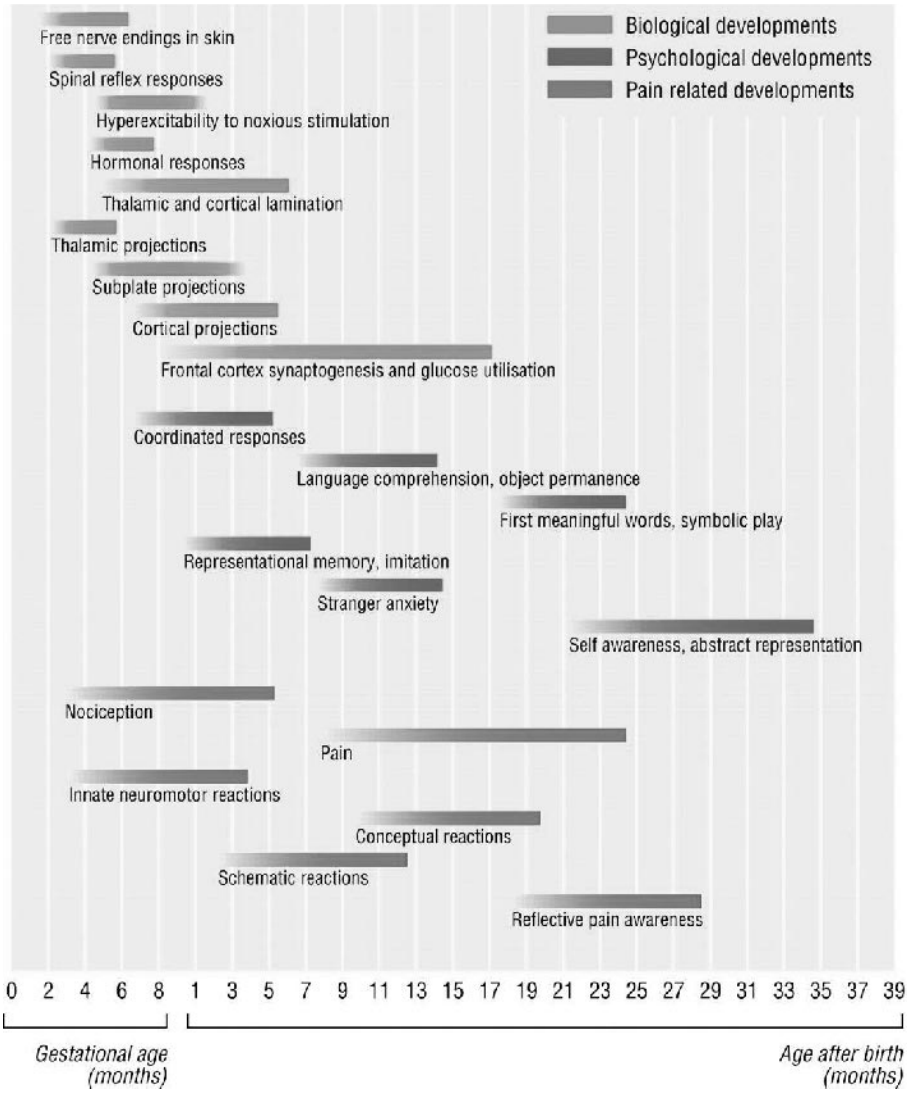


Fig. 4. Developmental stages prenatally and postnatally. Arranged by Derbyshire (2007).

expression of the immaturity of modulatory systems rather than an indicator of a pain threshold [12, 24, 40, 41].

Facial motor reflexes and facial expressions can specifically reflect painful emotions. This idea is supported by the fact that premature children born before the 26th gestational week have specific facial expressions associated with pain. These facial reflexes can be used for objective analyses of certain components which are similar to those found later in life. When the trigeminal nerve is stimulated, there is great variability in facial expressions and various somatic stimuli can be observed in very early periods of development. These movements are mostly coordinated

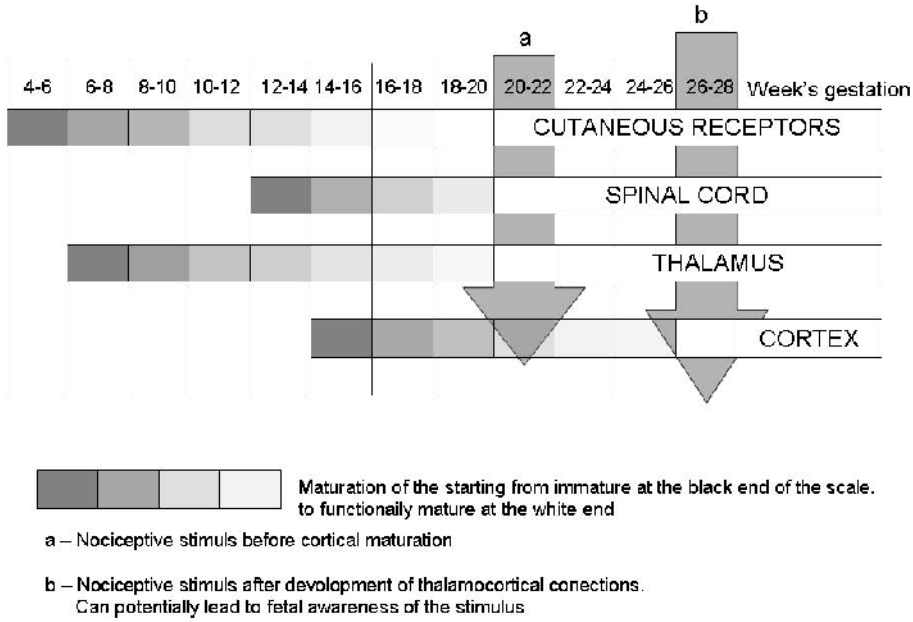


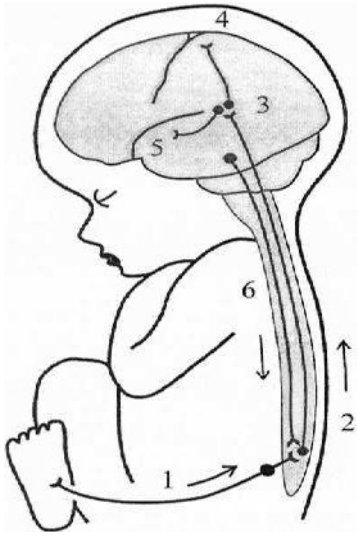
Fig. 5. Fetal pain pathways development. Arranged by Ismail et al. (2000).

by subcortical systems, which are concerned with the emotional motor system [27, 31, 32, 35, 39, 48].

The neuroanatomical pathways for tactile sensation, including touch and pain, are among the first sensorial perceptions to develop during the early gestational period. Pain is an important stimulus; the first nociceptors appear around the mouth during the 7th week of gestation, by the 20th week they are present all over the body. The electroencephalographic activity, reflecting integrity of the cortex and thalamocortical pathways, first appears during the 20th week, but synchronization only happens during the 26th week. The sleep / wake cycle is established during the 30th week.

Maturation of modulatory descendent pathways which are crucial for proper pain reactions appears very late. Animal experiments suggest that it only becomes functional during the second postnatal week. The reason for this is that functional maturation depends on the development of descendent noradrenergic and serotoninergic pathways and interneurons of the dorsal spinal cord. Strong reflexes on pain stimulation which we observe in fetuses and neonates are probably caused by the lack of maturation of this system. It is a minor control of entry of peripheral stimulations to the central nervous system [25, 51].

The most important common factor regarding all developmental pain is the probably massive and long lasting affect it has on the stress response with significant fluctuation of blood pressure, cerebral blood flow, and hypoxemia which can accentuate intracerebral bleeding. These changes of oxygenation and / or circulation



Nervous pathaways, which participate in pain:

1. Peripheral afferent nerves transfer signals to
2. Ascendent neurons in ascendent pathways in dorsal horns of spinal cord, where is synapse with other neuron which conduct nociceptive information to the thalamus.
3. In thalamus nociceptive(painful) information are transferred to two system which transfer signal either to in gyrus posterior(brodman areas 3,2,1)
4. Somato-sensorical, cortex = pain perception
5. Or to limbic cortex = affective component.
   When the pain information reaches the cerebral cortex, is consequently interpreted.
6. It is a lot of descencent neuronal pathways from the brain to horns of spinal cord which also modulate the ascendent nociceptive impulses.

Fig. 6. Nervous pathways, which participate in pain.

can be preventively resolved by adequate pain treatment. In infants, cortisol is still present in the saliva 6 months after the stress conditions associated with birth. Children, treated in intensive care units for 4 weeks, also demonstrate reduced behavioral and increased cardiovascular responses to pain or to pinching of the heel. These changes correlate very strongly with the quantity of invasive procedures linked to their treatment. Circumcision, without anesthesia, produces long lasting alterations in pain responses which can persist for 4–6 months. Repeated or very intensive experience with acute pain is always accompanied by long lasting changes to pain responses and physiological functions; the pain or stress which accompanies it increases the incidence of late complications during neurological and / or psychological development. Adequate pain treatment during these periods represents a preventative measure which can avoid undesirable consequences in the future [14, 34, 44, 47].

The fetal analgesia as a routine intervention against pain. The fetal HPA (hypothalamopituitaryadrenal axis) system has to be considered as functional from the 2nd trimester of pregnancy. Current research is working to determine the optimal period of drug activity, determine optimal dosage of drugs for fetal analgesia, and is

Table 2. Overview of management options for fetal and maternal anesthesia during *in utero* interventions.

	Maternal anesthesia	Fetal anesthesia
Open surgery	General anesthesia with or without epidural anesthesia	Fetus is anesthetized through placental passage, additional anesthesia can be obtained by direct fetal administration (IM or cord) of opioids (e.g. Fentanyl 10 μg/kg or sufentanil 1 μg/kg) and muscle relaxants (e.g. Pancuronium 0.3 mg/kg
Fetoscopic fetal surgery	Local anesthesia or regional anesthesia (spinal epidural of combined spinal epidural)	Direct fetal administration (IM or cord) of opioids (e.g. Fentanyl 10 μg/kg or sufentanil 1 μg/kg) and muscle relaxants (e.g. Pancuronium 0.3 mg/kg). Atropine (0.02-0.03 mg/kg) can be added
Fetoscopic surgery on placenta and cord	Local anesthesia or regional anesthesia (spinal epidural of combined spinal epidural)	Maternal IV administration of remifentanil 0.1-0.2 μg/kg/min or maternal IV administration of benzodiazepines
Late termination of pregnancy	Local anesthesia or regional anesthesia (if labor is induced and patient request regional analgesia for labor, epidural or combined spinal epidural)	Direct fetal administration (IM cord) of opioids (e.g fentanyl 10 μg/kg or sufentanil 1 μg/kg) and muscle relaxant (e.g. Pancuronium 0.3 mg/kg), followed by drugs to perform feticide (potassium or lidocaine)
Chronic in utero pain management or postoperative fetal pain management	None	Intra – amniotic administration of lipid soluble opioids

studying the effect of prenatal analgesia relative to postnatal pain thresholds and long term effects [1, 13, 15, 16, 22, 30, 33].

The prevention and pain treatment is a fundamental human right independent of age and should be extended to the fetus. In disregard of analgesia use, the developing child asks supression of nociceptive stimuli for optimize both short lasting and long lasting output. The actual development creates conditions for amelioration analgesia in children in all gestation periods and for the elimination of the risk.

It is very important for future research:

1. to clear up the molecular origin of stress and inflammation in the terms of gene expression in individual organs
2. to understand the state between stress and inflammation
3. to formulate approaches directed toward the elimination of stress responses and treatments which can manage general stress of the environment [17, 19, 21].

The development of autonomic and endocrine reflexes represent relatively non-specific indicators of the subjective painful state; this is also true in adult patients. During the 23rd week painful stimulation, of the fetus, increases cortisol and β endorphin in plasma after stimulation of the hepatic vein while stimulation of umbilical cord had no effect. Rudimentary pain perception already exists by the 23rd week even though the thalamocortical connections are not yet fully developed.

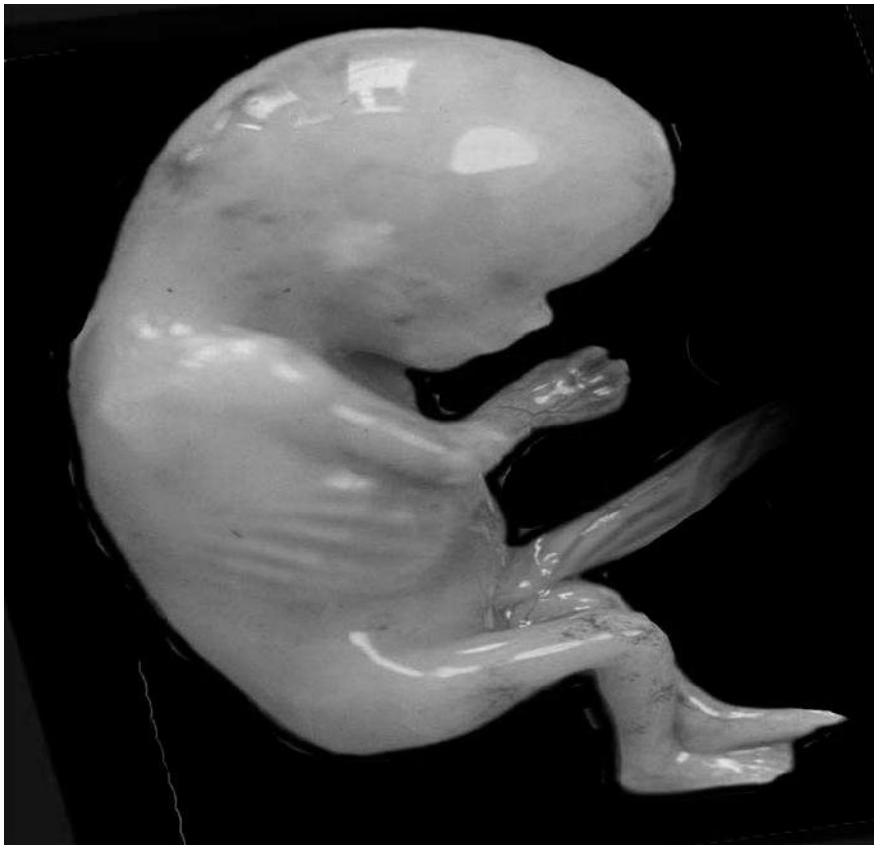


Fig. 7. Image of fetus Images courtesy of Prof. Jan Evangelista Jirásek (The Institute for Mother and Child, Prague-Podolí).

In this period the hypothalamopituitaryadrenal axis can start to be activated. Invasive procedures produce a deterioration of blood flow to the brain by the 18th week of gestation. A painful stimulus can cause a wide spectrum of responses in the central nervous system without reaching the level of the cerebral cortex. The hormonal, autonomic, and metabolic reflexes can, even at these early stages, be suppressed by analgesics. Fentanyl has been shown to suppress hormonal and autonomic reactions by the 28th gestational week. Adrenalin levels have been shown to be reduced by morphine by the 27th–31st gestational weeks in premature children born at intensive care units [20].

All this findings demonstrate that subcortical painful processes occur in fetuses some weeks before the painful stimulus is transmitted to the level of the cerebral cortex.

Acknowledgement. This study was supported by the Research Goal 00 216 208 16, CNS 1M 0517. CN LC 554

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This paper was previously published in Neuroendocrinology Letters, Vol. 29, No. 6, 2008.