Fetal Pain
A Systematic Multidisciplinary Review of the Evidence

Susan J. Lee, JD

Henry J. Peter Ralston, MD

Eleanor A. Drey, MD, EdM

John Colin Partridge, MD, MPH

Mark A. Rosen, MD

OVER THE LAST SEVERAL years, many states, including California, Kentucky, Minnesota, Montana, New York, Oregon, and Virginia, have considered legislation requiring physicians to inform women seeking abortions that the fetus feels pain and to offer fetal anesthesia. This year, Arkansas and Georgia enacted such statutes.[1,2] Currently, Congress is considering legislation requiring physicians to inform women seeking abortions 20 or more weeks after fertilization (ie, 22 weeks' gestational age) that the fetus has "physical structures necessary to experience pain," as evidenced by "draw[ing] away from surgical instruments." The physician must also offer anesthesia or analgesia "administered directly" to the fetus. Physicians who do not comply may be subject to substantial fines, license revocation, and civil suits for punitive damages.[3]

Although this legislation would not affect most US abortions because only 1.4% are performed at or after 21 weeks' gestational age,[4] this legislation raises important scientific, clinical, ethical, and policy issues. When does a fetus have the functional capacity to feel pain? If that capacity exists, what forms of anesthesia or analgesia are safe and effective for treating fetal pain? As a first

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Context Proposed federal legislation would require physicians to inform women seeking abortions at 20 or more weeks after fertilization that the fetus feels pain and to offer anesthesia administered directly to the fetus. This article examines whether a fetus feels pain and if so, whether safe and effective techniques exist for providing direct fetal anesthesia or analgesia in the context of therapeutic procedures or abortion.

Evidence Acquisition Systematic search of PubMed for English-language articles focusing on human studies related to fetal pain, anesthesia, and analgesia. Included articles studied fetuses of less than 30 weeks' gestational age or specifically addressed fetal pain perception or nociception. Articles were reviewed for additional references. The search was performed without date limitations and was current as of June 6, 2005.

Evidence Synthesis Pain perception requires conscious recognition or awareness of a noxious stimulus. Neither withdrawal reflexes nor hormonal stress responses to invasive procedures prove the existence of fetal pain, because they can be elicited by nonpainful stimuli and occur without conscious cortical processing. Fetal awareness of noxious stimuli requires functional thalamocortical connections. Thalamocortical fibers begin appearing between 23 to 30 weeks' gestational age, while electroencephalography suggests the capacity for functional pain perception in preterm neonates probably does not exist before 29 or 30 weeks. For fetal surgery, women may receive general anesthesia and/or analgesics intended for placental transfer, and parenteral opioids may be administered to the fetus under direct or sonographic visualization. In these circumstances, administration of anesthesia and analgesia serves purposes unrelated to reduction of fetal pain, including inhibition of fetal movement, prevention of fetal hormonal stress responses, and induction of uterine atony.

Conclusions Evidence regarding the capacity for fetal pain is limited but indicates that fetal perception of pain is unlikely before the third trimester. Little or no evidence addresses the effectiveness of direct fetal anesthetic or analgesic techniques. Similarly, limited or no data exist on the safety of such techniques for pregnant women in the context of abortion. Anesthetic techniques currently used during fetal surgery are not directly applicable to abortion procedures.

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step in answering these questions, we reviewed the literature on fetal pain and fetal anesthesia and analgesia.

EVIDENCE ACQUISITION

English-language articles involving human participants were searched using PubMed for (1) *fetal pain* (16 articles), *fetal anesthesia* (6 articles), and *fetal analgesia* (3 articles); (2) *fetus* and (*anesthesia or analgesia*) (1239 articles); (3) Medical Subject Headings (MeSH) an-

Author Affiliations: School of Medicine (Ms Lee), Department of Anatomy and W. M. Keck Foundation for Integrative Neuroscience (Dr Ralston), and Departments of Obstetrics, Gynecology and Reproductive Sciences (Drs Drey and Rosen), Pediatrics (Dr Partridge), and Anesthesia and Perioperative Care (Dr Rosen), University of California, San Francisco.
Corresponding Author: Mark A. Rosen, MD, Department of Anesthesia and Perioperative Care, University of California, San Francisco, 513 Parnassus Ave, San Francisco, CA 94143-0648 (rosenm@anesthesia.ucsf.edu).
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Figure. Spinal Reflex and Pain Perception Pathways
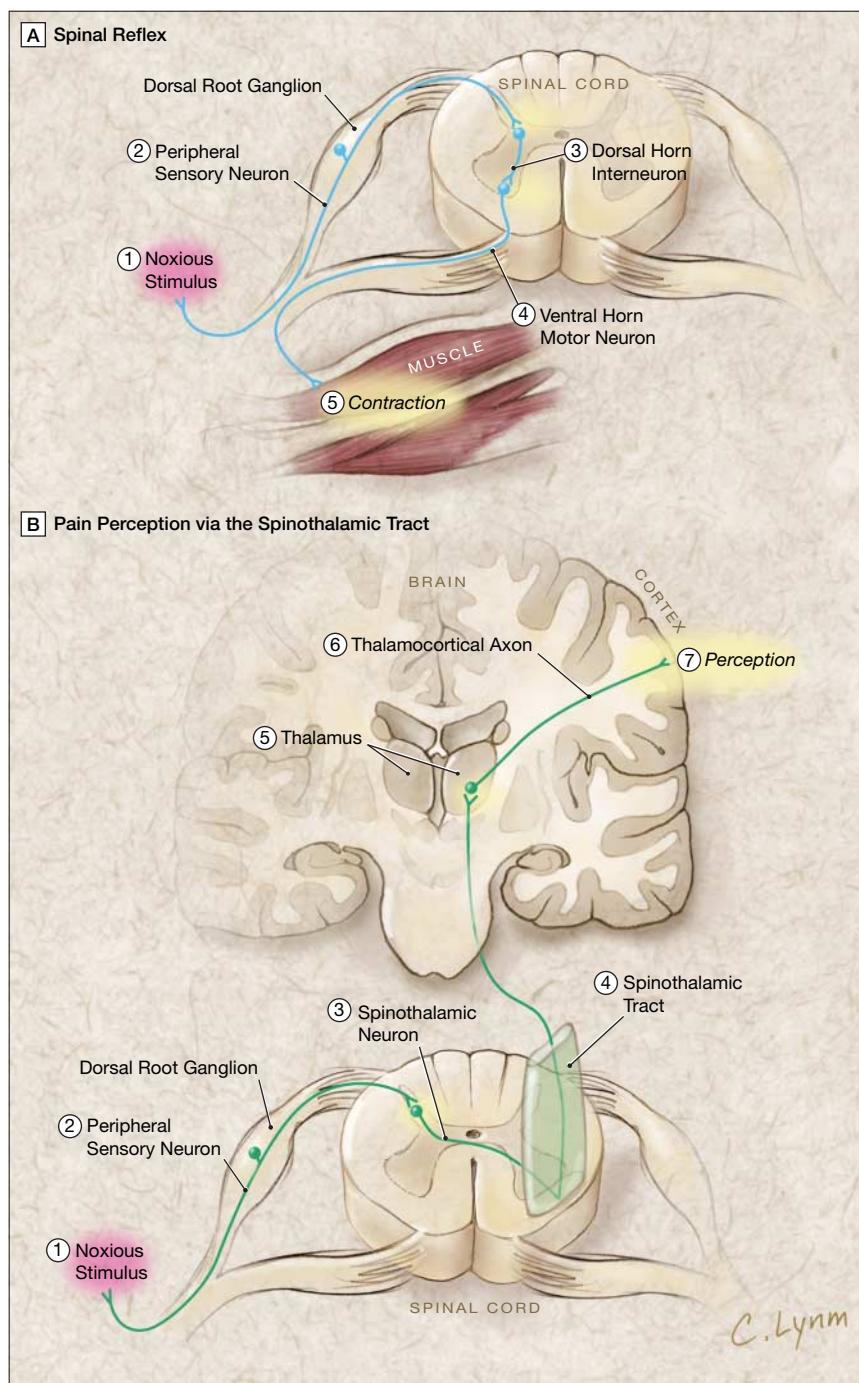
A, Reflex responses to noxious stimuli occur early in development, before thalamocortical circuits are functional; noxious stimuli trigger reflex movement without cortical involvement. Activated by a noxious stimulus (1), a peripheral sensory neuron (2) synapses on a dorsal horn interneuron (3) that in turn synapses on a ventral horn motor neuron (4), leading to reflex muscle contraction and limb withdrawal (5). B, Later in development, noxious stimuli (1) activate peripheral sensory neurons (2) that synapse on spinothalamic tract neurons (3), the axons of which extend up the spinal cord as the spinothalamic tract (4) to synapse on neurons of the thalamus (5). From here, thalamocortical axons synapse on cortical neurons, resulting in the conscious perception of pain.

algesics/administration and dosage and *fetus* (44 articles); (4) MeSH *anesthesia/ administration and dosage* and *fetus* (0 articles); (5) (*neurodevelopment or development or anatomy*) and (*fetus or fetal*) and (*pain or nociception or noxious*) (306 articles); (6) (*thalamocortical or thalamus or cortex*) and (*fetus or fetal*) and (*pain or nociception or noxious*) (13 articles); (7) (*electroencephalog* or EEG or evoked potential*) and (*fetus or fetal or premature neonate or premature infant or preterm neonate or preterm infant*) and (*pain or nociception or noxious or conscious**) (7 articles); (8) *fetal* and *pain* and (*response or assessment or facial expression*) (112 articles); and (9) *facial expression* and (*fetus or fetal*) or ([*neonate or neonatal or infant*] and [*premature or preterm*]) and (*pain or nociception or noxious*) (360 articles). The search was performed without date limitations and was current as of June 6, 2005. From these search results, we excluded articles that did not study fetuses of less than 30 weeks' gestational age or that did not specifically address fetal pain perception or nociception. With a focus on topics addressed by earlier review articles on fetal pain, anesthesia, and analgesia, articles were reviewed for additional references.

EVIDENCE SYNTHESIS
What Is Pain?

Pain is a subjective sensory and emotional experience that requires the presence of consciousness to permit recognition of a stimulus as unpleasant.[5-7] Although pain is commonly associated with physical noxious stimuli, such as when one suffers a wound, pain is fundamentally a psychological construct that may exist even in the absence of physical stimuli, as seen in phantom limb pain.[5,7] The psychological nature of pain also distinguishes it from nociception, which involves physical activation of nociceptive pathways without the subjective emotional experience of pain.[5,8] For example, nociception without pain exists below the level of a spinal cord lesion, where reflex withdrawal from a noxious stimulus occurs without conscious perception of pain (**FIGURE**, A).[5]

Table. Anatomical and Functional Development of Nociception and Pain Perception Pathways

Anatomical/Functional Characteristic	Description	Gestational Age, wk	Source
Peripheral cutaneous sensory receptors	Perioral cutaneous sensory receptors	7.5	Humphrey,[13] 1964
	Palmar cutaneous sensory receptors	10-10.5	
	Abdominal cutaneous sensory receptors	15	
Spinal cord	Spinal reflex arc in response to nonnoxious stimuli	8	Okado and Kojima,[14] 1984
	Neurons for nociception in dorsal root ganglion	19	Konstantinidou et al,[15] 1995
Thalamic afferents	Thalamic afferents reach subplate zone	20-22	Kostovic and Rakic,[16] 1990 Hevner,[17] 2000
	Thalamic afferents reach cortical plate	23-24	Kostovic and Rakic,[18] 1984 Kostovic and Goldman-Rakic,[19] 1983
Cortical function*	Somatosensory evoked potentials with distinct, constant components	29	Klimach and Cooke,[20] 1988 Hrbek et al,[21] 1973
	First electrocardiographic pattern denoting both wakefulness and active sleep	30	Clancy et al,[22] 2003 Torres and Anderson,[23] 1985

*Earliest evidence of functional thalamocortical connections required for conscious perception of pain.

Because pain is a psychological construct with emotional content, the experience of pain is modulated by changing emotional input and may need to be learned through life experience.[7,9,10] Regardless of whether the emotional content of pain is acquired, the psychological nature of pain presupposes the presence of functional thalamocortical circuitry required for conscious perception, as discussed below.

Fetal Capacity for Pain

Neuroanatomy and Development. Nociception may be characterized by reflex movement in response to a noxious stimulus, without cortical involvement or conscious pain perception. Nociception involves peripheral sensory receptors whose afferent fibers synapse in the spinal cord on interneurons, which synapse on motor neurons that also reside in the spinal cord. These motor neurons trigger muscle contraction, causing limb flexion away from a stimulus (Figure, A).[11]

In contrast, pain perception requires cortical recognition of the stimulus as unpleasant. Peripheral sensory receptor afferents synapse on spinal cord neurons, the axons of which project to the thalamus, which sends afferents to the cerebral cortex (Figure, B),[11] activating any number of cortical regions.[12] Sensory receptors and spinal cord synapses required for nociception develop earlier than the thalamocortical pathways required for conscious perception of pain (**TABLE**).

No human studies have directly examined the development of thalamocortical circuits associated with pain perception. The developmental age at which thalamic pain fibers reach the cortex has been inferred from studies of other thalamocortical circuits, which may or may not develop at the same time as thalamic fibers mediating cortical perception of pain.

These histological neurodevelopment studies typically describe fetal maturity in terms of developmental age, representing the number of weeks postovulation or postfertilization. Clinicians regularly use gestational age, representing weeks from the first day of the woman's last menstrual period. When referring to a fetus at the same point in development, the gestational age is approximately 2 weeks greater than the developmental age.

A histological study of the visual pathway in 8 human fetuses, each at a different developmental age, concluded that thalamic projections reach the visual cortex at 21 to 25 weeks' developmental age (approximately 23-27 weeks' gestational age), based on results from a fetus of 24 weeks' developmental age (26 weeks' gestational age).[18] A similar 7-fetus study found thalamic afferents reached the auditory cortical plate at 24 to 26 weeks' developmental age, with 1 specimen showing initial cortical plate penetration at 22 weeks' developmental age (24 weeks' gestational age).[24]

In a study of 8 human fetuses, mediodorsal thalamic afferents were first observed in the cortical plate at 22 weeks' developmental age (24 weeks' gestational age).[19] While connections between mediodorsal afferents and the anterior cingulate cortex[25] may be relevant to pain perception,[12,26] this study examined mediodorsal afferents to unspecified regions of the frontal cortex,[19] which serves numerous functions unrelated to pain perception.[19,27]

Another histological study of 12 specimens found that afferents from unspecified thalamic regions reached the developing prefrontal cortex in 1 preterm neonate of 27 weeks' developmental age, concluding that thalamic fibers begin entering the cortex between 26 and 28 weeks' developmental age (28 and 30 weeks' gestational age).[28] A different study found that thalamic afferents had not reached the somatosensory cortical plate by 22 weeks' developmental age (24 weeks' gestational age). By 24 weeks' developmental age (26 weeks' gestational age), the density of cortical plate synapses increased, although these were not necessarily from thalamic afferents.[16] Based on these studies, direct thalamocortical fibers that are not specific for pain begin to emerge between 21 and 28 weeks' developmental age (23 and 30 weeks' gestational age).

However, others have proposed that thalamocortical connections could also be established indirectly if thalamic afferents were to synapse on subplate neurons, which could synapse on cortical plate neurons.[29] The subplate is a transient fetal structure 1 layer deep to the cortical plate and serves as a "waiting compartment" for various afferents, including thalamic afferents, en route to the cortical plate.[16,29,30] The subplate recedes after 30 weeks' developmental age,[16,29] while the cortical plate matures into the 6 layers of the cerebral cortex.[28] In contrast to direct thalamocortical fibers, which are not visible until almost the third trimester, thalamic afferents begin to reach the somatosensory subplate at 18 weeks' developmental age (20 weeks' gestational age)[16] and the visual subplate at 20 to 22 weeks' gestational age.[17] These afferents appear morphologically mature enough to synapse with subplate neurons,[31] although no human study has shown that functional synapses exist between thalamic afferents and subplate neurons. Subplate neurons may synapse with cortical plate neurons and direct the growth of thalamic afferents to their final synaptic targets in the cortical plate.[29] Despite this developmental role, no human study has shown that synapses between subplate and cortical plate neurons convey information about pain perception from the thalamus to the developing cortex.

Electroencephalography. The histological presence of thalamocortical fibers is insufficient to establish capacity for pain perception. These anatomical structures must also be functional. Although no electroencephalographic "pain pattern" exists, electroencephalography may be one way of assessing general cortical function because electroencephalograms (EEGs) measure summated synaptic potentials from cortical neurons. However, EEG activity alone does not prove functionality, because neonates with anencephaly who lack functional neural tissue above the brainstem may still have EEG activity.[32]

Normal EEG patterns have been characterized for neonates as young as 24 weeks' postconceptional age (PCA) (ie, the gestational age plus number of weeks postpartum).[22] Electroencephalographic activity is normally asynchronous between the hemispheres and mostly discontinuous at less than 27 weeks' PCA,[23,33,34] becoming mostly continuous around 34 weeks' PCA.[23,34] Interhemispheric synchrony increases around 29 to 30 weeks' PCA, then declines, then increases again, reaching almost complete synchrony by term.[22,33] Given these baseline differences between neonatal and adult EEGs, patterns associated with impaired consciousness in adults[33,35] are inapplicable to the analysis of neonatal EEGs.

Some investigators contend that EEG patterns denoting wakefulness indicate when consciousness is first possible.[5,36] Wakefulness is a state of arousal mediated by the brainstem and thalamus in communication with the cortex.[5,22] In preterm neonates, the earliest EEG pattern representing wakefulness appears around 30 weeks' PCA.[22,23] However, wakefulness alone is insufficient to establish consciousness, as unconscious patients in a persistent vegetative state may also have wakeful EEGs.[5,36]

Somatosensory evoked potentials (SEPs) may also provide evidence of pain processing in the somatosensory cortex, although they are not used clinically to test pain pathways. SEPs test the dorsal column tract of the spinal cord, which transmits visceral pain sensation to the somatosensory cortex via the thalamus.[12] SEPs with distinct and constant N1 components of normal peak latency are present at 29 weeks' PCA, indicating that thalamic connections with the somatosensory cortex are functional at that time.[20,21]

Behavioral Studies. Although widely used to assess pain in neonates, withdrawal reflexes and facial movements do not necessarily represent conscious perception of pain. Full-term neonates exhibit a "cutaneous withdrawal reflex" that is activated at a threshold much lower than that which would produce discomfort in a child or adult.[37] This threshold increases with 24 weeks' postconceptional age (PCA) PCA, suggesting that the capacity of the neonate to distinguish between noxious and nonnoxious stimuli is maturing.[37] Furthermore, flexion withdrawal from tactile stimuli is a noncortical spinal reflex exhibited by infants with anencephaly[38] and by individuals in a persistent vegetative state[39] who lack cortical function.

Behavioral studies have also identified a distinct set of neonatal facial movements present during invasive procedures such as heel lancing but absent during noninvasive procedures.[40-46] These facial movements, which are similar to those of adults experiencing pain,[47,48] were evident in neonates at 28 to 30 weeks' PCA but not at 25 to 27 weeks' PCA.[40] Facial movements may not necessarily be cortically controlled.[49] One study found no difference in facial activity during heel lancing of neonates with and without significant cortical injury, suggesting that facial activity even around 32 weeks' PCA may not represent conscious perception of pain.[50]

Stress Responses. Hemodynamic and neuroendocrine changes in fetuses undergoing stressful procedures have also been used to infer pain perception.[51] As early as 16 weeks' gestational age, fetal cerebral blood flow increases during venipuncture and transfusions that access the fetal hepatic vein through the innervated fetal abdominal wall but not during venipuncture and transfusions involving the noninnervated umbilical cord.[52] Increased cerebral blood flow is not necessarily indicative of pain, as this response is thought to constitute a "brain sparing" mechanism associated with hypoxia[53] and intrauterine growth restriction.[54]

Other investigators measured increases in fetal plasma concentrations of cortisol, β-endorphin, and noradrenaline associated with intrauterine needling procedures, finding that increases during blood sampling from the hepatic vein were greater than those during sampling from the umbilical cord.[55,56] However, these neuroendocrine responses do not constitute evidence of fetal pain,

because the autonomic nervous system and hypothalamic-pituitary-adrenal axis mediate them without conscious cortical processing.[57] Additionally, these responses are not specific for painful stimuli. Plasma noradrenaline concentrations may increase after umbilical cord transfusion,[56] and plasma β-endorphin concentrations may increase after repeated cordocenteses.[58] Plasma cortisol and β-endorphin concentrations increase during innocuous activities such as exercise.[59] Moreover, in adults, neuroendocrine stress responses may persist despite well-controlled postoperative pain.[60]

Vital signs also have been used to assess neonatal pain.[42,43,45,51,61] However, heart rate, respiratory rate, and transcutaneous oxygen and carbon dioxide levels do not necessarily differ significantly between alcohol-swabbing and lancing the heels of preterm neonates.[40] Another group found that a similar proportion of neonates became hypoxic during tracheal suction, as well as during nonnoxious routine care such as washing and weighing.[62]

Fetal Anesthesia and Analgesia

Anesthetics and analgesics are commonly used to alleviate pain and discomfort. Despite ongoing debate regarding fetal capacity for pain, fetal anesthesia and analgesia are still warranted for surgical procedures undertaken to promote fetal health. When long-term fetal well-being is a central consideration, evidence of fetal pain is unnecessary to justify fetal anesthesia and analgesia because they serve other purposes unrelated to pain reduction, including (1) inhibiting fetal movement during a procedure[63-65]; (2) achieving uterine atony to improve surgical access to the fetus and to prevent contractions and placental separation[66-70]; (3) preventing hormonal stress responses associated with poor surgical outcomes in neonates[71,72]; and (4) preventing possible adverse effects on long-term neurodevelopment and behavioral responses to pain.[73-75]

These objectives are not applicable to abortions. Instead, beneficence toward the fetus represents the chief justification for using fetal anesthesia or analgesia during abortion—to relieve suffering if fetal pain exists. As with any clinical decision, thorough safety and risk-benefit analyses should be undertaken before performing an intervention. Because the principle of beneficence also requires the woman's physician to act in her best interests, potential fetal benefit must be weighed against real risks to the woman's health. The safety and effectiveness of proposed fetal anesthesia and analgesia techniques are discussed below.

General Anesthesia for Fetal Surgery. Fetal surgery involving laparotomy, hysterotomy, or both requires general or regional anesthesia.[68,76] Regional anesthesia, such as epidural anesthesia, does not anesthetize the fetus.[76] General anesthesia is more commonly used because it induces uterine atony and fetal immobilization.[65,77] Studies of inhalational agents in pregnant ewes determined that a dose capable of anesthetizing the ewe also anesthetized the fetus.[78] Administering fentanyl, pancuronium, or vecuronium to the fetus intramuscularly may supplement analgesia or immobilization.[64,65,77,79]

For pregnant women, general anesthesia is associated with increased morbidity and mortality, particularly because of airway-related complications[80-82] and increased risk of hemorrhage from uterine atony.[70] Historically, general anesthesia was used in abortions, even in the first trimester, until studies found that general anesthesia was a leading cause of abortion-related mortality.[83-85] In addition to safety concerns, general anesthesia increases the cost of abortion, making it prohibitively expensive for the majority of patients who pay out of pocket.[86]

Anesthesia and Analgesia in Minimally Invasive Fetal Procedures. In contrast to fetal surgery requiring regional or general anesthesia, minimally invasive fetal procedures do not involve maternal laparotomy or hysterotomy and instead use needles or endoscopy to access the fetus. For the sake of reducing pain, the increased risks of general anesthesia are unjustified for these procedures; adults typically undergo similar procedures with no analgesia or only local analgesia.[67] No established fetal analgesia protocol exists for these procedures, although 3 techniques have been proposed, namely, direct delivery of medications to the fetus, delivery of medications to the fetus via maternal intravenous infusion, and intra-amniotic delivery of medications.

Direct Delivery. One group has examined the effects of analgesics delivered directly to human fetuses during minimally invasive procedures.[87] Twenty-eight fetuses that received intravenous fentanyl before hepatic vein blood transfusions had diminished changes in plasma β-endorphin concentration and cerebral blood flow, compared with fetuses not receiving fentanyl. The cortisol response was not significantly decreased with fentanyl. The investigators did not examine risks for the woman, such as infection or uncontrolled bleeding.[76] Furthermore, reducing the stress response is distinct from reducing pain. For example, plasma glucose and cortisol concentrations may not differ significantly between adults with and without postoperative pain.[60]

Delivery via Maternal Intravenous Infusion. To achieve presumably effective fetal plasma concentrations of fentanyl by placental transfer, potentially unsafe doses would need to be administered to the woman.[88] Although standard doses of fentanyl are generally safe for maternal analgesia during labor,[89] fentanyl can pose serious risks such as hypoventilation if maternal doses are significantly increased to achieve more extensive placental transfer.[67,68] Severe maternal hypoventilation may require endotracheal intubation, which increases risks and costs for the woman, as described above.

No data exist on the dosing or efficacy of using medications such as diazepam and morphine for fetal analgesia via maternal intravenous infusion, although studies have characterized the placental transfer of these medications.[90-92] Two related studies found that

low-dose remifentanil via maternal intravenous infusion achieved fetal immobilization during laser coagulation of placental vessels.[93,94] However, immobilization is not the equivalent of pain reduction, and these procedures did not involve surgery on the fetus.

Intra-amniotic Delivery. Intra-amniotic injection would be technically simpler than direct fetal injection, although the drug must be absorbed through fetal membranes and skin. Intra-amniotic sufentanil injection in 10 pregnant ewes resulted in fetal plasma concentrations that would control postoperative pain in human adults.[95,96] Sufentanil concentrations in the ewes also reached adult human therapeutic concentrations without causing significant hemodynamic changes.[96] However, the study did not evaluate fetal response to noxious stimuli, and no data exist regarding safety or effectiveness in humans.

CONCLUSIONS

Pain is an emotional and psychological experience that requires conscious recognition of a noxious stimulus. Consequently, the capacity for conscious perception of pain can arise only after thalamocortical pathways begin to function, which may occur in the third trimester around 29 to 30 weeks' gestational age, based on the limited data available. Small-scale histological studies of human fetuses have found that thalamocortical fibers begin to form between 23 and 30 weeks' gestational age, but these studies did not specifically examine thalamocortical pathways active in pain perception.

While the presence of thalamocortical fibers is necessary for pain perception, their mere presence is insufficient—this pathway must also be functional. It has been proposed that transient, functional thalamocortical circuits may form via subplate neurons around midgestation, but no human study has demonstrated this early functionality. Instead, constant SEPs appear at 29 weeks' PCA, and EEG patterns denoting wakefulness appear around 30 weeks' PCA. Both of these tests of cortical function suggest that conscious perception of pain does not begin before the third trimester. Cutaneous withdrawal reflexes and hormonal stress responses present earlier in development are not explicit or sufficient evidence of pain perception because they are not specific to noxious stimuli and are not cortically mediated.

A variety of anesthetic and analgesic techniques have been used for fetal surgery, including maternal general anesthesia, regional anesthesia, and administration of medications for placental transfer to the fetus. However, these techniques are not necessarily applicable to abortions. Surgical procedures undertaken for fetal benefit use anesthesia to achieve objectives unrelated to pain control, such as uterine relaxation, fetal immobilization, and possible prevention of neuroendocrine stress responses associated with poor surgical outcomes. Thus, fetal anesthesia may be medically indicated for fetal surgery regardless of whether fetal pain exists.

In the context of abortion, fetal analgesia would be used solely for beneficence toward the fetus, assuming fetal pain exists. This interest must be considered in concert with maternal safety and fetal effectiveness of any proposed anesthetic or analgesic technique. For instance, general anesthesia increases abortion morbidity and mortality for women and substantially increases the cost of abortion. Although placental transfer of many opioids and sedative-hypnotics has been determined, the maternal dose required for fetal analgesia is unknown, as is the safety for women at such doses. Furthermore, no established protocols exist for administering anesthesia or analgesia directly to the fetus for minimally invasive fetal procedures or abortions. Experimental techniques, such as administration of fentanyl directly to the fetus and intra-amniotic injection of sufentanil in pregnant ewes, have not been shown to decrease fetal pain and are of unknown safety in humans.

Because pain perception probably does not function before the third trimester, discussions of fetal pain for abortions performed before the end of the second trimester should be noncompulsory. Fetal anesthesia or analgesia should not be recommended or routinely offered for abortion because current experimental techniques provide unknown fetal benefit and may increase risks for the woman. Instead, further research should focus on when pain-related thalamocortical pathways become functional in humans. If the fetus can feel pain, additional research may lead to effective fetal anesthesia or analgesia techniques that are also safe for women.

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The polymorphic visions of the eyes and the spirit are contained in the uniform lines of small or capital letters, periods, commas, parentheses—pages of signs, packed as closely together as grains of sand, representing the many-colored spectacle of the world on a surface that is always the same and always different, like dunes shifted by the desert wind.

—Italo Calvino (1923-1985)