AAPLOG Practice Bulletin No. 2: Fetal Pain

American Association of Pro-Life Obstetricans & Gynecologists*

ABSTRACT: 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.[1] 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."[2] 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.[3] Both of these neural pathways are associated with neurohormonal responses including epinephrine, cortisol, and endorphins. Nociceptive signaling differs throughout human

* Committee on Practice Bulletins. This document was developed by the Practice Bulletin Committee to provide evidence for pro-life practice. Because of the gravity of issues addressed by AAPLOG, variation in practice regarding matters of fetal life should be undertaken only after serious consideration of the literature cited by this document.

development, with neonates using different structures than adults.[4] 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.[5,6]

In fetuses, different structures have neurologic function at different times in development, analogously to the two sets of functioning nephrologic structures in fetal life.[7] "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 have illustrated that sensory receptors, including nociceptors, are present throughout the fetus between 10 and 14 weeks gestational age, starting as early as 7 weeks.[11-17] 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 "vigorous 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.[8,58-69] 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.[4,55,57]

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. The risks of cesarean delivery should be weighed against the risk to life of the maternal patient with continuation of the pregnancy, as well as the respect for the bodily integrity of the fetal patient (even if this patient is viewed as a non-personal organism). Balancing these risks prompts serious consideration of cesarean delivery if induction of labor is expected to take too long for the proportionate risk to the woman's life. 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 longterm 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

[1] Henschke N, Kamper SJ, Maher CG. The epidemiology and economic consequences of pain. *Mayo Clinic Proceedings*. 2015 Jan;90(1):139-47.

[2] Sneddon, LU. Pain Perception in fish: indicators and endpoints. *ILAR Journal*. 2009;50(1):338-342.

[3] Fenton BW, Shih E, Zolton J. The neurobiology of pain perception in normal and persistent pain. *Pain Management*. 2015;5(4):297-317.

[4] Fitzgerald M. The development of nociceptive circuits. *Nature Reviews Neuroscience*. 2005;6(7):507-20.

[5] Edelman DB, Baars BJ, Seth AK. Identifying hallmarks of consciousness in non-mammalian species. *Consciousness and Cognition*. 2005;14(1):169–87.

[6] Hobert, O., Specification of the nervous system. WormBook. 2005. doi/10.1895/wormbook.1.7.1, http://www.wormbook.org.

[7] Sadler T. *Langman's Medical Embryology*. 2011:235-263.

[8] Anand KJS. Fetal pain? *Pain: Clinical Updates*. 14:2(2006)1-4.

[9] White MC, Wolf AR. Pain and stress in the human fetus. *Best Practice & Research Clinical Anaesthesiology*. 2004;18(2):205-20.

[10] Killackey HP, Dawson DR. Expansion of the Central Hindpaw Representation Following Fetal Forelimb Removal in the Rat. *European Journal of Neuroscience*. 1989;1(3):210-21.

[11] Smith S. *Commission of Inquiry into Fetal Sentience*. London: CARE 1996.

[12] Derbyshire SW. Foetal pain? *Best Practice & Research Clinical Obstetrics & Gynaecology*. 2010;24(5):647-55.

[13] Anand K, Hickey P. Pain and Its Effects in the Human Neonate and Fetus. *New England Journal of Medicine*. 1987;317(21):1321-9.

[14] Humphrey T. Some Correlations between the Appearance of Human Fetal Reflexes and the Development of the Nervous System. *Growth and Maturation of the Brain Progress in Brain Research*. 1964;4:93-135

[15] Valman HB, Pearson JF. What the fetus feels. *BMJ*. 1980;280(6209):233-4.

[16] Vanhatalo S, Nieuwenhuizen OV. Fetal pain? *Brain and Development*. 2000;22(3):145-50.

[17] Brusseau R. Developmental Perspectives: Is the Fetus Conscious? *International Anesthesiology Clinics*. 2008;46(3):11-23.

[18] Simons SH, Tibboel D. Pain perception development and maturation. *Seminars in Fetal and Neonatal Medicine*. 2006;11(4):227-31.

[19] Rollins MD, Rosen MA. Anesthesia for Fetal Intervention and Surgery. *Gregory's Pediatric Anesthesia*. 2011:444–74.

[20] Scheltema PNAV, Bakker S, Vandenbussche F, Oepkes D. Fetal Pain. *Fetal and Maternal Medicine Review*. 2008;19(04):311-324.

[21] Glover V, Fisk NM. Fetal pain: implications for research and practice. ***BJOG: An International Journal of Obstetrics and Gynaecology***. 1999;106(9):881-6.

[22] Lee SJ, Ralston HJP, Drey EA, Partridge JC, Rosen MA. Fetal Pain. ***JAMA***. 2005;294(8):947.

[23] Kostovic I, Rakic P. Developmental history of the transient subplate zone in the visual and somatosensory cortex of the macaque monkey and human brain. ***The Journal of Comparative Neurology***. 1990;297(3):441-70.

[24] Gupta R, Kilby M, Cooper G. Fetal surgery and anaesthetic implications. ***Continuing Education in Anaesthesia, Critical Care & Pain***. 2008;8(2):71-5.

[25] Velde MVD, Buck FD. Fetal and Maternal Analgesia/Anesthesia for Fetal Procedures. ***Fetal Diagnosis and Therapy***. 2012;31(4):201-9.

[26] Glover V. The fetus may feel pain from 20 weeks. ***Conscience***. 2004-2005 Winter 25(3):35-7.

[27] Myers LB, Bulich LA, Hess P, Miller NM. Fetal endoscopic surgery: indications and anaesthetic management. ***Best Practice & Research Clinical Anaesthesiology***. 2004;18(2):231-58.

[28] KadićAS, PredojevićM. Fetal neurophysiology according to gestational age. ***Seminars in Fetal and Neonatal Medicine***. 2012;17(5):256-60.

[29] Derbyshire SW. Fetal Pain: Do We Know Enough to Do the Right Thing? ***Reproductive Health Matters***. 2008;16(sup31):117-26.

[30] Fitzgerald M. Neurobiology of fetal and neonatal pain. ***Textbook of Pain***. 1994:153-63.

[31] Giannakoulopoulos X, Glover V, Sepulveda W, Kourtis P, Fisk N. Fetal plasma cortisol and ćendorphin response to intrauterine needling. ***The Lancet***. 1994;344(8915):77-81.

[32] Williams C. Framing the fetus in medical work: rituals and practices. ***Social Science & Medicine***. 2005;60(9):2085-95.

[33] Giannakoulopoulos X, Teixeira J, Fisk N, Glover V. Human Fetal and Maternal Noradrenaline Responses to Invasive Procedures. ***Pediatric Research***. 1999;45(4, Part 1 of 2):494-9.

[34] Gitau R. Fetal Hypothalamic-Pituitary-Adrenal Stress Responses to Invasive Procedures Are Independent of Maternal Responses. ***Journal of Clinical Endocrinology & Metabolism***. 2001Jan;86(1):104-9.

[35] Teixeira JM, Glover V, Fisk NM. Acute cerebral redistribution in response to invasive procedures in the human fetus. ***American Journal of Obstetrics and Gynecology***. 1999;181(4):1018-25.

[36] Smith RP, Gitau R, Glover V, Fisk NM. Pain and stress in the human fetus. ***European Journal of Obstetrics & Gynecology and Reproductive Biology***. 2000 Sep;92(1):161-5.

[37] Anand KJS, Hickey PR. Halothane-Morphine Compared with High-Dose Sufentanil for Anesthesia and Postoperative Analgesia in Neonatal Cardiac Surgery. ***Survey of Anesthesiology***. 1992;36(5).

[38] Anand K, Sippell W, Aynsley-Green A. Randomised trial of fentanyl anaesthesia in preterm babies undergoing surgery: Effects on the stress response. ***The Lancet***. 1987;329(8524):62-6.

[39] Anand KJS. Pain, plasticity, and premature birth: a prescription for permanent suffering? ***Nature Medicine***. 2000Jan;6(9):971-73.

[40] Johnston CC, Stevens BJ. Experience in a neonatal intensive care unit affects pain response. ***Pediatrics***. 1996;98(5):925-30.

[41] Taddio A, Katz J, Ilersich AL, Koren G. Effect of neonatal circumcision on pain response during subsequent routine vaccination. ***The Lancet***. 1997;349(9052):599-603.

[42] Taylor A, Fisk NM, Glover V. Mode of delivery and subsequent stress response. ***The Lancet***. 2000;355(9198):120.

[43] Rosen MA. Anesthesia for Fetal Surgery and Other Intrauterine Procedures. ***Chestnut's Obstetric Anesthesia: Principles and Practice***. 2009:123-40.

[44] Giuntini L, Amato G. Analgesic Procedures in Newborns. ***Neonatal Pain***. 2007:73-81.

[45] Velde MVD, Schoubroeck DV, Lewi LE, Marcus MA, Jani JC, Missant C, et al. Remifentanil for Fetal Immobilization and Maternal Sedation During Fetoscopic Surgery: A Randomized, Double-Blind Comparison with Diazepam. ***Anesthesia & Analgesia***. 2005;101(1):251-8.

[46] Anand KJS, Maze M. Fetuses, Fentanyl, and the Stress Response. ***Anesthesiology***. 2001;95(4):823-5.

[47] Danzer E, Johnson MP, Adzick NS. Fetal surgery for myelomeningocele: progress and perspectives. ***Developmental Medicine & Child Neurology***. 2011Nov;54(1):8-14.

[48] Sudhakaran N, Sothinathan U, Patel S. Best practice guidelines: Fetal surgery. ***Early Human Development***. 2012;88(1):15-9.

[49] Fisk NM, Gitau R, Teixeira JM, Giannakoulopoulos X, Cameron AD, Glover VA. Effect of Direct Fetal Opioid Analgesia on Fetal Hormonal and Hemodynamic Stress Response to Intrauterine Needling. ***Anesthesiology***. 2001;95(4):828-35.

[50] Rychik J, Tian Z, Cohen MS, et al. Acute cardiovascular effects of fetal surgery in the human. ***Circulation***. 2004;110:1549-56.

[51] Teixeira J, Fogliani R, Giannakoulopoulos X, Glover V, Fisk N. Fetal haemodynamic stress response to invasive procedures. ***The Lancet***. 1996;347(9001):624.

[52] Desborough JP. The stress response to trauma and surgery. ***BJA: British Journal of Anaesthesia***. 2000 Jan; 85 (1):109-17.

[53] Sneddon, LU. Pain in aquatic animals. ***Journal of Experimental Biology***. 2015;218: 967-76.

[54] Coghill RC, Mchaffie JG, Yen Y-F. Neural correlates of interindividual differences in the subjective experience of pain. ***Proceedings of the National Academy of Sciences***. 2003;100(14):853842.

[55] Niven CA. Fetal Awareness: Report of a Working Party. The Royal College of Obstetricians and Gynaecologists. 1997, updated 2010.

[56] Brusseau R, Myers L. Developing consciousness: fetal anesthesia and analgesia. Seminars in Anesthesia, ***Perioperative Medicine and Pain***. 2006;25(4):189-95.

[57] Mellor DJ, Diesch TJ, Gunn AJ, Bennet L. The importance of 'awareness' for understanding fetal pain. ***Brain Research Reviews***. 2005;49(3):455-71.

[58] Anand KJS. Consciousness, cortical function, and pain perception in nonverbal humans. ***Behavioral and Brain Sciences***. 2007;30(01):82-83.

[59] Penfield W, Jasper HH. ***Epilepsy and the functional anatomy of the human brain***. 1954.

[60] Marin-Padilla M. Developmental neuropathology and impact of perinatal brain damage. ***Journal of Neuropathology & Experimental Neurology***. 1997;56:219-35.

[61] Takada K, Shiota M, Ando M, et al. Porencephaly and hydranencephaly: a neuropathological study of four autopsy cases. ***Brain Development***. 1989;11:5156.

[62] Shewmon DA, Holmes GL, Byrne PA. Consciousness in congenitally decorticate children: developmental vegetative state as self-fulfilling prophecy. ***Developmental Medicine & Child Neurology***. 1999;41:364-74.

[63] Merker B. Consciousness without a cerebral cortex: a challenge for neuroscience and medicine. ***Behavioral and Brain Sciences***. 2007;30:63-81.

[64] LeDoux JE, Risse GL, Springer SP, Wilson DH, Gazzaniga. Cognition and commissurotomy. ***Brain***. 1997;100L:87-104.

[65] Shewmon DA. A critical analysis of conceptual domains of the vegetative state: sorting fact from fancy. ***Neurorehabilitation***. 2004;19:343-7.

[66] Schiff NDM. fMRI reveals large-scale network activation in minimally conscious patients. ***Neurology***. 64(205)514-23.

[67] Counter SA. Preservation of brainstem neurophysiological function in hydranencephaly. ***Journal of Neuroscience***. 2007;263:198-207.

[68] McAbee GN, Chan A, Erde EL. Prolonged survival with hydranencephaly: report of two patients and literature review. ***Pediatric Neurology***. 2000;23:8084.

[69] Beshker M. The presence of consciousness in the absence of the cerebral cortex. ***Synapse***. 2008;62:553-56.

[70] Bellieni CV, Buonocore G. Is fetal pain a real evidence? *J Maternal-Fetal and Neonatal Medicine*. 2012;1-6.

[71] Brusseau R. Developmental perspectives: Is the fetus conscious? *International Anesthesiology Clinics*. 2008;46(3):11-23.

[72] Brooks JK, Zamreanu L, Godinez A, et al. Somatotopic organization of the human insula to painful heat studied with high resolution functional imaging. *Neuroimage*. 2005;27:201-09.

[73] Craig AD. Interoception: the sense of the physiological condition of the body. *Current Opinion in Neurobiology*. 2003;13:500-05.

[74] Nandi D, Aziz T, Carter H, et al. Thalamic field potentials in chronic central pain treated by periventricular gray stimulation: a series of eight cases. *Pain*. 2003;101:97-107.

[75] Nandi D, Liu X, Joint C, et al. Thalamic field potentials during deep brain stimulation of periventricular gray in chronic pain. *Pain*. 2002;97:47-51.

[76] Morsella E, Krieger SC, Bargh JA. Minimal neuroanatomy for a conscious brain: homing in on the networks constituting consciousness. *Neural Networks*. 2010;23;14-15.

[77] O'Donnell K, Glover V. New insights into prenatal stress: immediate and long-term effects on the fetus and their timing. *Neonatal Pain*. 2008:60.

[78] Seeds JW, Corke BC, Spielman FJ. Prevention of fetal movement during invasive procedures with pancuronium bromide. *American Journal of Obstetrics and Gynecology*. 1986;155:818-19.

[79] Rosen MA. Anesthesia for procedures involving the fetus. *Seminars in Perinatology*. 1991;12:410-41.

[80] Cauldwell CB. Anesthesia for fetal surgery. *Anesthesiology Clinics of North America*. 2000; 20:211-26.

[81] Schwarz U, Galinkin JL. Anesthesia for fetal surgery. *Seminars on Pediatric Surgery*. 2003;12:196-201.

[82] Jatlaoui T, Ewing A, Mandel M, et al. Abortion surveillance: United States, 2013. *MMWR Surveill Summ* 2016;65(No. SS-12).

[83] Chauhan SP, Magann EF, Wiggs CD, et al. Pregnancy after classic cesarean delivery. *Obstetrics and Gynecology*. 2002 Nov;100(5 Pt 1):946-50.

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