



Fetal Pain: What is the Scientific Evidence?

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ABSTRACT

The American College of Pediatricians (ACPedS) maintains that it is unethical to intentionally harm an innocent human being even in the absence of the individual’s ability to perceive pain. However, in this paper, ACPeds reviews the laboratory and clinical evidence which indicates that as early as 12 weeks gestation (and possibly earlier) exposure to noxious stimuli negatively affects immature human beings. Because of the resulting acute stress responses and subsequent potential long-term negative effects, the ACPeds holds that avoiding, mitigating, and directly treating fetal, neonatal, and pediatric pain is a medical and ethical obligation.

Introduction

Many have questioned whether pain exists for neurologically immature human beings. Despite how controversial this question may be when raised in the context of elective abortion, there is significant scientific consensus regarding early fetal neuroanatomy and physiology. How pain is defined, however, does not enjoy a similar consensus. Some argue that for pain to be experienced it requires two components, a sensory *and* an emotional/conscious component.² If this is true, then human beings’ ability to experience pain is limited from conception through the first two years after birth due to neurological immaturity. Others argue against the need for a mature conscious awareness and claim that this same population of children is pain capable. Since the ability of unborn children, infants, and toddlers to communicate the nature of their distress is limited, surrogate markers of pain need to be considered. Such markers are demonstrated in an increasing body of scientific research and include stress and withdrawal responses as well as measurable physiologic changes. Therefore, despite debate over the definition of pain, the medical standard of care currently practiced by pediatricians, neonatologists, and anesthesiologists, is to treat all children, infants, and premature babies (including those still in-utero), as though they are pain capable. While it is clearly unethical to intentionally harm innocent human beings whether or not they cannot perceive pain, that is not this statement’s focus. What this paper provides is a brief overview of the scientific evidence behind this standard of care and argues that the 2-component (sensory and emotional) definition of pain is scientifically and ethically untenable.

The science of infant pain

Four decades ago, the medical consensus was that babies do not feel pain. “Until the late 1980’s surgical procedures with neonates were mostly performed without anesthesia because of safety concerns and because it was assumed the neonate was not neurologically sophisticated enough to experience pain”.³ But in 1987 *The New England Journal of Medicine (NEJM)* published Drs Anand and Hickey’s

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landmark paper showing evidence to the contrary.⁴ The authors stated, the “focus on pain *perception* [emphasis added] in neonates and confusion over its differentiation from nociceptive activity and the accompanying physiologic responses have obscured the mounting evidence that nociception is important in the biology of the neonate.”⁴ In other words, concern over whether pain can be perceived by a person who does not yet have a mature, conscious awareness, has obscured actual evidence that an immature person’s physiology is changed by pain. Dr. Anand’s paper drew upon results from their own work as well as multiple studies in an extensive review of the anatomic requirements for pain perception, the associated neurochemical systems, the physiologic and behavioral changes associated with pain, and the memory of pain in neonates. They concluded, “none of the cited data herein tell us whether neonatal nociceptive activity and associated responses are experienced subjectively...However, the evidence does show that marked nociceptive activity clearly constitutes a physiological and perhaps even a psychological form of stress in premature or full-term neonates.”⁴ Based on published evidence, they recommended re-evaluating the medical standard of care in favor of providing local and general anesthesia during invasive procedures.⁴

Unequivocally corroborating their previous paper’s conclusion, the same group’s 1992 *NEJM* publication was arguably even more demonstrative of the effects of pain on newborns and by today’s standards, ethically troubling. This was a randomized trial comparing the outcomes of 4 to 10 day old neonates with congenital heart defects, who were eligible for surgical repair.⁵ In the operating room, one group received “lighter anesthesia”, the other group “deep anesthesia”. When the babies’ pain was effectively treated their outcomes were considerably improved, including statistically significant differences in intra-operative and post-operative markers of stress (stress hormones, hyperglycemia, lactic acidemia), and fewer postoperative deaths (4 of the 15 neonates died prior to discharge in the light anesthesia group, none of the 30 in the deep anesthesia group died prior to discharge home. This lower rate of mortality “was significantly lower than hospital mortality in other neonates undergoing cardiac surgery with bypass and circulatory arrest during the study period”).⁵ Because of how compelling these results were, this study could not ethically be repeated. Driven by the data, medical practice in neonatology, pediatrics, and anesthesiology changed; today, babies who are term, premature, or operated on in utero, receive appropriate anesthesia.¹

The 1992 cardiac surgery study was done with term infants, but with ongoing research and survival at decreasing gestational ages, by 2016, the American Academy of Pediatrics’ (AAP) revised policy, *Prevention and Management of Procedural Pain in the Neonate: An Update*, specifically states that even premature babies’ pain should be treated, minimized, and/or prevented, “not only because it is ethical but also because repeated painful exposures have the potential for deleterious consequences”.⁶ The consequences of experiencing pain include: “physiologic instability, altered brain development, and abnormal neurodevelopment, somatosensory, and stress response systems, which can persist into childhood.”⁶ Dr. Johnston and Dr. Steven’s study is one example of a study that demonstrates a premature baby’s capacity to acutely react to noxious stimulation and then retain a procedural memory. The authors evaluated the physiologic responses to painful stimuli in two groups of babies at 32 weeks gestation. They compared newborn 32-week babies, and babies born earlier at 28 weeks gestation whose responses were measured four weeks later when they reached 32 weeks gestation.⁷ Measurements included heart rates and oxygen saturation levels before, during, and after a heel stick (commonly used for blood draws in this population), and not only was there an acute response associated with the heel stick in both groups, clear statistical differences between the two groups were also documented. The 4-week-old babies who had experienced this procedure many times previously had even “higher heart rates and lower oxygen saturations than the newborn infants of the same gestational age who had not already had this experience.”⁷ (figures 1 and 2).

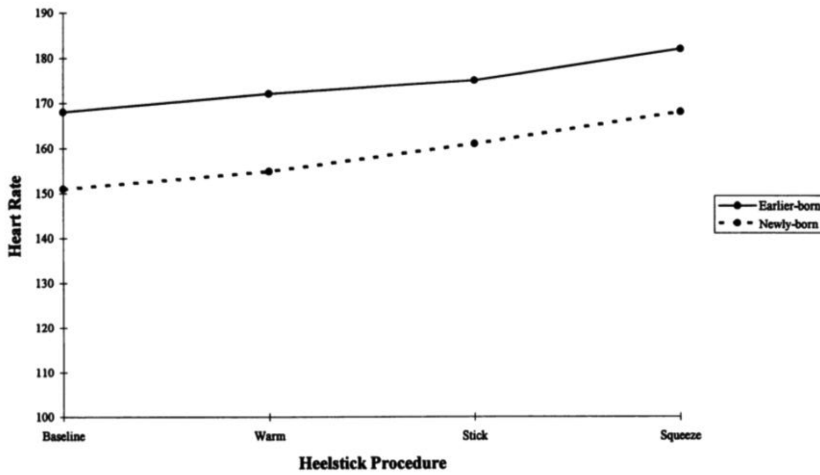


Fig 1. Based on repeated measures analysis of variance, there are differences ($P < .01$) between the two groups and across heel stick procedure.

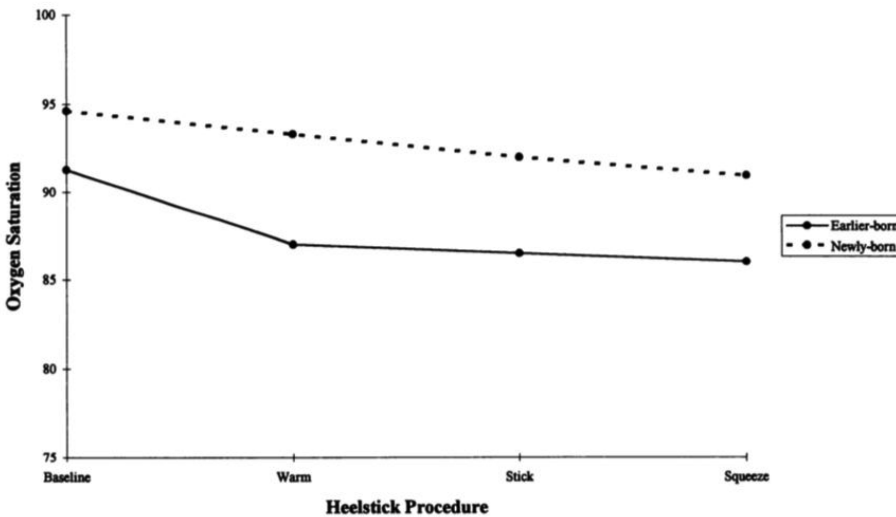


Fig 2. Based on repeated measures analysis of variance, there are differences ($P < .01$) between the two groups and across heel stick procedure.

Premature babies who had already been exposed to painful stimulation showed evidence of being more stressed when the same procedure was repeated than those of the same gestational age who did not have prior experience. The physiologic reactions of premature babies found in this and other studies are why the AAP’s recommendations to avoid, mitigate, or treat procedural pain in premature babies is medically and ethically appropriate.⁶

The AAP’s 2016 recommendations stated that “nociceptive pathways are active and functional as early

as 25 weeks' gestation,"⁶ but premature babies at even younger gestational ages are now routinely cared for in NICUs, and additional data shows that decreasing not only obviously painful procedures but also rethinking how the entire NICU environment affects particularly the youngest and most vulnerable patients, improves their outcomes.⁸⁻⁹ Two examples of practice changes include: (1) increased use of "kangaroo care" where the premature baby is placed in skin-to-skin contact with either the mother's or father's chest, and (2) cue-based care times, by which instead of checking vital signs every three hours, the staff tries not to interrupt valuable sleep and uses, within reason, the babies' cues that they are awake or in need of being tended to. Multiple centers involved in performance improvement projects associated with the Vermont Oxford Network (an international consortium of more than 1300 hospitals working to improve neonatal care),¹⁰ have made these and other changes to intentionally decrease noxious stimuli from a variety of sources. This has led to the creation of "small baby units" within NICUs, and many hospitals have presented their versions of small baby units as part of their performance improvement results at VON's annual national conference, as well as in formal publications.⁹ Again, evidence indicates that our most vulnerable patients are healthier when noxious stimuli is reduced.

Can reactions from premature babies be extrapolated to how they react while in-utero? Because premature babies are now being successfully resuscitated at approximately 22-23 weeks gestation, with a number of cases even a bit lower¹¹ many premature babies cared for in today's NICUs have predominantly *fetal* physiology. "During the fetal period (9th week after conception to birth), differentiation and growth of the organs formed during the embryonic period occur."^{12,13} Despite premature babies' fetal physiology, their daily witnessed reactions to noxious stimulation, as well as the amelioration of these symptoms with treatment, questions persist as to whether "fetal pain perception can be assessed by reference to the prematurely born infant."¹⁴ This concern is supported by studies that demonstrated a group of chemicals within the intrauterine environment called intrauterine endocrine neuroinhibitors (specifically adenosine, pregnanolone and prostaglandin D2) that may anesthetize the infant.¹⁴⁻¹⁵ This concern was cited by the Royal College of Obstetricians and Gynaecologists in 2010 to rule against fetal pain capability, but their primary evidence is an extrapolation of the chemical environment of fetal sheep.¹⁶ A more recent review of neuroinhibitory studies cited three different publications that found the "neural inhibition effects of both adenosine and PGD2 have been recorded only when they are artificially administered in particular into the brain of test animals and the effect was not analgesic but just sedative."¹⁷ Even if neuroinhibitors do contribute to keeping a fetus predominantly asleep, the chemicals' effect is insufficient to keep them asleep when external stimuli are applied.¹⁷ Another publication noted that "although mild noxious stimuli do not seem to be perceived during such fetal sleep, major tissue injury occurring as a result of fetal trauma or fetal surgical intervention generates behavioral and physiologic arousal."¹⁸ Thus, the make-up of the in-utero chemical milieu may participate in providing the ideal place for immature human beings to develop, but this environment is not equipped to blockade the effects of external painful stimuli.

In-vivo human studies done while still in utero provide additional evidence that noxious stimulation is not blocked. Gitau et al studied the responses of human fetuses who required in-utero blood transfusions. The stress hormone levels when their abdomens were accessed to reach the intrahepatic vein (IHV) for their in-utero blood transfusion, were compared to the stress hormone levels of those who received their transfusion through the placental cord insertion site (PCI), a site that is without innervation.¹⁹ Statistically significant increases in stress hormone levels were documented in the group whose intrahepatic vein was accessed through their abdomen, with "fetal B-endorphin responses apparent from 18 weeks gestation and fetal cortisol responses apparent from 20 weeks gestation...consistent with the maturation of the fetal pituitary before the fetal adrenal [gland]".¹⁹ (See figure 3)

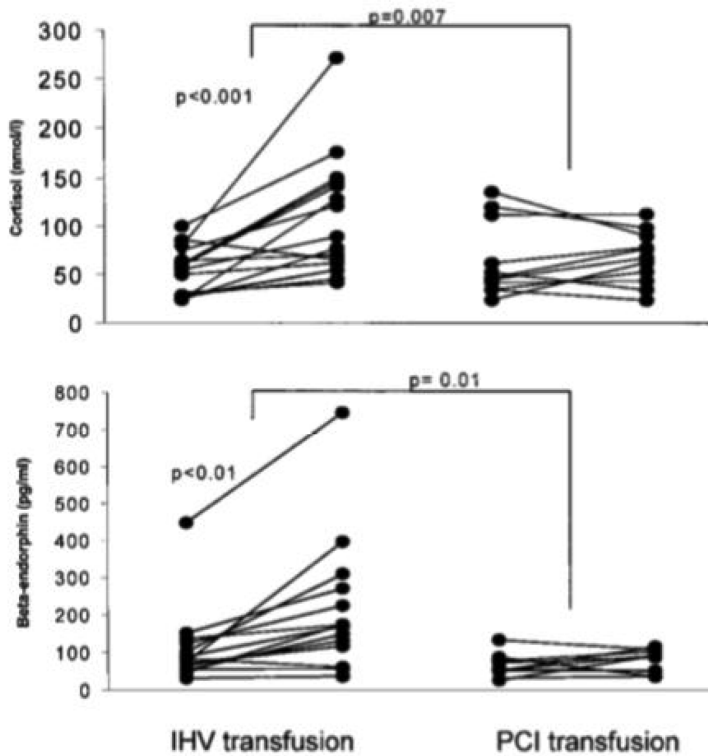


FIG. 3. Fetal plasma cortisol and β -endorphin concentrations before and after transfusion at the IHV and the PCI.

Importantly, this study not only confirmed the findings of an earlier similar study, but by simultaneously measuring the maternal hormone levels (which stayed level between groups) they also showed that the fetal elevations were not due to increased maternal stress hormone levels.¹⁹ Therefore, even while in the normal intrauterine chemical environment, noxious stimulation caused increases in stress hormones, echoing what has been documented in premature and term infants who have already been born. The consistent evidence of stress responses changed pediatricians', neonatologists', and anesthesiologists' medical practice; noxious stimulation is avoided or treated.

Despite the extensive evidence and resulting changes to medical practice, the updated 2020 International Association for the Study of Pain's (IASP) definition of pain continues to exclude immature human beings. The IASP restated that pain must have the 2 components of "an unpleasant sensory and emotional experience associated with, or resembling that associated with, actual or potential tissue damage."² They also specifically clarify, "Pain and nociception are different phenomena. Pain cannot be inferred solely from activity in sensory neurons."² This separation of noxious stimuli induced physical responses from emotional, experiential awareness of pain originated with Merskey, the chair of the IASP Subcommittee on Taxonomy. He believes "pain [is] a psychological concept and not a physical measure and that the experience of pain [has] to be distinguished from noxious stimulation."² His previously published philosophy is that pain is a "psychic event and not a physical event" because "the

physical side is the physiologic mechanism of impulses and signaling—the sense data. The pain is not these sense data but the perceptual experience of discomfort.”²⁰ According to Merskey and the IASP, how pain makes us consciously feel is indicative of whether or not pain exists, anatomical reception via neurologic messaging and resultant physiologic reaction to painful stimulation is irrelevant.

Dismissing neurologic impulses activated by noxious stimuli and their subsequent multi-organ stress responses as immaterial to the presence of pain is problematic for several reasons. For one, as already noted from Johnston & Steven’s data, premature babies who were repeatedly poked for heel sticks at a time when they lacked a mature conscious awareness or ability to verbally recall and complain about previous pokes, had heightened responses to this painful procedure compared to unexposed premature babies.⁷ Yet, “the earlier born infants had higher heart rates and lower oxygen saturations than the newly born infants, before as well as during, the procedure.”⁷ Taddio et al also found that newborns “exposed to repeated heel lances in the first 24 to 36 hours of life learned to anticipate pain and exhibited more intense pain responses during venipuncture than normal infants”²¹ Both of these studies demonstrate what Van de Velde & De Buck called a “procedural memory”.²² From their review of the literature, they concluded that “although early painful memories are not accessible to conscious recall, they may be encoded in ‘procedural memory’ and lead to abnormal behavioral patterns or altered sensory processing in later life.”²²

Interestingly, the hypersensitization of the immature nervous system to noxious stimulation (especially when repetitive), that these authors document, makes physiologic sense given the nervous system’s developmental stage. Fitzgerald, who has multiple published studies on this topic summarizes the developmental complexities stating, “a lack of balance between inhibitory and excitatory supraspinal controls may mean that infants are less able to mount effective endogenous control over noxious inputs than adults”²³. Hatfield further explains that there is also a “receptor field” in the spinal cord of infants that is “larger than adult fields until 42 weeks gestation, [and] then declines to adult size by 43-44 weeks gestation... This accentuates the low pain threshold of preterm infants and is thought to be associated with the increased vulnerability of excitotoxic damage in the newborn brain.”²⁴ Based on the evidence, the AAP’s 2016 update, “*Prevention and Management of Procedural Pain in the Neonate*” also noted this “increased excitability of nociceptive neurons in the dorsal horn of the spinal cord accentuates the infant’s sensitivity to subsequent noxious and non-noxious sensory stimuli.”²⁶ Despite the philosophy of the IASP, immature human beings are not only pain capable, they have an increased sensitivity which makes them more vulnerable to its effects than adults.

In addition to premature infants’ likely heightened pain sensitivity, the IASP’s belief that pain exists only when there is an adult-level of conscious awareness is prima facie problematic. How can conscious awareness be adequately defined? Are we to perform abdominal surgery without anesthesia on patients with Alzheimer’s Disease? When humans are immature and particularly when still in-utero, no one actually knows to what degree human beings are aware. However, as explained by Lowery et al in their neurodevelopmental review article, we do know that the developing neural elements may be immature, but they are not inactive.²⁵ In response to noxious stimulation, this immature but developmentally appropriate and scientifically documented activity is dismissed by IASP because the activity is not equivalent to an adult’s neurologic response. Interestingly, Professors Peter Singer, Adam Shriver, and Nicholas Shea share this philosophy and were the IASP’s ethical consultants. Professor Singer previously published, “the potential of a fetus to become a rational, self-conscious being, cannot count against killing it at a stage when it lacks these characteristics.”²⁶ It is not surprising that “Singer and colleagues proposed” that the IASP definition state “to be in pain is to have a particular conscious experience...”.²² The ability to describe an experience, whether it occurred as an adult or earlier in life when neurologically immature, does not determine whether or not something occurred.

Because no one can prove whether or not the subjective feeling of pain is an integral part of intrauterine life, the use of nociception (which refers to the anatomical and physiological responses to hurtful stimuli), is a better expression.¹³ Nociceptive responses are consequential because they result in measurable, physiologic changes that affect the baby. Therefore, broadening this definition to acknowledge the ultimately damaging effects of noxious stimulation in the gestationally and developmentally immature infant, would provide greater accuracy.

Derbyshire and Bockmann agree, stating that the IASP's definition "restricts pain almost exclusively to fairly mature human beings" and the "evidence...points towards an immediate and unreflective pain experience mediated by the developing function of the nervous system from as early as 12 weeks."³ This particular statement is remarkable for several reasons. For one, the authors admit that their views on abortion ethics are divergent and that "fetal pain has long been a contentious issue, in large part because fetal pain is often cited as a reason to restrict access to termination of pregnancy or abortion."³ In fact Derbyshire, an abortion advocate, previously published that pain perception was dependent upon processing in the cortex cerebri²⁷ and others agreed.²⁸ However, informed by a more recent review of the data, Derbyshire came to a different conclusion. He and co-author Bockman could not support a categorical rejection of fetal pain. They noted that the IASP's definition was appropriate for adult patients presenting with pain, but it does not consider the kind of pain an in utero infant might plausibly experience.³

Previously, 24 weeks gestation was the earliest fetal pain was thought possible due to the timing of connections forming between the thalamus (which receives information from peripheral pain receptors via the spinal cord), and the cerebral cortex. However, there is now evidence that pain does not require the cortex, *subcortical* structures are sufficient.^{3,18,25,29} These subcortical structures include the brain stem, basal ganglia, amygdala, and the hypothalamic-pituitary axis, all of which may be capable of processing pain-instigated impulses from noxious stimuli several weeks prior to the development of thalamic-cortical connections.^{25,29,30} Because subcortical processing of pain occurs without conscious intent, these impulses are, by definition, reflexes. However, not all reflexes are the same. Instigating the patellar reflex can amuse grammar school children, triggering subcortical pain processing by noxious stimulation can affect an immature human's development.²⁹

Relying on connections to the cortex for the existence of pain is also refuted by clinical evidence in adults suggesting that neither ablation nor stimulation of the primary somatosensory cortex alters pain perception.¹⁸ Reliance on the cortex for pain is also disproved by infants who are either missing or have minimal cortex (anencephalic and hydranencephalic babies) who have been exposed to painful and consoling stimuli and then respond appropriately.^{18,30} Taken together, the findings of these studies suggest that definitions of pain which hinge on possessing a mature conscious capacity requiring cortical functioning and connectedness, are outdated.

CONCLUSION

It is unethical to intentionally harm an innocent human being irrespective of the individual's ability to perceive pain. However, a large body of scientific evidence demonstrates that painful or noxious stimulation adversely affects immature human beings, both before and after birth. This paper highlights both where the standard of care for pain management in this population once was, where it is now, and the evidence behind the changes. Natural law ethics are not addressed here, nor are the related political and legal rights of humans before and after birth. This paper specifically presents the scientific data that has resulted in dramatic medical practice improvements in neonatal and pediatric pain management. That medical practice significantly changed despite these ongoing political, legal, and ethical disputes

only illustrates the strength of this data is. Regarding specifically pain capability during intrauterine life, Derbyshire and Bockman note, “Whether there was ever consensus... it is now clear that the consensus is no longer tenable.”³ The IASP’s definition of pain is too narrow specifically because even without conscious awareness, “especially in fetuses, noxious stimuli may have adverse effects on the developing individual regardless of the quality of the level of processing in the brain.”²⁹ The likelihood of noxious stimulation-induced changes in developing human beings cannot be ethically ignored. In Anand’s 1987 landmark publication, the authors acknowledged the difference between “nociceptive activity” and pain’s “strong emotional associations” but also immediately noted that belaboring this point had already “obscured the mounting evidence that nociception is important in the biology of the neonate”.⁴ Informed by the evidence, ACPeds advocates the need for in-utero, neonatal, and pediatric pain prevention, mitigation, and treatment. Medicine’s double standard of acknowledging pain capability in wanted premature babies while denying it in unwanted unborn babies of the same gestational age is unconscionable.

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The American College of Pediatricians is a national medical association of licensed physicians and healthcare professionals who specialize in the care of infants, children, and adolescents. The mission of ACPeds is to enable all children to reach their optimal, physical and emotional health and well-being.

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