

Science of Fetal Pain

Babies as young as 20 weeks post-fertilization can survive and thrive with appropriate care and treatment

Groundbreaking *New England Journal of Medicine* study demonstrates that babies delivered as young as 20 weeks post-fertilization (22 weeks gestation) can survive, and active intervention for treatment greatly improves their survival.¹ Doctors who consider these preterm babies as patients demonstrate that active treatment significantly benefits these young babies.

Unborn babies are treated as patients by fetal surgeons, and receive pain medication

Fetal surgeons recognize unborn babies as patients. Perinatal medicine now treats unborn babies as young as 16 weeks post-fertilization (18 weeks gestation). Pain medication for unborn patients is routinely administered as standard medical practice.²

- One of the premier fetal surgeons makes the obvious point: “Fetal therapy is the logical culmination of progress in fetal diagnosis. In other words, the fetus is now a patient.”³
- A European fetal surgery team states: “The administration of anesthesia directly to the fetus is critical in open fetal surgery procedures.”⁴
- The leading textbook on clinical anesthesia says: “It is clear that the fetus is capable of mounting a physiochemical stress response to noxious stimuli as early as 18 weeks gestation.”⁵
- Here is what is told to the mother before fetal surgery by a group who have done many such surgeries:⁶ “You will be given general anesthesia, and that anesthesia will put your baby to sleep as well. In addition, during the prenatal surgery, your unborn baby will be given an injection of pain medication and medication to insure that the baby doesn’t move.”

Unborn babies can feel pain by 20 weeks post-fertilization or earlier

Previous uninformed notions that unborn and newborn babies could not feel pain, or misinformation on ability of preterm infants to survive, are refuted by a growing body of scientific evidence. Legislation should reflect the scientific facts.

Brain responses and connections. A new 2015 study used functional magnetic resonance imaging (fMRI) to measure pain response in newborns (1-6 days old) vs. adults (23-36 years old).⁷ The authors found that “the infant pain experience closely resembles that seen in adults.” Babies had 18 out of 20 brain regions respond like adults, also showing much greater sensitivity to pain, responding at a level four times as sensitive as adults.

In 2013 a study used that same fMRI technique to study the brains of healthy human babies still within the womb, from 22-37 weeks post-fertilization (24-39 weeks gestation). They found that functional neuronal connections

¹ Rysavy MA *et al.*, Between-Hospital Variation in Treatment and Outcomes in Extremely Preterm Infants, *N Engl J Med* 372, 1801, May 7, 2015

² See, *e.g.*, Ramirez MV, Anesthesia for fetal surgery, *Colombian Journal of Anesthesiology* 40, 268, 2012; Tran KM, Anesthesia for fetal surgery, *Seminars in Fetal & Neonatal Medicine* 15, 40, 2010; Schwarz U and Galinkin JL, Anesthesia for fetal surgery, *Semin Pediatr Surg* 12, 196, 2003

³ Adzick NS, Prospects for fetal surgery, *Early Human Development* 89, 881, 2013

⁴ Mayorga-Buiza MJ *et al.*, Management of fetal pain during invasive fetal procedures. Lessons learned from a sentinel event, *European Journal of Anaesthesiology* 31, 88, 2014

⁵ Brusseau R and Bulich LA, Anesthesia for fetal intervention, in *Essential Clinical Anesthesia*, Charles Vacanti, Pankaj Sikka, Richard Urman, Mark Dershwitz, B. Scott Segal, Eds., Cambridge University Press, NY; July 2011; 772-776

⁶ Adzick NS *et al.*, A Randomized Trial of Prenatal versus Postnatal Repair of Myelomeningocele, *N Engl J Med* 364, 993, 2011 (from the Informed Consent section of the supplementary Protocol to the paper)

⁷ Goksan S *et al.*, fMRI reveals neural activity overlap between adult and infant pain, *eLife* 4:e06356, 2015

sufficient to experience pain already exist by 22 weeks post-fertilization (24 weeks gestation).⁸

Increased sensitivity to pain. In 2010 one group noted that “the earlier infants are delivered, the stronger their response to pain.”⁹ This increased sensitivity is due to the fact that the neural mechanisms that inhibit pain sensations do not begin to develop until 32-34 weeks post-fertilization (34-36 weeks gestation), and are not complete until a significant time after birth.¹⁰ This means that unborn, as well as newborn and preterm infants, show “hyperresponsiveness” to pain.¹¹

Fetal reactions provide evidence of pain response. The unborn baby reacts to noxious stimuli with avoidance reactions and stress responses. As early as 6 weeks post-fertilization (8 weeks gestation) the baby exhibits reflex movement during invasive procedures.¹² There is extensive evidence of a hormonal stress response by unborn babies as early as 16 weeks post-fertilization (18 weeks gestation)¹³ including “increases in cortisol, beta-endorphin, and decreases in the pulsatility index of the fetal middle cerebral artery.”¹⁴

Two independent studies in 2006 used brain scans of the sensory part of unborn babies’ brains, showing response to pain.¹⁵ They found a “clear cortical response” and concluded there was “the potential for both higher-level pain processing and pain-induced plasticity in the human brain from a very early age.”

Dr. Ruth Grunau, a pediatric psychologist at the University of British Columbia, said, “We would seem to be holding an extraordinary standard if we didn’t infer pain from all those measures.”¹⁶

Embryological development shows presence of pain sensory mechanisms. The basic organization of the human nervous system is established by 4 weeks (28 days) post-fertilization (6 weeks gestation).¹⁷ The earliest neurons in the cortical brain (the part responsible for thinking, memory and other higher functions) are established during the fourth week.¹⁸ Nerve synapses for spinal reflex are in place by 8 weeks post-fertilization (10 weeks gestation).¹⁹ Sensory receptors for pain (nociception) develop first around the mouth at 5 weeks post-fertilization (7 weeks gestation), and are present throughout the skin and mucosal surfaces by 18 weeks post-fertilization (20 weeks gestation).²⁰ Connections between the spinal cord and the thalamus (which functions in pain perception in fetuses as well as adults) are relatively complete by 18 weeks post-fertilization (20 weeks gestation).²¹

⁸ Thomason ME *et al.*, Cross-Hemispheric Functional Connectivity in the Human Fetal Brain, *Sci Transl Med* 5, 173ra24, 2013

⁹ Badr LK *et al.*, Determinants of Premature Infant Pain Responses to Heel Sticks, *Pediatric Nursing* 36, 129, 2010

¹⁰ Brusseau R and Bulich LA, Anesthesia for fetal intervention, in Essential Clinical Anesthesia, Charles Vacanti, Pankaj Sikka, Richard Urman, Mark Dershwitz, B. Scott Segal, Eds., Cambridge University Press, NY; July 2011; 772-776

¹¹ Greco C and Khojasteh S, Pediatric, Infant and Fetal Pain, *Case Studies in Pain Management*, Alan David Kaye and Rinoo V. Shah, Eds., (Cambridge: Cambridge University Press, 2014), 379

¹² Ohashi Y *et al.*, Success rate and challenges of fetal anesthesia for ultrasound guided fetal intervention by maternal opioid and benzodiazepine administration, *J Maternal-Fetal Neonatal Medicine* 26, 158, 2013

¹³ Myers LB *et al.*, Fetal endoscopic surgery: indications and anaesthetic management, *Best Pract Res Clin Anaesthesiol* 18, 231, 2004; Brusseau R and Mizrahi-Arnaud A, Fetal Anesthesia and Pain Management for Intrauterine Therapy, *Clinics in Perinatology* 40, 429, 2013

¹⁴ Lin EE and Tran KM, Anesthesia for fetal surgery, *Seminars in Pediatric Surgery* 22, 50, 2013

¹⁵ Slater R *et al.*, Cortical Pain Response in Human Infants, *J Neuroscience* 25, 3662, 2006; Bartocci M *et al.*, Pain Activates Cortical Areas in the Preterm Newborn Brain, *Pain* 122, 109, 2006

¹⁶ Qiu J, Does it hurt?, *Nature* 444, 143, 2006

¹⁷ Carlson BM, Patten’s Foundations of Embryology, Sixth Edition, McGraw-Hill, Inc., New York; 1996.

¹⁸ Bystron I *et al.*, The first neurons of the human cerebral cortex, *Nature Neuroscience* 9, 880, 2006.

¹⁹ Okado N *et al.*, Synaptogenesis in the cervical cord of the human embryo: Sequence of synapse formation in a spinal reflex pathway, *J. Comparative Neurol.* 184, 491, 1979; Okado N, Onset of synapse formation in the human spinal cord, *J. Comparative Neurol.* 201, 211, 1981

²⁰ Brusseau R, Developmental Perspectives: Is the Fetus Conscious?, *International Anesthesiology Clinics* 46, 11, 2008; Lowery CL *et al.*, Neurodevelopmental Changes of Fetal Pain, *Seminars in Perinatology* 31, 275, 2007

²¹ Van de Velde M and De Buck F, Fetal and Maternal Analgesia/Anesthesia for Fetal Procedures, *Fetal Diagnosis and Therapy* 31, 201, 2012; Van Scheltema PNA *et al.*, Fetal Pain, *Fetal and Maternal Medicine Review* 19, 311, 2008