Fetal Pain

The evidence that fetuses feel pain at earlier gestational ages than previously thought prompts a call for universal management rather than individual practice. The purpose of this document is to present the available evidence for fetal pain, discuss implications for procedures in pregnancy, and to provide recommendations for situations requiring termination of pregnancy.

Background

Pain Defined

The definition of “pain” is much debated among embryologists, family planning professionals, ethicists, and politicians. Certainly, the adult person’s perception of pain is a complex physical and psychological interplay with long-term consequences for society. Since psychology or behavior are currently impossible to detect in human fetuses, discussion of fetal pain is often seen as meaningless. However, in literature on non-human organisms, pain has been defined as “aversive behavioral and physiological reactions and a suspension of normal behavior in response to noxious stimuli that cause pain in other animals and humans.” For the purposes of this document, pain will be defined this way.

Embryology and Fetal Development

In adults, painful stimuli are received by nociceptors in the skin and viscera; these communicate impulses via afferent sensory neurons through the spinal cord, are processed in the thalamus, and are received by the sensory cortex before a motor response is elicited. Adults also have reflex arcs that operate through motor neurons in the spinal cord’s dorsal root ganglia, allowing the body to bypass the cortex for the sake of speed. Both of these neural pathways are associated with neurohormonal responses including epinephrine, cortisol, and endorphins. Nociceptive signaling differs throughout human development, with neonates using different structures than adults. In non-human animals, nervous systems are much simpler, with some of the lowest animals with three germ layers such as nematodes or octopi reacting to noxious stimuli with only nerves and ganglia.

In fetuses, different structures have neurologic function at different times in development, analogously to the two sets of functioning nephrologic structures in fetal life. “Clinical and animal research shows that…the structures used for pain processing in early development are unique and different from those in adults, and that many of these fetal structures and mechanisms are not maintained beyond specific periods of early development. The immature pain system thus uses
the neural elements available during each stage of development to carry out its signaling role.”^4,8,9 Van Sheltema et al have argued that this means “the lack of development of certain connections is not sufficient to support the argument that fetuses can not [sic] feel pain until late gestation.”^10 Most agree that differences in structure imply some difference in function or potency, much like the fetal mesonephros; Killackey and Dawson noted that in rats, dividing early neuronal connections had disastrous consequences for developing later connections.\(^10\)

Decades of histologic research has illustrated that sensory receptors, including nociceptors, are present throughout the fetus between 10 and 14 weeks gestational age, starting as early as 7 weeks.\(^11\) This begins in the perioral area at 7 weeks, followed by the palms and soles at 11 weeks, and the remainder of the integument by 20 weeks.\(^18,19\) Superficial nociceptors, followed later by nociceptors in viscera, are connected by afferent fibers from the spinal column to the thalamus and from the thalamus to the subcortical plate between 16 and 20 weeks gestational age.\(^20-24\) These afferent fibers “appear morphologically mature enough to synapse with subplate neurons” and cause a central response, possibly as early as 16 weeks’ gestational age.\(^22,25\) Peripheral afferent fibers that control movement grow into the spinal cord at 8 weeks gestation.\(^19\) These are the three tissue components of a reflex arc in the adult.

Experience of fetal surgeons and other physicians performing invasive procedures (e.g. peritoneal transfusion) matches these histologic findings. As early as 7.5 to 8 weeks’ gestational age, a fetus moves in response to stimuli.\(^24,26-28\) “Responses to touch begin at 7-8 weeks gestation when touching the peri-oral region results in a contralateral bending of the head. The palms of the hands become sensitive to stroking at 10-11 weeks gestation and the rest of the body becomes sensitive around 13-14 weeks gestation.”^29,30 Language varies in reports of fetal responses but Giannakoulopoulos et al describe this response as “vigorou body and breathing movements” and Williams reports “coordinated responses signaling the avoidance of tissue injury.”^31,32 Certainly no later than 22 weeks’ gestational age, the fetus responds to what an adult would consider painful, such as a needle penetrating the skin.\(^24\)

**Developmental Endocrinology**

There is evidence that fetuses have a neurohormonal response similar to adults, when faced with noxious stimuli.\(^31,33,34\) While the role of the cortex, as discussed above, is still under discussion, it is clear that cortical tissue receives this neurohormonal response as early as 16-18 weeks gestational age.\(^35,36\) Identical hormonal responses in neonates are known to produce poorer outcomes.\(^37,38\)

**Long-Term Effects of Stimuli and Fetal Anesthesia**

Noxious stimuli have long-term side effects including those on neurological and psychological development, such as hyperalgesia.\(^16,24,39\) Again, this mirrors neonatal data.\(^40-42\)

Seeing the adverse effects of noxious stimuli, fetal surgeons have adopted protocols for fetal anesthesia regardless of viewpoint on fetal consciousness, over and above paralytics.\(^19,20,22,24,25,27,43-48\) This lowers the hormonal response to stimuli\(^36,38,49-51\) as in adults.\(^52\)
Conclusions
Although language and subjective experience of pain is hotly debated, if “pain” be defined as “perception and response to noxious stimuli,” it is clear that fetuses are capable of pain by 22 weeks’ gestational age at the latest; possibly earlier, as fetuses do respond to touch as early as 7.5 to 8 weeks.

Questions and Recommendations
Q Should the word “pain” be used when speaking of organisms which may not have consciousness?
“Pain” is used in other biology literature to mean the perception and response to noxious stimuli that would be considered painful by a human person. It is irrelevant to many disciplines, such as marine biology, whether fish or crustaceans are conscious; advocates for these organisms see fit to use the word “pain” out of common sense, to refer to a mutually understood concept of evolutionary response to adverse external stimuli.2,53

It is difficult to look at the evidence of histology (fully formed structures resembling those found in adults) and the experience of physicians operating on fetuses and conclude that the fetus is not sensitive to adverse external stimuli.

Q Does the ability to experience pain depend on the cerebral cortex and afferent thalamocortical fibers?
Afferent thalamocortical fibers develop closer to the third trimester, and some neuroscientists advocate the cortex as primary for pain perception.22,54 If cortical activity is required for fetal perception of pain, then fetuses do not feel pain until closer to 23-30 weeks gestation.22,55-57 This assumption and corollary is best articulated by Lee et al: “Pain perception requires conscious recognition or awareness of a noxious stimulus. Neither withdrawal reflexes nor hormonal stress response to invasive procedures prove the existence of fetal pain, because they can be elicited by nonpainful stimuli and occur without conscious cortical processing.”22

However, recent studies suggest that cortical activity is not necessary for the experience of pain in humans. This is largely from experience with decorticate children, lacking functional cortex due to congenital anomalies, perinatal brain damage, or comissurotomy.8-69 In fact, these children can interact socially in simple ways, such as to faces and music.70 Moreover, it appears that if the cortex is not strictly speaking required for basic perception of pain, the thalamus is the next level of neurological centralization; the thalamus, as noted above, is connected to peripheral nociceptors between 16 and 20 weeks’ gestational age.22,25,71 This would match what occurs in adults: cortical input does not alter pain perception, but thalamic input does.59,72-75 Even more dramatically, in the adult with loss of significant amount of cerebral cortex, consciousness can be preserved.76

It is possible that pain, which can be induced in adults simply with the imagination, utilizes the cortex and pain in simpler organisms, including human fetuses, may not require a functional cortex while still being painful in a way different from a fully developed human organism. The conclusion that fetuses are unable to feel pain because they lack complete cortical inputs may be “unduly definite.”77

Q Are fetuses awake in utero?
It has been asserted that “the fetus never experiences a state of true wakefulness in utero and is kept, by the presence of its chemical
environment, in a continuous sleep-like unconscious or sedation” due to elevated levels of neuroinhibitors like adenosine and pregnanolone.4,5,57

The hypothesis that endogenous inhibitory factors lead to sleep is not rigorously tested. Further, this asserts a double standard: should these chemicals be seen as more important than the neurohormonal response associated with stimuli (above)? Should the “vigorous body and breathing movements” that require paralytics in fetal surgery be viewed as part of a sleep state? 31,36,78-81

Q How should fetuses undergoing surgery be anesthetized?
Following the lead of fetal surgeons, analgesia should be provided in addition to paralysis. This document is not meant to make assertions regarding fetal surgery, which is outside the scope of practice of most AAPLOG members and outside the scope of practice of the committee.

Q Can D&E, D&C, D&X be performed for deceased fetuses?
Dilation and removal of products of conception causes no pain if an embryo or fetus is deceased. There are no ethical issues with these procedures, although pastoral or clinical difficulties may arise when piecemeal removal of a desired fetus is performed.

Q Should abortion by dismemberment or extraction be performed after gestational ages when fetal susceptibility to pain is documented?
After 22 weeks’ gestational age, abortions requiring dismemberment should be avoided. Dividing the fetal body with traditional instruments, or piercing the cranium and evacuating the contents, would constitute noxious stimuli. Dismemberment should be seen as especially noxious, since there is evidence that dividing afferent tracts has effects similar to painful stimuli in adults (long-term effects demonstrated in an animal model).10 Evacuating cranial contents may lead to more rapid cessation of pain (due to direct destruction of the brain stem and thalamus) but must still be seen as a noxious stimulus.

Q Should termination of pregnancy by any other method be performed after gestational ages when fetal susceptibility to pain is documented?
Saline induction leads to constriction of capillaries in skin, the gastrointestinal tract, the respiratory tract, and the placenta. Animal models suggest that the mechanism of death of these fetuses is suffocation which is likely associated with a neurohormonal response associated with stress. Moreover, constriction of capillaries and tissue necrosis likely results in nociceptive feedback after nociceptors are present at 10-14 weeks gestational age.

Early induction of labor does lead to the end of pregnancy but results in delivery of an intact and possibly living fetus. Induction of labor is fundamentally different from the previously described methods of termination of pregnancy because its purpose is not to end the life of the fetus. Although induction may be initiated before viability, although particularly fragile fetuses (e.g. those with growth restriction) may not be born alive, and although parents of periviable infants may elect not to proceed with resuscitation, induction of labor still remains fundamentally different in its moral object: it does not aim to end the life of the fetus.
Q Should abortion by any other method be performed after the lowest age of viability?
When there is need to separate the mother from the fetus at or greater than 22 weeks, delivery of a live fetus, followed by adequate neonatal analgesia (even when neonatal resuscitation is impossible or not desired by the parents) should be preferred to abortion by any method.

Q Would legislation to prohibit abortions after 22 weeks gestational age ban all abortions?
Bans on abortions after 22 weeks gestational age will only ban abortions affecting potentially viable fetuses. In 2013, the most recent year for which the CDC has provided data as of publication, 1.3% of abortions occur at greater than 21 weeks.82

Q Would legislation to prohibit abortions after 22 weeks gestational age be dangerous for the maternal patient?
Most 22 week abortion bans have an exception which allows the physician to legally use any method of separation of the mother and fetus when the life of the mother is at stake. A surgical abortion at this gestational age would typically take at least ten minutes, and a saline induction would take several hours (up to two days). There are comparable alternatives which do not affect fetal body integrity or cause pain: if there is need for immediate separation, cesarean section can be accomplished in as little as one minute from decision to separation. If more time is available, an induction of labor can be sought, which often takes up to two days.

Q Is fetal pain proportionate to the present and future morbidity of a classical cesarean section?
One in four women with a classical cesarean section will suffer morbidity, including uterine rupture, asymptomatic dehiscence, postpartum hemorrhage, and need for transfusion of blood products.83 These risks should not be taken lightly. However, when these are weighed against the life of the maternal patient and the respect of the integrity of the fetal patient (even if this patient be viewed as a non-personal organism) prompts serious consideration of this delivery method if induction of labor is expected to take too long. It should be kept in mind, especially with cardiovascular threats such as pulmonary hypertension or peripartum cardiomyopathy, that vaginal delivery is preferable and most fluid shifts occur postpartum regardless of mode of delivery.

Summary of Recommendations and Conclusion

The following statements are based on good and consistent scientific evidence (Level A):

1. Fetuses of 22 weeks’ gestational age respond with aversive behavioral, physiological reactions, and a suspension of normal behavior to noxious stimuli that cause pain in other animals and humans, which is called “experience of pain” in disciplines such as animal biology.

2. Between 10 and 22 weeks’ gestational age, a fetus perceives external stimuli in varying and as-yet incompletely understood ways depending on the locus of the stimulus and the age of the fetus.

The following recommendations are based on limited and inconsistent scientific evidence (Level B):

1. Subjecting an un-anesthetized fetus to noxious stimuli is associated with long-term adverse neurodevelopmental effects such as hypersensitivity to pain.
The following recommendations are based primarily on consensus and expert opinion (Level C):

1. Abortions involving noxious stimuli, such as the effects of saline on derivatives of the ectoderm and endoderm, or dismemberment, should be avoided after 22 weeks’ gestational age.
2. Termination of pregnancy after 22 weeks’ gestational age should be carried out by induction or cesarean section, depending on clinical circumstance.
3. Analgesia should be provided to neonates delivered in this way even if no neonatology resuscitation is planned.

References

66. Schiff NDM. fMRI reveals large-scale network activation in minimally conscious patients. Neurology. 64(205)514-523.


The MEDLINE database, bibliographies of relevant guidelines, and AAPLOG’s internal sources were used to compile this document with citations from 1985 to the publication date. Preference was given to work in English, to original research, and to systematic reviews. When high-quality evidence was unavailable, opinions from members of AAPLOG were sought.