CHARLOTTE LOZIER INSTITUTE

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To Chairman Derickson, Vice-Chair Ginter and honored members of the Committee on Community and Family Advancement.

Thank you for the opportunity to offer written testimony IN SUPPORT of SB 127, the Pain-Capable Unborn Child Protection Act. My apologies that I am unable to be present for oral testimony.

I want to make sure you understand that there is significant, compelling scientific evidence that an unborn child at 20 weeks post-fertilization can indeed feel pain, and that this evidence comes from numerous reliable sources.

I am a cell and developmental biologist, currently working for the Charlotte Lozier Institute in Washington, D.C. as Vice President and Research Director; I also serve as an adjunct professor at a Washington, D.C. university, and as an Advisory Board Member for the Midwest Stem Cell Therapy Center, a unique comprehensive stem cell center in Kansas. Previously I spent 10 years as Senior Fellow for Life Sciences at another policy think tank in Washington, D.C., and prior to that almost 20 years as Professor of Life Sciences at Indiana State University, and Adjunct Professor of Medical and Molecular Genetics, Indiana University School of Medicine. Before that I was a faculty member in the Department of Obstetrics, Gynecology and Reproductive Sciences, University of Texas Medical School at Houston. I have done federally-funded laboratory research, lectured, and advised on these subjects extensively in the U.S. and internationally. I've taught embryology, developmental biology, molecular biology and biochemistry for over 30 years to medical and nursing students, as well as undergraduate and graduate students. I am testifying in my capacity as a scientist and on behalf of the Charlotte Lozier Institute.

Pain, also termed nociception, is an aversive response to a physically harmful or destructive stimulus. **There is significant evidence from peer-reviewed scientific studies that unborn children as young as 20 weeks after fertilization, and probably younger, can experience pain.** In 1987, Dr. Kanwaljeet Anand published a ground-breaking review of pain studies, in the *New England Journal of Medicine*.[1] Dr. Anand found that the pain receptor nerves are already present throughout the developing human body by 20 weeks gestation (18 weeks post fertilization). He also found that neonates and fetuses could feel pain as early as 20 weeks because the cortex, which begins development at 8 weeks, has a full complement of neurons at 20 weeks. His review included *in utero* studies measuring the brain electrical activity (EEG) of unborn babies.

[1] Anand KJS and Hickey PR, Pain and Its Effects in the Human Neonate and Fetus, *N Engl J Med* 317, 132, 1987

The **basic organization of the human nervous system is established by 4 weeks** (28 days) post-fertilization (6 weeks gestation.)[2] At this stage of development the patterning of the early nervous system is in place, prepared for tremendous growth and increases in complexity that build upon this basic pattern. The earliest neurons in the cortical brain (the part responsible for thinking, memory and other higher functions) are established during the fourth week.[3] The evidence points to the formation of synapses (the communication connections between neurons) in the seventh week, and that the neural connections for the most primitive response to pain, the spinal reflex, are in place by 8 weeks post-fertilization (10 weeks gestation).[4] Furthermore, sensory receptors for pain (nociception) develop first in the perioral area (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.)[5] Thus, there is evidence that the fetus can begin to experience pain as early as this point in development.

The evidence also shows that **significant cortical neuronal connections are in place** by 8-10 weeks post-fertilization,[6] and further that **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-conception (20 weeks gestation)**.[7]

You may hear that that the science of fetal pain is disputed, quoting a *JAMA* review from 2005 that claims pain sensation does not develop until 29-30 weeks gestation, and requires development of a functioning cortex in the brain.[8] That study, while widely quoted, was published by physicians with significant ties to the abortion lobby. That 2005 paper ignored numerous studies showing that the thalamus,[9] not the cortex, is needed for pain sensation. In fact, children born without a cortex are conscious.[10] The 2005 *JAMA* review also didn't address other evidence such as studies demonstrating that premature babies feel pain as early as 20 weeks; its biased conclusions have been discredited.

Significant documentation shows that the fetus reacts to noxious stimuli, with avoidance reactions and stress responses. As early as 6 weeks post-fertilization (8 weeks gestation) the fetus exhibits reflex movement during invasive procedures, resulting from spinal reflex pathways.[11] There is also extensive literature indicating the **hormonal stress response by unborn babies, as early as 16 weeks post-**

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[2] Carlson BM, Patten's Foundations of Embryology, Sixth Edition, McGraw-Hill, Inc., New York; 1996.

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

[4] 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

[5] 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

[6] Vasung L *et al.*, Development of axonal pathways in the human fetal fronto-limbic brain: histochemical characterization and diffusion tensor imaging, *J. Anatomy* 217, 400, 2010

[7] 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; Kostovic I and Goldman-Rakic PS, Transient cholinesterase staining in the mediodorsal nucleus of the thalamus and its connections in the developing human and monkey brain, *J. Comparative Neurol.* 219, 431, 1983

[8] Lee SJ et al., Fetal Pain: A Systematic Multidisciplinary Review of the Evidence, *JAMA* 294, 947, 2005

[9] *E.g.*, Boccard SG *et al.*, Long-term outcomes of deep brain stimulation for neuropathic pain, *Neurosurgery* 72, 221, 2013; Brooks JCW *et al.*, Somatotopic organisation of the human insula to painful heat studied with high resolution functional imaging, *Neuroimage* 27, 201, 2005; Nandi D *et al.*, Thalamic field potentials during deep brain stimulation of periventricular gray in chronic pain, *Pain* 97, 47, 2002

[10] Merker B, Consciousness without a cerebral cortex: A challenge for neuroscience and medicine, *Behavioral and Brain Sciences* 30, 63, 2007

[11] 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

fertilization (18 weeks gestation)[12] including "increases in cortisol, beta-endorphin, and decreases in the pulsatility index of the fetal middle cerebral artery."[13]

Modern imaging techniques and analysis also document the pain experience of unborn and newborn babies. In 2006, two independent studies used brain scans measuring blood flow in the sensory part of the brain to show response to pain.[14] Brain scans were performed to measure their response to painful stimuli in the cortex, the higher portion of the brain which processes pain sensation in adults. They found that there was a "clear cortical response". The authors concluded that "noxious information is transmitted to the preterm infant cortex from 25 weeks, highlighting the potential for both higher-level pain processing and pain-induced plasticity in the human brain from a very early age." Looking at the results of the studies, 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."[15]

A 2008 study validates these earlier studies in terms of how pain is usually measured in contrast to feeling pain.[16] The study's authors found that infants showed cortical responses indicating pain, but often did not show response to pain as measured by typical pain scoring methods used in the clinical setting. This indicates that observers may often not recognize or may underestimate infant pain. The authors went on to note that:

> "While painful stimulation generally evokes parallel cortical and behavioral responses in infants, pain may be processed at the cortical level without producing detectable behavioral changes."

In an interesting application of 4-D ultrasound, a 2013 study used newer scan technology to measure **facial movements in healthy unborn children**, at 22 to 34 weeks post-fertilization (24-36 weeks gestation.) The authors of the study found that unborn children showed distinct and recognizable facial expressions expressing pain or distress, providing a directly measurable tool.[17] Another study done in 2014 found that complicated facial expressions such as yawning, smiling and scowling occurred in unborn children from 18-22 weeks post-fertilization (20-24 weeks gestation), and increased with age of development.[18]

Another study in 2013 validated the earlier studies regarding potential for pain processing in the human fetal brain. Scientists at Wayne State University used **functional magnetic resonance imaging (fMRI) to study the brains of healthy human fetuses within the womb**, from 22-37 weeks post-fertilization (24-39 weeks gestation). They found that functional connections existed as early as 22 weeks post-fertilization (24 weeks gestation), and that the healthy human fetal brain has functional connections

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[12] 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

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

[14] 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

[15] Qiu J, Does it hurt?, Nature 444, 143, 2006

[16] Slater R *et al*., How Well Do Clinical Pain Assessment Tools Reflect Pain in Infants?, *PLOS Medicine* 5, e129, 2008

[17] Reissland N *et al.*, Can Healthy Fetuses Show Facial Expressions of 'Pain' or 'Distress'?, *PLOS One* 8, e65530, 2013

[18] Sato M *et al.*, 4D ultrasound study of fetal facial expressions at 20–24 weeks of gestation, *Int J Gynecol Obstet* 126, 275, 2014

between the brain hemispheres as well as regional connections within brain hemispheres, all sufficient to experience pain.[19]

These areas of the brain were included in measures of **pain response in newborns and adults**, in a new study just published in 2015. An Oxford University team used fMRI to measure pain response in newborns (1-6 days old) versus adults (23-36 years old).[20] The authors noted that: "Brain regions that encode sensory and affective components of pain are active in infants, suggesting that the infant pain experience closely resembles that seen in adults." In fact, 18 out of 20 brain regions in the newborns showed responses similar to the adults. Moreover, the newborns showed greater sensitivity to even a mild pain stimulus, responding at a level that required four times the pain stimulus in adults to achieve the same response.

This **increased sensitivity to pain** has previously been recognized in the literature. For example, Badr *et al.* noted that "the earlier infants are delivered, the stronger their response to pain."[21] The reason for this increased sensitivity is that the **neuronal mechanisms that inhibit or moderate pain sensations do not begin to develop until 32 to 34 weeks post-fertilization** (34-36 weeks gestation), and are not complete until a significant time after birth. The lack of these inhibitory neural pathways prior to term birth means that unborn as well as newborn and preterm infants show a "hyperresponsiveness" to pain, compared to older infants or adults.[22]

These young preterm patients keep getting younger, and surviving more. The concept and timing of viability keeps changing, especially with advances in medicine and recognition of challenges of fetal physiology, including fetal pain. As just one example, **very preterm infants are now surviving**. A study in *JAMA* in 2009 found that "1-year survival of infants born alive at 22 to 26 weeks of gestation in Sweden was 70% and ranged from 9.8% at 22 weeks to 85% at 26 weeks."[23]

Now a groundbreaking *New England Journal of Medicine* study published in May emphasizes that premature babies born earlier and earlier can indeed live. The new study demonstrates that **babies delivered as young as 20 weeks post-fertilization (22 weeks gestation) can survive, and even thrive, and active intervention for treatment greatly improves their survival**.[24] Doctors who consider these preterm babies as patients demonstrate that active treatment significantly benefits these young babies.

The recognition of fetal pain has been key to the development of fetal surgery. Previously it was thought that unborn children, and even newborns, did not experience pain. Substantial evidence, such as that already presented, now shows that assumption is false, and has led to improvements in fetal surgery and fetal anesthesia.[25] Tran states the obvious:

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

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

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

[22] 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

[23] Blennow M et al., One-Year Survival of Extremely Preterm Infants After Active Perinatal Care in Sweden, *JAMA* 301, 2225, 2009

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

[25] Ngamprasertwong P *et al.*, Update in fetal anesthesia for the ex utero intrapartum treatment (EXIT) procedure, Int Anesthesiol Clin. 50, 26, 2012

> "Invasive fetal procedures clearly elicit a stress response…"[26]

Perinatal medicine has advanced rapidly in recent years, **saving ever younger preterm babies and rapidly expanding treatments *in utero***. A leader in this area is the Children's Hospital of Philadelphia (CHOP), which maintains a separate fetal surgery unit that is the most advanced of its kind in the world. The Center for Fetal Diagnosis and Treatment has performed over 1,200 surgeries on babies as young as 16 weeks post-fertilization (18 weeks gestation). Fetal surgery units can now be found in St. Louis, Nashville, Cincinnati, Kansas City, Boston, and several other cities.

The fetal surgeons and their teams at these centers recognize the existence of fetal pain in their young patients, and address this aspect of care. **It is routine procedure to use anesthesia and analgesia for unborn and premature infants undergoing surgery**, including additional doses of anesthetics **administered directly to the unborn baby** to supplement general anesthesia for the mother, and to provide postoperative relief.[27]

Mayorga-Buiza *et al.* state:

> "The administration of anesthesia directly to the fetus is critical in open fetal surgery procedures. Fetal pain response with bradycardia should make us consider that the fetus is not adequately anesthetized."[28]

The **leading textbook on clinical anesthesia** puts it this way:

> "A significant body of evidence, however, has grown to suggest the importance of mitigating the fetal stress response to enhance fetal outcome and possibly limit preterm labor. It is clear that the fetus is capable of mounting a physiochemical stress response to noxious stimuli as early as 18 weeks gestation. Given the state of current knowledge, it is impossible to know exactly when the fetus first becomes capable of experiencing pain, although most agree that the gestational age range in which this occurs is between 20 and 30 weeks. It so happens that this range coincides with the gestational ages during which most fetal interventions occur. **Indeed, the fetal experience of pain may be even greater than that of the term neonate or young child, due to the immaturity of systems of descending inhibition**."[29]

The study guide for the medical boards, noting that it is providing up-to-date, accurate information, echoes the textbook:

> "**The fetus is able to mount a physicochemical stress response to pain starting around 18 weeks of gestation**. It becomes capable of experiencing pain between 20 and 30 weeks of gestation."[30]

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[26] Tran KM, Anesthesia for fetal surgery, *Seminars in Fetal & Neonatal Medicine* 15, 40, 2010

[27] See, e.g., Ramirez MV, Anesthesia for fetal surgery, *Colombian Journal of Anesthesiology* 40, 268, 2012; Schwarz U and Galinkin JL, Anesthesia for fetal surgery, *Semin Pediatr Surg* 12, 196, 2003

[28] 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

[29] 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

[30] Kloesel B and Farber MK, Anesthesia for fetal intervention, in Essential Clinical Anesthesia Review: Keywords, Questions and Answers for the Boards, Linda S. Aglio, Robert W. Lekowski, Richard D. Urman, Eds., Cambridge University Press, NY; March 2015; 399-400

That recognition of the existence of fetal pain and the need for compassion has advanced medical care for mothers and babies alike. **As just one example, here is what is told to the mother before fetal surgery by a group who has done large numbers of such surgeries**:[31]

> "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."** (from the Informed Consent section of the supplementary Protocol to the paper)
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> "The fetus was given an intramuscular injection of fentanyl (20 mcg/kg) and vecuronium (0.2mg/kg)." (from the Supplementary Appendix to the paper)

Fentanyl is an analgesic (a pain medication) stronger than morphine. Vecuronium is a muscle relaxant.

These are indeed young patients needing special care. As clinical anesthetists put it:

> "Anesthesia provision for fetal intervention differs from most other anesthetic situations insofar as the anesthesiologist (or anesthesiologists) must care for two, or possibly more, patients – each with potentially conflicting requirements."[27]

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."[32]

The published scientific evidence documents that the developing human being (the human fetus) can and does experience pain as early as 20 weeks in the womb. This young human being is indeed a patient, deserving of care and compassion.

I urge you to pass SB 127, the Pain-Capable Unborn Child Protection Act.

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[31] Adzick NS et al., A Randomized Trial of Prenatal versus Postnatal Repair of Myelomeningocele, New England J Med 364, 993, 2011

[32] Adzick NS, Prospects for fetal surgery, Early Human Development 89, 881, 2013