The Challenge of Fetal Pain: What do we know?

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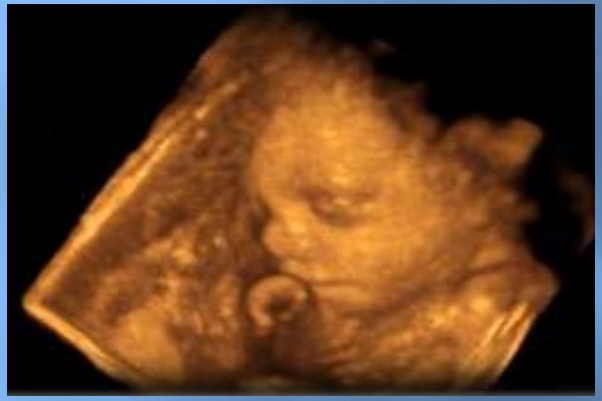
DISCLOSURE

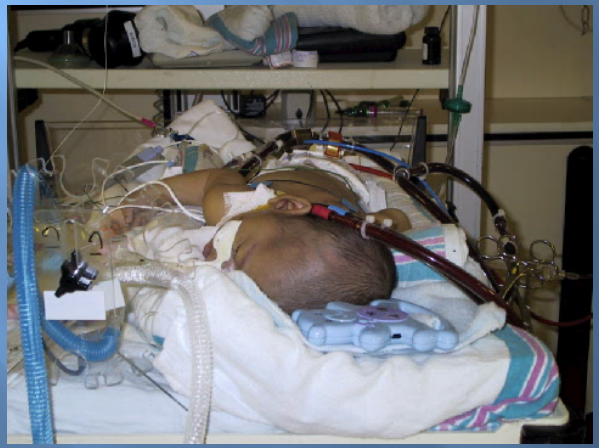
I, Jonathan Ponesse, have no relationships with any commercial interests.

Important Questions

- Can the human fetus feel pain?
- If so, how would we know?
- When would this capacity begin?
- What fetal structures and functions support this capacity?

Inside and Outside the Womb



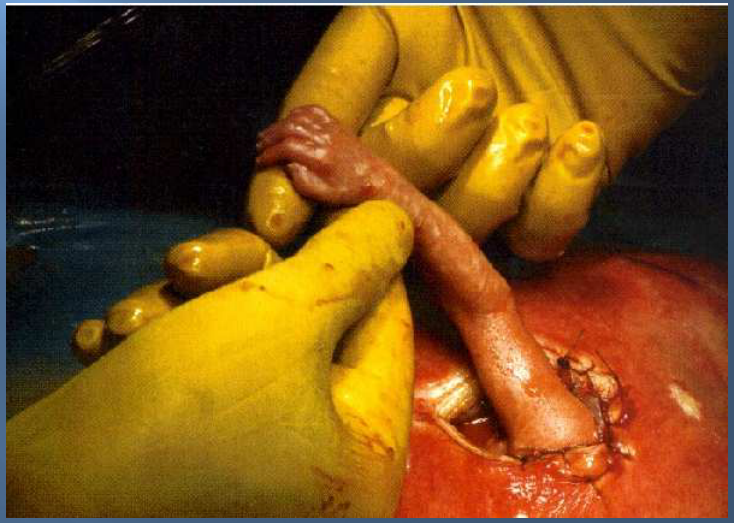


23 weeks GA

- Infants born prematurely have the same anatomy and physiology as their unborn counterparts.
- By studying the premature infant outside the womb we are allowed to understand what is happening inside the womb.

Fetal Surgery

- Advances into fetal surgery have called for new advances into fetal anesthesia and fetal monitoring.
- 19-26 weeks



Fetal Pain - Not a new science

- More than 30 years of data
  - Anand in 1987 reported on premature infants that were operated upon without anesthesia.
  - measured ‘fight and flight’ hormones during and after surgery and clearly demonstrated that these infants not only felt pain, but had an intense response.
  - further showed that the untreated pain led to a poorer health and development outcome in these infants.

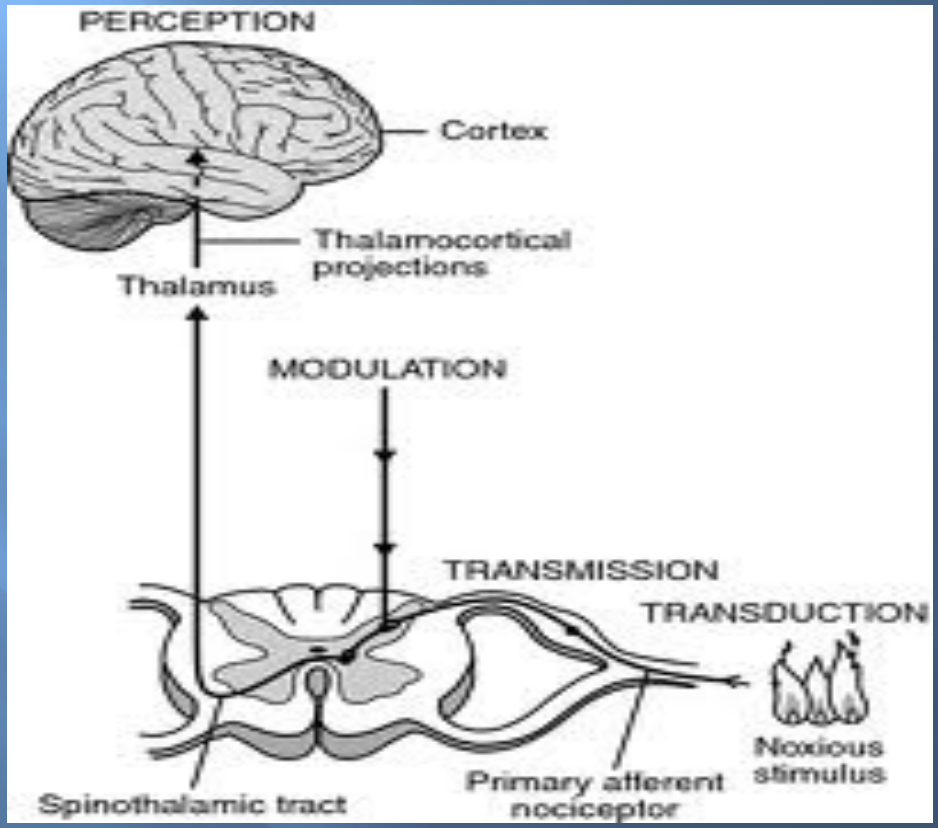
1987 Turning Point

- It wasn't until two landmark articles published in 1987 (Anand and Green, Lancet,1987, and Anand and Hickey NEJM, 1987) that the practice of pediatric anesthesia began to change broadly.
- It soon became unacceptable to operate on premature infants without meeting their pain and stress needs.

Nociception vs pain

- Involves the physical activation of specific nervous pathways without the conscious perception and subjective emotional experience of pain
  - Subcortical
  - We don’t sense pain, we sense noxious stimulation

Nociception



Prerequisites to feeling pain

- Peripheral input
  - Peripheral pain receptors
  - Afferent neural pathway to spinal cord
- Processing structures
  - HPA axis – hormones – “fight or flight”
  - Amygdala – memory and emotional state
  - Brain stem - inhibition
- Conscious experience
  - Thalamocortical circuit

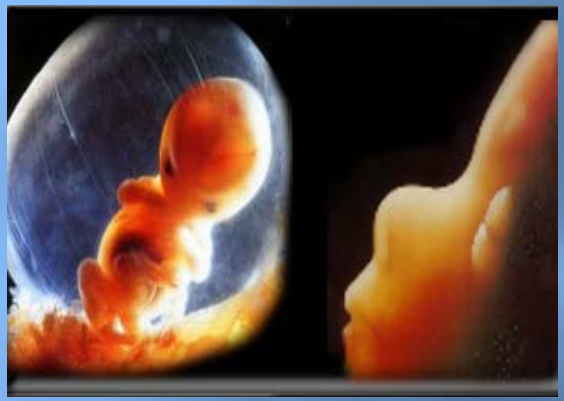
Objection #1

- “Immaturity of the fetal nervous system means that the nociceptive pathways are non-functional”
  - Assumption:
    - Pain perception during fetal life must engage same neural structures as those used by adults

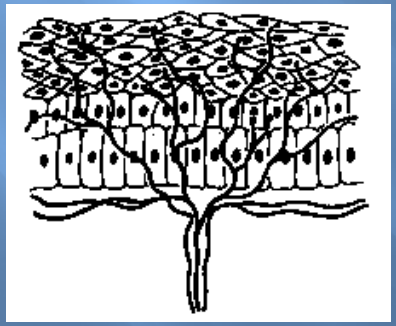
Response

- The fetus uses the anatomy/physiology existing at that particular time to communicate nociception
- First functional and anatomic pathways may substantially differ from their mature counterparts
  - Fetuses are not tiny adults

Carrying the signal



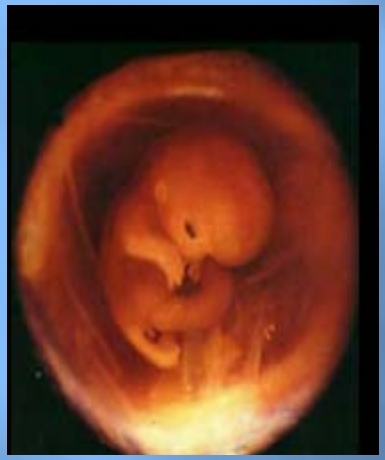
8 and 13 weeks



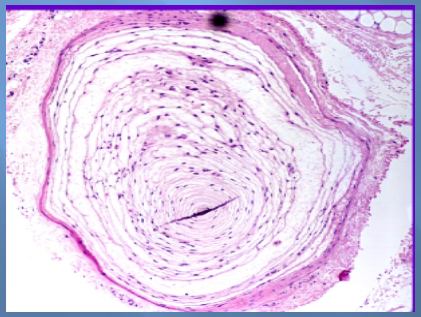
Nerve fibers penetrate skin

- Until specific nociceptive nerve fibres are mature and coated with myelin, the pain signals are carried by fibres from cutaneous touch receptors
- The skin is very thin, leaving the nerve fibers closer to the surface.

Distribution of these receptors



7 week fetus

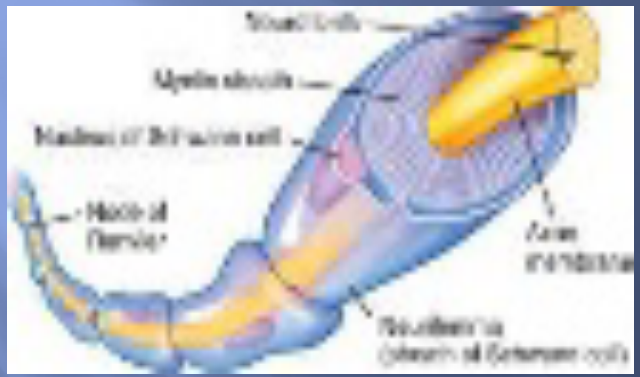


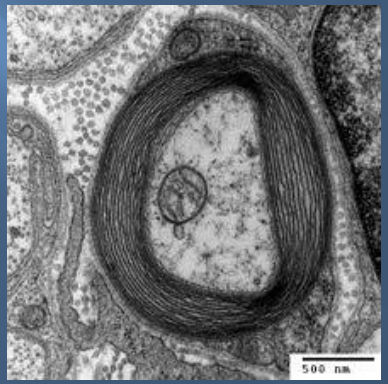
Cutaneous touch receptors

- These are seen at 7 weeks around the mouth and face, and cover the entire body by 20 weeks.
- They are more densely configured per square inch than on an adult.

Objection #2

- “Lack of myelination of the nociceptive pathways signifies diminished nociception.”





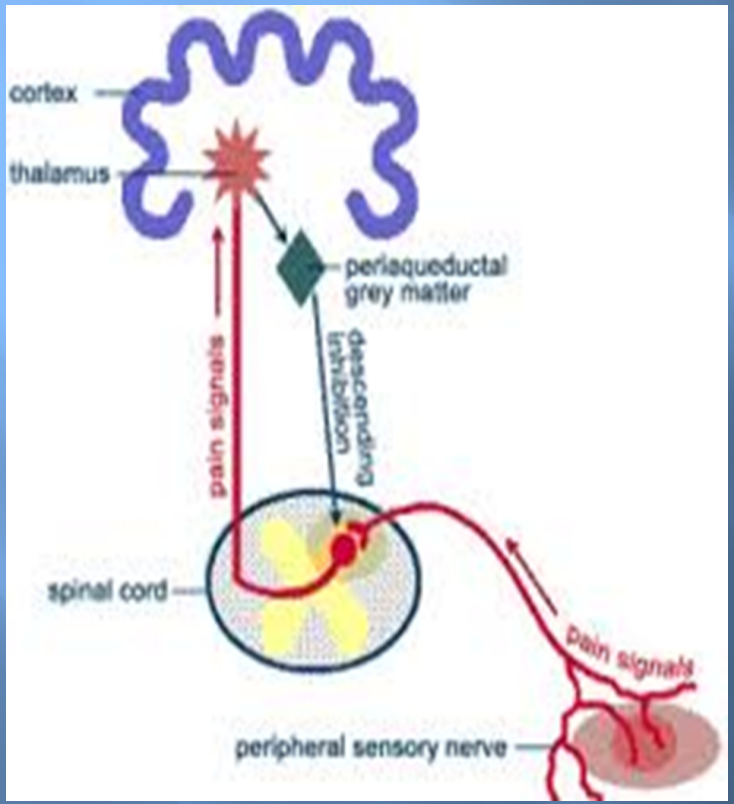
Response

- But nociceptive impulses in adults carried through unmyelinated (C-polymodal) and thinly myelinated (A-delta) fibres
  - Merely implies slower conduction velocity
- slower conduction speed in nerves of fetuses would be offset by smaller inter-neuron distances traveled by the impulse.
- Moreover, nociceptive nerve tracts in spinal cord and CNS undergo complete myelination during $2^{nd}/3^{rd}$ trimesters

Objection #3

- “Immaturity of the fetal nervous system would indicate that nociceptive input is diminished”

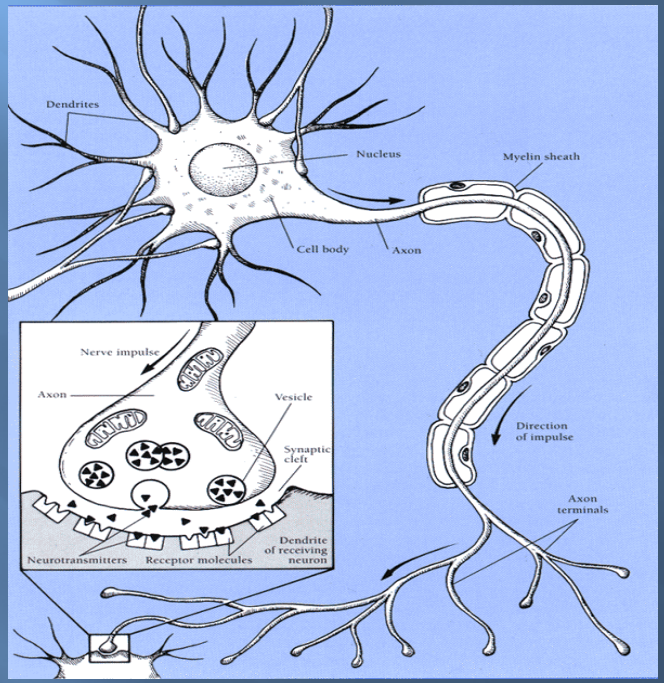
Response



- With maturity, nociception is modulated by inhibitory pathways
- In the fetus, the ability to modulate (or inhibit pain) does not develop until 36 - 40 weeks gestation
  - Descending noradrenergic and serotonergic
  - Dorsal horn interneuron

Objection #4

- “Nociceptive neurochemistry is functionally immature”



19 - 21 weeks

Neurotransmitters bind with specific receptors in a lock and key fashion.

Substance P (a tachykinin)

- opioid receptor labeling
- receptors found in high density in fetal brain stem
  - ca 12-16 w GA

Objection #4

- “We will never get anywhere with the fetal pain question, because we have little ability to gauge the functional maturity of the fetal nervous system”

Non-verbal markers of Pain

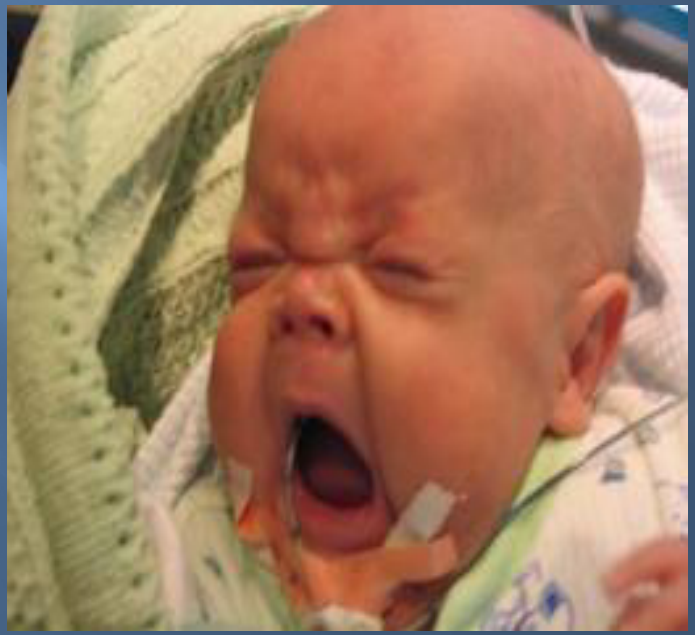
- The human fetus is incapable of verbal expression
- Vocalizations
  - From age of viability in preemies
- Withdrawal reflexes
  - First motor reflex
    - Head tilting after perioral touch
    - 7.5 weeks GA
  - Hands touch sensitive at 10.5 weeks

Cutaneous Flexor Reflex

- has a lower threshold in pre-term neonates than in term neonates or adults.
- The study of this reflex has been used to establish when connection between the skin and the spinal cord are first made in the fetus.
  - Averaging 20 wks GA
- This reflex has been shown to parallel pain perception exactly in terms of threshold, peak intensity, and sensitivity to analgesics.

Facial expressions and pain

- 26 week prems have pain-specific facial expressions
  - Coordinated by a subcortical system
    - “emotional-motor system”



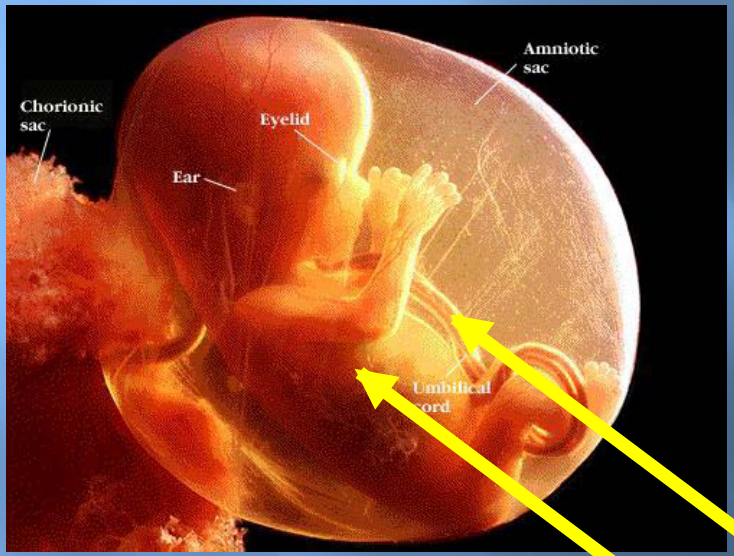
Physiologic Responses

- In utero studies of living fetuses demonstrate the ability to generate ‘fight or flight’ hormones in response to painful stimuli as early as 16 weeks.
  - Fetal blood sampling
  - Body Cavity aspirations
  - Fetal amniotic shunts
- Catecholamines, B-endorphins, Cortisol
- Blood flow to the brain was decreased within 70 seconds after a painful stimulation
- Thalamus-, not cortex-dependent

Physiologic Responses

- When a needle is placed through the liver to give the fetus a transfusion, these hormones are released. The abdominal wall has pain fibers.
- When the needle is placed in the umblical vein, which has no pain fibers, no consistent neurohormonal responses occurred.
- Whereas the liver aspiration produced changes proportional to the stimulus.
  - Infer a pain response
  - even in absence of thalamocortical connections

Response to pain relief



16 week fetus

- The hormonal, autonomic and metabolic responses were reduced when fentanyl
  - a pain relieving opiate
- was administered directly to the fetus.

Umbilical vein placement

Transabdominal and liver placement

Objection #5

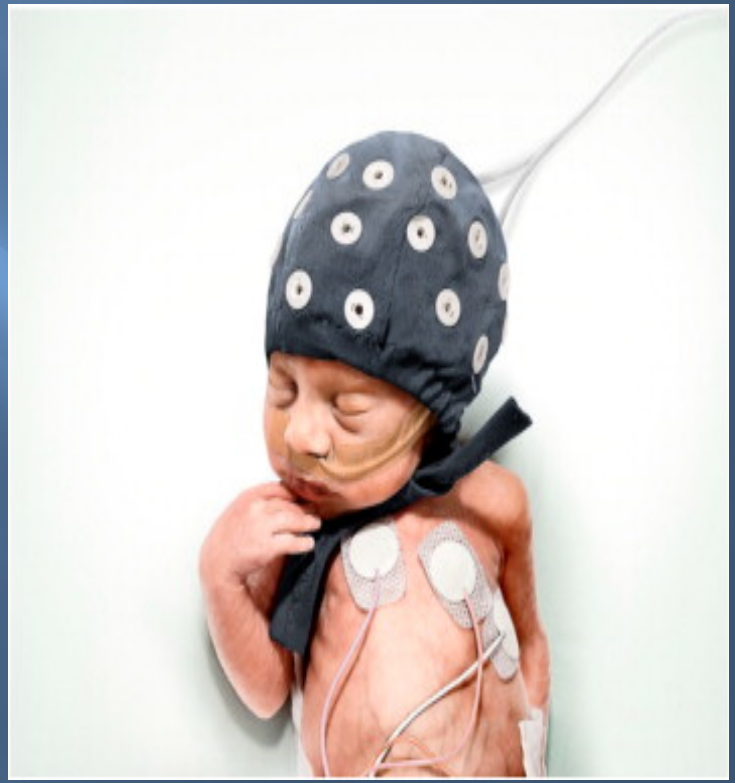
- “ The cortex is required to “feel” pain”
  - Psychological nature of pain presupposes the presence of functional thalamocortical circuitry required for conscious perception

Response

- In adults, stimulation or ablation of the cerebral cortex does not alter pain perception
  - While stimulation or ablation of the thalamus does
- Evidence exists for children missing the bulk of their cerebral cortex nevertheless experience pain
  - Hydranencephaly
  - Anencephaly

Evidence of functional maturity of cerebral cortex

- EEG patterns
  - Wakefulness, sleep
  - 20-21 weeks GA
    - =thalamo-cortical integrity



Summary

- Markers of fetal nociception/pain perception start at the 7th week and mature over the next 12 weeks.
- Requisite structures
  - Nociceptors
  - Sensory nerves
  - Dorsal column
  - thalamus
- By week 20, the anatomy of the nervous system and the physiology of responding to the pain impulse draws a clear cause and effect relationship.

Summary

- Ramifications
  - After spinal cord afferent development at GA 10
    - May be no age limit at which one can be sure noxious stimuli are not harmless

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