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Fetal Pain Facts and the Informed Consent Conundrum

Pregnant women, medical professionals, and society are concerned about fetal pain. The topic is complex, and communication of accurate information requires a working knowledge of current fetal pain research. This research can broadly be categorized as follows: 1) The fetus responds to skin-breaking procedures with significant changes in behavior, facial expressions, stress hormones, and metabolism from the earliest stages studied; 2) Anatomic and behavioral evidence suggests that the fetus is capable of pain awareness by 15-20 weeks gestation and possibly by 12 weeks; 3) The brain does not need to be fully developed to experience pain. Different standards of care exist in fetal surgery, neonatology, and obstetrics regarding pain management in age-matched populations. Fetal surgeons and anesthesiologists administer direct fetal anesthesia during fetal surgery, as early as 15-16 weeks gestation. Neonatologists in the neonatal intensive care unit (NICU) provide pain management to the earliest premature infants at approximately 22 weeks gestation, and the embryology of fetal neuroanatomy demonstrates that cortical circuitry begins with thalamic connections to the cortical subplate at 12-15 weeks gestation. Despite medical practice and known fetal physiology, most obstetric associations state that during an induced abortion, the fetus is unconscious and cannot feel pain until after 24-28 weeks or later. This overlaps a substantial number of neonates in the NICU and fetal surgical patients. The 2024 Society of Family Planning (SFP) and the Society for Maternal-Fetal Medicine (SMFM) update states that there is no pain capability "until at least 29-32 weeks."[1] The value-based divergence in medical recommendations for anesthetic and analgesic medical care between those who perform induced abortion and those who provide medical care for fetuses and premature neonates present a medical and ethical dilemma. This document reviews the research that informs fetal pain management and the basis for informed consent.

Background

Introduction

Pregnant women, medical professionals, and society care about fetal pain.[2-5] A working knowledge of fetal pain research is essential for the provision of excellent medical care and informed consent. However, based on varying evaluations of data leading to contradictory conclusions, differing standards of care in fetal surgery, neonatology, and obstetrics regarding the

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provision of pain management in age-matched populations now exist.

Specifically, the American Society of Anesthesiologists, the North American Fetal Therapy Network, and numerous fetal surgery experts recommend fetal anesthesia in all invasive fetal procedures, regardless of gestational age.[6-8] This is because noxious stimulation, defined as damaging or threatening to damage normal tissues,[9] during fetal procedures at 16-20 weeks (the earliest ages studied) elicits significant neuroendocrine and hemodynamic responses.[10-12] Additionally, injecting preoperative intramuscular anesthetic into the fetal thigh provokes acute pain-related fetal facial expressions. These expressions are visible on 4-dimensional (4D) fetal ultrasounds,[13] including a 23-week gestation fetus, the youngest studied.[14] In 2024, blinded reviewers characterized fetal responses to acute pain using a scale previously validated for neonates called the Fetal-7 scale. This is based on sonographic visualization of fetal facial expressions in response to stimuli. To differentiate an acute pain response from a startle, the different fetal responses to pain (anesthetic injection), to acoustic stimulation (startle), and at rest were compared. This study demonstrated the ability of fetuses at 26 to 28 weeks to differentiate painful stimulation from a startle response and from rest, and in 2024, this fetal pain scale was validated.[7] This pain scale "opens the possibility of… identification and treatment [of fetal] pain."[7]

Similarly, neonatologists use pain management strategies in their patient population, which includes the youngest neonates of approximately 22 weeks gestation.[15] This management has become the neonatal standard of care as neonatal pain is associated with "adverse neurodevelopmental, behavioral, and cognitive outcomes"[16] and with documented improvements when pain is mitigated or treated.[15] Pain management strategies for neonates at decreasing gestational ages highlights the neonatal standard of care outlined by the American Academy of Pediatrics in 2016, which is to avoid, mitigate, or directly treat pain in the earliest premature babies.[16]

Simultaneously, obstetrics associations including the Royal College of Obstetricians and Gynecologists (RCOG), the Society for Maternal-Fetal Medicine (SMFM), and the American College of Obstetricians and Gynecologists (ACOG) state that due to an immature cortex, the fetus is unconscious and cannot feel pain during an induced abortion until after 24-28 weeks or later.[17-19] It is during this range of gestational ages that thalamocortical connections to the cortical plate develop, making high-level cortical processing possible. These organizations hold that specifically "high-level cortical processing" is necessary for fetal pain perception.[18] Thus, these obstetric groups view fetal and neonatal responses to noxious stimuli prior to 24-28 weeks or later, including acute pain-related facial expressions, as unconscious, reflexive, subcortical reactions, not indicative of pain

or suffering.[18] Thus, informed by a variety of research, a discrepancy in pain management prior to thalamocortical connections at 24-28 weeks has developed. This discrepancy has significant ramifications not only for the preborn and premature population's medical care, but also for obtaining accurate informed maternal consent. To resolve this ethical and medical conundrum, reexamination of the research informing medical practice is necessary.

Fetal Pain: Where We Were

Until the 1980s, physicians claimed that full-term neonates, as well as premature infants, could not feel pain, due to an immature cortex.[20-22] This viewpoint changed when egregious cases of anesthetic neglect were published in the U.S. and the U.K., causing public outcry.[23-26] In 1985, at approximately 25 weeks gestation, Jeffrey Lawson underwent surgery (ligation of his patent ductus arteriosus) without anesthesia. His mother's account of his procedure, the aftermath, and her baby's demise (see footnote 1), as well as another mother's story (see footnote 2), publicized the lack of neonatal pain management strategies.[27] Yet it was not until the 1990s, after additional research was compiled,[20] including a randomized trial comparing neonates undergoing cardiac surgery with and without sufficient anesthesia,[28] that practice changes were initiated. Neonatal pain management was "born out of a marriage of science and public concern."[26] Graphic parental descriptions served to heighten awareness,[23-26] while the measurable responses and outcomes from surgical interventions made neonatal pain a practical and ethical consideration.[20,28]

During the 1990s, fetuses of all gestations were considered incapable of pain. Invasive fetal procedures were conducted without

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[1] **Letter from Jeffrey's mother, published in the medical journal *Birth*, 1986:**

"Jeffrey was born at 25-26 weeks gestation… had holes cut on both sides of his neck, another cut in his right chest, an incision from his breastbone around to his backbone, his ribs pried apart, and an extra artery near his heart tied off. This was topped off with another hole cut in his left side. The operation lasted hours. Jeffrey was awake through it all. The anesthesiologist paralyzed him with Pavulon, a drug that left him unable to move, but totally conscious. When I questioned the anesthesiologist later she said Jeffrey was too sick to tolerate powerful anesthetics. Anyway, she said, it had never been demonstrated to her that premature babies feel pain.[25]

Postoperatively, Jeffrey developed shock and multi-organ failure prior to his death in March 1985.[26]

[2] **Letter from Edward's mother, published in the medical journal *Birth*, 1986:**

"[O]ur prematurely born son, Edward [28 weeks gestation], was shunted for hydrocephalus while paralyzed with curare. Although he could not move, cry, or react in any way, he could see, hear, and feel as large incisions were cut in his scalp, neck, and abdomen; as a hole was drilled in his skull; as a tube was inserted into the center of his brain, then pushed down under the skin of his neck, chest, and abdomen and implanted deep in his abdominal cavity… To this day, our severely retarded son will allow no one to touch his head, neck, or abdomen. Even heavily tranquilized, he reacts to the simplest medical procedures or the mere sight of the hospital with violent trembling, profuse sweating, screaming, struggling, and vomiting… Another [NICU] parent noted the similarity between the aversive behavior of some NICU babies and the psychologic problems of adult torture victims."[24,27]

anesthesia, until studies demonstrated measurable fetal hemodynamic and hormonal stress responses[11,12,29,30] that were mitigated by anesthesia (discussed in more detail below).[31] Today, these ethically troubling studies could not be repeated,[32] and the need for direct fetal anesthesia during therapeutic fetal surgery is no longer disputed.[7,8]

Fetal Pain: Where We Are

Since the 1990s, advances in fetal surgery, anesthesiology, neonatology, and prenatal fetal imaging have expanded the understanding of pain perception at earlier gestational ages. The following section summarizes fetal pain research findings that inform these medical fields (see Table 1). Ethical considerations in this population continue to be important factors that affect what research is possible and how it is obtained.

1. The fetus responds to skin-breaking procedures with dramatic changes in behavior, stress hormones, and hemodynamics from the earliest ages studied.[6]

Table 1 summarizes the published research on fetal responses to noxious stimuli, which are the same pain responses that are seen in infants, older children, and adults.[33-41] These responses include: pain-related facial expressions,[14] vigorous body and breathing movements by 18 weeks,[12,30] brisk withdrawal by 15 weeks,[35] hemodynamic changes by 16 weeks,[11] and sharp increases in neuroendocrine stress hormones by 18 weeks.[36] These reactions are also seen in newborns experiencing acute pain.[7,20,28,30,42] When anesthesia is given, fetal responses are alleviated.[31]

The first published research revealing fetal reactions to noxious stimuli occurred in the 1990s. Studies demonstrated significant neuroendocrine and hemodynamic responses following unanesthetized puncture of the fetal trunk during blood transfusions.[11,12,29,30] Early fetal surgical research by Gitau et al. confirmed that the fetal neuroendocrine stress response to noxious stimuli is independent from maternal stress hormone levels.[36] Studies in the early 2000s provided the first published data of direct fetal analgesia administered during invasive fetal procedures. Use of anesthesia in the fetal population substantially increased after Fisk et al. found that direct fetal analgesia blunts the hormonal and hemodynamic stress responses to puncture and needling of the fetal trunk.[31] Such studies can no longer ethically be conducted; however, a case report in 2017 described fetal surgery in a 24-week fetus (open myelomeningocele repair) in which fetal anesthesia was inadvertently omitted.[41] Fetal bradycardia, a known reliable indicator of fetal distress,[10] ensued, resolving only after direct fetal anesthesia was administered.[41] Thus, published studies demonstrate that the fetus responds to noxious stimulation with acute physiologic responses that are mitigated by anesthesia.

Table 1: Direct studies of fetal responses to noxious stimuli			
Source	**# in test group & GA**	**Noxious stimulus[a]**	**Fetal response**
Giannakoulopoulos et al. (1994)[30]	N = 16 23-29 weeks GA	Needling of IHV via puncture of fetal trunk	- Significant increase in β-endorphin 590% and cortisol 183% at IHV - Vigorous body and breathing movements
Petrikovsky and Kaplan (1995)[35]	N = 7 15-18 weeks GA (Case series)	Inadvertent contact of amniocentesis needle with fetal limb	- Brisk withdrawal of the involved part (except in one fetus with limb paralysis)
Teixeira et al. (1996)[29]	N = 28 18-36 weeks GA (Pilot study)	Needling of IHV via puncture of fetal trunk	- Significant decrease in MCA PI in response to transgression of fetal trunk, consistent with redistribution of blood supply to the brain (brain-sparing effect)
Giannakoulopoulos et al. (1999)[12]	N = 42 18-37 weeks GA	Needling of IHV via puncture of fetal trunk	- Significant elevation in fetal noradrenaline with needling involving transgression of fetal trunk - Dislodgement of needle in two cases of IHV needling due to vigorous fetal movements
Teixeira et al. (1999)[11]	N = 130 (136 procedures) 15-37 weeks GA	Needling procedures involving puncture of fetal trunk[b]	- Significant decrease in MCA PI within 70 seconds after painful stimulation, consistent with redistribution of blood supply to the brain (brain-sparing effect) from 16 weeks GA
Fisk et al. (2001)[31]	N = 16 20-35 weeks GA	IHV transfusion via puncture of fetal trunk, with or without fentanyl	- Direct fetal analgesia blunts the hormonal and hemodynamic stress response to intrahepatic vein needling (β-endorphin and MBA PI responses, respectively)
Gitau et al. (2001)[36]	N = 51 18-35 weeks GA	Fetal blood sampling and intrauterine transfusion at IHV via puncture of fetal trunk; compared to maternal blood samples	- Significant increase in fetal β-endorphin and cortisol with transfusions at IHV (innervated) compared to PCI (non-innervated) - Fetal responses are independent of maternal responses. - Fetal β-endorphin and cortisol responses are apparent from 18 and 20 weeks GA respectively
Gitau et al. (2004)[37]	N = 32 17-38 weeks GA	IHV blood sampling or transfusion via puncture of fetal trunk compared to PCI (control)	- Increase in fetal cortisol with IHV transfusion compared to PCI - Increase in fetal corticotrophin with IHV needling compared to PCI
van Scheltema et al. (2009)[38]	N = 25 23-36 weeks GA	IHV transfusion via puncture of fetal trunk compared to PCI (control)	- Significant decrease in fetal MCA PI with transfusions at both IHV (innervated) and PCI (non-innervated) - No difference in decrease between the two groups[c]

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Table 1 (cont.): Direct studies of fetal responses to noxious stimuli			
Source	**# in test group & GA**	**Noxious stimulus[a]**	**Fetal response**
van Scheltema et al. (2011)[39]	N = 11 20-35 weeks GA (11 fetuses; 12 IHV transfusions)	IHV transfusion via puncture of fetal trunk after IHV administration of paralytic agent compared to PCI transfusion (control)	- Significant decrease in fetal noradrenaline and MCA PI with both IHV and PCI transfusions - No significant change in fetal cortisol pre- and post-IHV or PCI transfusions - No measurable difference in decrease between the two groups[c]
Kosinksa-Kaczynska et al. (2012)[40]	N = 6 (6 fetuses; 29 IHV transfusions) 20-33 weeks GA	Two punctures of fetal trunk per IHV transfusion: 1) for fetal intraperitoneal administration of paralytic agent; 2) for IHV transfusions; compared to PCI transfusion (control)	- Approximately 4-fold increase in fetal ACTH post-IHV transfusion (innervated tissue) compared to PCI transfusion (non-innervated tissue) - Significant increase in fetal cortisol post-IHV transfusion compared to PCI
Mayorga-Buiza et al. (2017)[41]	N = 1 24 weeks GA (Case study)	Open fetal surgery for myelomeningocele repair, inadvertently initiated without administration of fetal anesthesia	- Fetal bradycardia - Fetal recovery after epinephrine and administration of fetal anesthesia
Bernardes et al. (2018)[45]	N = 1 32 weeks GA (Case report)	Preoperative anesthetic intramuscular injection (fetal thigh)	- 10 facial actions coded by blinded investigators, before and after anesthetic puncture - Pre-puncture score 0/10; post-puncture score, 8-10/10
Bernardes et al. (2021)[13]	N = 13 28-33 weeks GA	Preoperative anesthetic intramuscular injection (fetal thigh) compared to nonpainful startle and rest (control)	- Fetuses demonstrate discriminative facial expressions in response to painful stimuli. - Presence of five out of seven pain-related facial expressions discriminated pain from nonpainful startle and rest
Bernardes et al. (2022)[14]	N = 1 23 weeks GA	Preoperative anesthetic intramuscular injection (fetal thigh)	- Facial expressions of acute pain following intramuscular injection - Rated 5 out of 7 on fetal pain score by blinded investigators
Bernardes et al. (2024)[7]	Step 1: N = 2 (test group); 26.2-28.8 weeks GA Step 2: N = 2 (test group); 28.1 weeks GA (Validation study)	Preoperative anesthetic intramuscular injection (fetal thigh)	- Complex facial expressions of acute pain in fetuses following preoperative intramuscular injection were accurately differentiated from healthy fetuses at rest (sensitivity 100%, specificity 94.4%) using a 7-point fetal pain scoring system by blinded investigators. - All facial expressions of acute pain validated for neonates could be identified in fetuses undergoing injection. - Cut-off score ≥5 differentiated acute pain from control groups (rest, acoustic stimuli) - First validated fetal pain scoring system (Fetal-7 scale) for third-trimester fetuses

Table 1 (cont.): Direct studies of fetal responses to noxious stimuli

GA, gestational age; IHV, intrahepatic vein (innervated); PCI, placental cord-insertion (non-innervated); MCA PI, middle cerebral artery pulsatility index; wk, weeks.

[a]Fetuses were exposed to noxious stimuli during clinically indicated procedures.

[b]Needling procedures involving transgression of fetal trunk: shunt insertion, tissue biopsy, ovarian cyst aspiration, urine aspiration, drainage of ascites, and fetal blood sampling and intrauterine transfusion via intrahepatic vein.

[c]van Scheltema et al. noted that greater severity of fetal anemia, higher baseline concentrations of stress hormones, and possible dilutional effects from higher volume blood transfusions in their studies may have been confounding factors.[38,39]

Table 1 adapted from Bellieni and Anand[33] and Thill.[34]

However, fetal pain perception continues to be disputed by ACOG, RCOG, and SMFM.[17-19] All three obstetric organizations endorse each other's fetal pain position statements, which propose four main points: (i) fetal pain perception requires "high-level cortical processing" and is therefore not possible until after 24-28 weeks gestation or later;[18] (ii) fetal behavioral, hormonal, and physiologic responses to noxious stimuli are stereotyped, brainstem reflexes without high-level cortical input and "do not reflect any experiences of pain or suffering;"[18] (iii) the fetus cannot discriminate painful from non-painful stimulation until after 33 weeks gestation;[17] (iv) extrapolation of extrauterine neonatal facial pain scales to the intrauterine environment is not appropriate as such fetal pain scales have not been validated.[18]

The first two points (i) and (ii) are addressed in sections 2 and 3 below. The third point (iii), the ability to discriminate between painful and non-painful stimulation, is controversial. A 2019 study by Green et al. concluded that preterm neonates, assessed with a 3-point neonatal facial pain scale (modified from the validated 7-point Premature Infant Pain Profile-Revised, PIPP-R), cannot reliably discriminate painful from non-painful stimulation until after 33 weeks gestation.[43] Notably, the validated PIPP-R scale uses seven parameters in their neonatal pain scale (including physiologic, behavioral, contextual parameters, and variables known to modify pain responses in premature infants).[16] Green et al. scored only three facial expressions from the PIPP-R scale, which is not a validated scoring tool.[43] Yet, RCOG cites the Green study to deny the existence of fetal discrimination between noxious and non-noxious stimulation prior to 33 weeks gestation.[17] Subsequent neonatal studies by Van der Vaart et al.[44] and fetal studies by Bernardes et al.[7,13,14] demonstrated that the use of multidimensional pain assessment tools, cut-off values, and more than three parameters, can reliably show fetal discrimination between noxious and non-noxious stimulation in the earliest ages studied (23-28 weeks gestation).

The fourth point (iv) refers to the extrapolation of neonatal pain scales to the fetus. SMFM argues that neonatal pain scales may not meaningfully apply to fetal facial expressions because these pain scales have not been validated for such use.[18]

However, with the assistance of 4D ultrasound, Bernardes et al. subsequently published data on neonatal facial pain scales with cut-off values to analyze fetal facial expressions immediately after preoperative intramuscular anesthetic injections.[7,13,14,45] In 2024, this led to the development of the first validated fetal pain scale (Fetal-7) comprised of 7 indicators: 1) "brow lowering," 2) "eyes squeezed shut," 3) "deepening of the nasolabial furrow," 4) "open lips," 5) "horizontal mouth stretch," 6) "vertical mouth stretch," 7) "neck deflection."[7] Thirty blinded reviewers independently appreciated multiple, measurable, acute pain-related behaviors in fetuses at 26 to 28 weeks gestation (earliest ages studied), compared to controls. The authors noted that while facial expressions of pain, such as facial grimacing, may be observed spontaneously in the fetus at rest,[7,46] the Fetal-7 cut-off value of ≥5/7 different facial movements reliably discriminated between fetuses at the youngest ages in this trial (>26 weeks) experiencing noxious stimuli and controls (sensitivity 100%; specificity 94.4%).[7]

The pain responses of extremely premature neonates can be accurately compared to fetal responses. We know this because premature infants at the edge of extrauterine viability have predominantly fetal physiology, and with insufficient or absent pain management, they have worse outcomes.[16] The fetal period of development starts at the beginning of the 9th week of gestation and extends until term.[47] Thus, the neonatologist's goal is to assist the successful transition of premature babies from fetal physiology needed during the intrauterine period to physiology compatible with extrauterine life. Though some organ systems, such as the skin, will mature more quickly in the extrauterine environment, the fetal developmental period is not avoided or ended by a premature birth. In the developing neurologic system, there is no on-off switch that confers pain capability.[48] During the fetal developmental period, the immature nervous system can be likened to a dimmer switch with a progressive ability to sense, localize, and effectively respond to pain. This uniquely human organ system continues to mature well into early adulthood. Meanwhile, in the NICU, daily eyewitness encounters with premature neonates who have predominantly fetal physiology provide a window into gestationally age-matched intrauterine fetal neurologic responses.

Neonatologists unanimously acknowledge their patients' need for pain management. Newer neonatal research includes direct pain treatment as just one of the multimodal components involved in improving neurodevelopmental outcomes.[49] This ongoing research is being led by the Vermont Oxford Network (an international consortium of 1,400 hospitals dedicated to data-driven improvements in neonatal care). Such research highlights that while debate continues regarding exactly how early in gestation pain perception occurs, (and studies indicate an unreflective pain experience may occur as young as 12 weeks gestation),[50] treating pain in neonates with

predominantly fetal physiology is the uncontroversial neonatal medical standard. This medical standard is practiced at gestational ages when RCOG, ACOG, and SMFM state no pain capacity exists.

2. Anatomic and behavioral evidence suggests the fetus is capable of pain awareness.

Numerous areas of the brain are implicated in consciousness and pain perception.[51] By 12-15 weeks, pain transmission pathways develop that are capable of sending pain signals from the skin to multiple areas of the brain, including thalamus and cortical subplate.[2,50,52,53] By 14 weeks, the fetus demonstrates purposeful behavior, action planning, and social awareness in twin studies.[54,55] By 16 weeks, the fetus hears and responds to music with movements of the mouth and tongue.[56]

Because the fetus and neonate respond to painful stimuli prior to thalamocortical connections, researchers have suggested that a neural network involving the cortical subplate and/or subcortical structures is sufficient to facilitate pain perception prior to 24 weeks gestation.[50] The cortical subplate, a unique and transient structure present only in the fetus and neonate, is the thickest and most voluminous cortical layer in the midfetal period (17-25 weeks gestation),[52,57] and forms the predominant cortical circuitry during the first to third trimesters, prior to high-level cortical connections.[58-60] The subplate first exhibits synaptic activity between 9-10 weeks gestation,[61] receiving projections from the thalamus at 12 weeks.[50] In animal studies, subplate neurons are the first cortical neurons to respond to sensory stimuli.[57,62] There is evidence that these thalamic projections to the subplate at 12 weeks are functionally equivalent to later-developing high-level thalamocortical connections which in the post-term period, will form the permanent cortical circuitry.[50] By 24-28 weeks gestation, the developing cortical plate receives a dual circuitry of thalamic afferents extending from the subplate as well as directly from the thalamus. During the third trimester, the cortical circuitry of the subplate coexists with the newer circuitry of the cortical plate. Subplate neurons then migrate to the cortical plate, as the subplate regresses, becoming a remnant by 3 months post-term.[58]

Obstetric medical groups acknowledge that there is no specific pain center in the brain.[1,18] Despite this, newer obstetric publications continue to maintain that high-level processing in the cortex is necessary for pain perception.[18] In their updated 2024 statement, the Society of Family Planning and SMFM state that there is no pain capability "until at least 29-32 weeks"[1] in defense of inducing fetal asystole before abortions at "periviable gestations and after fetal viability."[1] Such policies are ethically untenable. They also demonstrate how an overreliance on neuroanatomical hypotheses, rather than correlation with clinical behavior, context, and other markers of pain perception, is dangerous.[34]

High-level cortical connections in children and adults are not mandatory for pain capacity or consciousness. Neonates at <24-28 weeks demonstrate pain responses via validated pain indicators. Two additional groups provide evidence contradicting the need for high-level cortical connections. First, neurologically injured adults with extensive damage to or absence of cortical structures, including the insula and operculum, continue to experience and express pain to noxious stimuli.[51,63,64] In one particular instance, "[a]gainst expectations, the patient's expression and experience of pain was found to be intact across multiple pain measures including self-report, facial expression, vocalization, withdrawal reaction, and autonomic response."[64] Consistent with adults that maintain consciousness and pain capacity despite widespread cortical damage, babies and children with hydranencephaly whose cerebral cortex is either absent or malformed, also demonstrate responsiveness and expressive behavior.[65,66] Their "responses to noxious stimulation… are purposeful, coordinated, and similar to those of intact children."[67]

3. The brain does not need to be fully developed to experience pain.

Research has demonstrated that pain perception and consciousness exist even when the cortex is absent, damaged, or immature.[51,64,65,68] The brain has redundant pain pathways,[51,69] and neural networks vary by age. The fetal brain, in particular, has thalamic connections to the cortical subplate that do not exist in older children or adults.[70,71]

The International Association for the Study of Pain (IASP) defines pain as an unpleasant sensory and emotional experience caused by tissue damage.[72] The updated 2020 IASP definition acknowledges that verbal report is just one indicator of pain.[72] Because pain can be sensed long before it can be named, indirect markers of pain, such as behavioral, neuroendocrine, and physiologic responses, form the basis of pain assessment in nonverbal populations such as the fetus, infant, and the neurologically impaired.[16]

Nociception is defined by the IASP as "the neural process of encoding noxious stimuli."[9] Although nociceptive neural activity usually results in pain perception, pain cannot be inferred solely from activity in sensory neurons.[9] For example, when general anesthesia is administered or nerve transection occurs, nociceptors appropriately detect and transmit noxious stimuli, but pain perception is prevented. Thus, detecting pain in nonverbal populations does not rely on activity in sensory pathways but instead on observable, measurable behavioral and physiologic changes.[16,73] These changes are not simple reflex arcs causing a stereotyped muscular response. Instead, as occurs in a fetal response to noxious stimulation, it involves transmission of a neural impulse via the spinal cord to multiple areas of the brain, eliciting behavioral changes such as acute pain-related facial expressions, and causing changes in physiologic, hormonal, and

hemodynamic parameters (Table 1). These responses are more coordinated and complicated than tapping the knee to induce the patellar reflex. Data indicates that these behavioral, hormonal, and physiologic parameters in the context of noxious stimuli are indicative of fetal pain experience.

Ironically, due to their immature nervous system, evidence suggests that fetuses and preterm infants likely experience more pain than adults, not less.[74] This is due to underdeveloped pain inhibition mechanisms, lower pain thresholds, and larger receptive fields.[75] This greater susceptibility to pain likely contributes to under-recognition and undertreatment of pain in the fetus and extremely premature neonate.[33] These documented effects occur at gestational ages where obstetric medical groups state pain perception is not possible.

Discussion

The fetal developmental period is defined not only by cellular growth but also by organ systems changing shape, position, and 3-dimensional configuration. Despite its immaturity, the fetal nervous system is sufficiently functional that noxious stimuli transmit to the brain, resulting in the generation of a pain response. This capacity to be affected by pain is consistent with fetal neuroanatomy showing thalamic connections to the cortical subplate beginning at 12-15 weeks gestation, witnessed during fetal surgery and in extremely premature neonates, and confirmed by measurable, statistically significant findings, resulting in data-driven medical practice.

Data demonstrates that prevention and treatment of fetal pain is medically and ethically indicated. Every major medical organization recognizes that prevention and treatment of pain is a human right,[76,77] yet not all extend this right to the human fetus. Conveying the facts about fetal pain is important not only for treating the preborn and premature, but also for pregnant women and society. Accurate facts are integral to obtaining informed consent, and these facts impact women's decisions regarding abortion.[50] Research indicates that fetal pain perception is likely by 15-20 weeks gestation[75,78] and possible as early as 12 weeks.[50] Informed by the data, fetal pain is treated during fetal surgery as early as 15 weeks,[79,80] and in neonates at 22-23 weeks or earlier. Simultaneously, a number of obstetric groups state that due to an immature cortex, fetal pain is impossible during an induced abortion until 24-28 weeks or later.[17-19]

It appears that abortion ideology may be preventing the use of unbiased data that informs medical practice and informed consent. The differing standards of medical care between those who perform induced abortions and those who provide medical care to fetuses and neonates present a medical and ethical conundrum. Even if a pregnancy is unplanned or there is a suspected life-limiting anomaly, there is never a reason to intentionally inflict pain. Given the already proven data

demonstrating early pain capacity, and continuing advances in neonatology and fetal surgery, we suggest that all branches of medicine acknowledge fetal pain's likely existence. Although it may be difficult to definitely prove the presence of fetal pain in earlier gestations, the burden of proof should be placed on those performing the potentially painful procedures, not on the fetuses experiencing them.

Clinical Questions and Answers

Q *Is high-level cortical processing necessary for the fetus or neonate to experience pain?*

No. Functional thalamocortical connections to the cortical plate and somatosensory cortex have long been proposed as a requirement for conscious pain perception after 24-28 weeks.[81] But much has changed in fetal surgical and neonatal interventions, as well as advances in high-resolution prenatal ultrasound. These clinical advances, combined with neonatal and fetal research, support pain awareness prior to high-level cortical connections. Research documents measurable and observable pain responses in fetuses and neonates prior to 24 weeks gestation, while published reports of pain perception and awareness even when the cortex is absent, damaged, or immature likewise highlight this discrepancy.

Q *Are fetal behavioral, hormonal, and physiologic responses to noxious stimuli reflexive or are they indicative of pain and suffering?*

While pain is a subjective experience, behavioral and physiologic pain parameters are universally accepted and validated as pain indicators in nonverbal populations, including neonates.[16] These indirect markers of pain perception have also guided efforts to understand pain perception during the fetal period. The neonate and fetus both respond to skin-breaking procedures with measurable and significant changes in behavior, stress hormones, and metabolism from the earliest ages studied. The same markers of pain that are seen in extremely premature neonates are also seen in the fetus (Table 1). Researchers have noted that fetal neuroendocrine, hemodynamic, and behavioral responses to noxious stimuli are the same responses as those observed in infants who are experiencing acute pain. These changes are not simple reflex arcs causing a stereotyped muscular response. Instead, these changes require transmission of a neural impulse via the spinal cord to multiple areas of the brain, triggering pain responses such as acute pain-related facial expressions, and changes in physiologic, hormonal, and hemodynamic parameters (Table 1).

Q *When can the fetus or preterm neonate discriminate between touch and pain?*

Studies as early as 15-16 weeks gestation support the fetus experiencing pain (Table 1). Fetuses undergoing noxious procedures at earlier gestations have not

been studied, but have formed neural pathways for pain perception as early as 12 weeks gestation.[50] Neonatal studies by Van der Vaart et al.[44] and fetal studies by Bernardes et al.[7,13,14] noted that the use of multidimensional pain assessment tools with cut-off values and more than three parameters reliably discriminated between responses to noxious and non-noxious stimulation at the earliest ages studied (23-28 weeks gestation).

Q *Can pain responses in the extremely premature neonate be extrapolated to the intrauterine fetus?*

Yes. Premature infants at the edge of extrauterine viability have predominantly fetal physiology. The fetal developmental period is not avoided or ended by a premature birth. Likewise, functional thalamocortical connections do not develop in the fetus or in the preterm neonate until after 24-28 weeks, yet pain management in neonatology and fetal surgery is guided by measurable, observable pain responses that are mitigated by anesthesia.

Q *Does the in utero environment protect the fetus from feeling pain?*

No. It was hypothesized by Mellor et al. in 2005 that the fetus is continually unconscious and incapable of pain perception until birth due to the presence of endocrine neuroinhibitors in utero.[82] Subsequent publications disproved this hypothesis, noting that: 1) the concentration of intrauterine neuroinhibitors is insufficient to cause an anesthetic effect; and 2) the human fetus is arousable and responsive to external stimuli.[70] In its updated 2022 statement, RCOG removed its previous support of a supposed analgesic effect induced by intrauterine neuroinhibitors.[17]

Q *Have fetal pain scales been validated?*

Yes. In 2024, the Fetal-7 became the first validated pain assessment tool for assessing fetal pain after 26 weeks, the earliest gestation in this trial.[7]

Conclusion

Extensive scientific and clinical data support the recognition and treatment of pain in the fetus. During surgery for infants, older children, and adults, anesthesia is required to guarantee the least possible pain. A fetus who can perceive pain during fetal surgery has the capacity to feel pain during an induced abortion. Consistent recognition of fetal pain capacity offers the clearest picture of these facts.

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