



Society for Maternal-Fetal Medicine Consult Series #59: The use of analgesia and anesthesia for maternal-fetal procedures ☆☆☆★☆☆

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ABSTRACT

Pain is a complex phenomenon that involves more than a simple physical response to external stimuli. In maternal-fetal surgical procedures, fetal analgesia is used primarily to blunt fetal autonomic responses and minimize fetal movement. The purpose of this Consult is to review the literature on what is known about the potential for fetal awareness of pain and to discuss the indications for and the risk-benefit calculus involved in the use of fetal anesthesia and analgesia. The recommendations by the Society for Maternal-Fetal Medicine are as follows: (1) we suggest that fetal paralytic agents be considered in the setting of intrauterine transfusion, if needed, for the purpose of decreasing fetal movement (GRADE 2C); (2) although the fetus is unable to experience pain at the gestational age when procedures are typically performed, we suggest that opioid analgesia should be administered to the fetus during invasive fetal surgical procedures to attenuate acute autonomic responses that may be deleterious, avoid long-term consequences of nociception and physiological stress on the fetus, and decrease fetal movement to enable the safe execution of procedures (GRADE 2C); and (3) due to maternal risk and a lack of evidence supporting benefit to the fetus, we recommend against the administration of fetal analgesia at the time of pregnancy termination (GRADE 1C).

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1. Introduction

Pain is a complex phenomenon that involves more than a simple physical response to external stimuli. The components of the experience of pain are processed at multiple different levels of the

nervous system. Experiencing pain in response to external stimuli requires peripheral sensory receptors (nociceptors), a somatosensory cortex able to interpret these stimuli as painful, and intact pathways to relay these messages from the nociceptors to the cortex. Analgesics and anesthetics include medications used to manage pain; analgesia is pain relief without a loss of consciousness, whereas anesthesia is loss of sensation.

When tissue is injured, nociceptive pathways trigger protective behaviors including reflex movements mediated by motor circuits in the spinal cord and the brainstem. At the same time, the brainstem and the hypothalamic circuits are activated, which affects the cardiovascular, respiratory, and endocrine systems. These are subcortical reflex responses. For tissue injury to lead to a perception of pain, high-level cortical processing is needed for the unique sensory and emotional qualities that characterize pain and suffering [1]. The neural response to noxious, tissue-damaging stimuli can be simple, involving only a single neuron, or complex, resulting in hemodynamic changes. However, nociception, or these responses, are not the same as pain, nor are they sufficient for the experience of pain. Rather, pain is a unique sensory and emotional experience that requires activity in a number of cortical structures and functional connections between these structures.

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Summary of recommendations		
Number	Recommendations	GRADE
1	We suggest that fetal paralytic agents be considered in the setting of intrauterine transfusion, if needed, for the purpose of decreasing fetal movement.	2C Weak recommendation, low-quality evidence
2	Although the fetus is unable to experience pain at the gestational age when procedures are typically performed, we suggest that opioid analgesia should be administered to the fetus during invasive fetal surgical procedures to attenuate acute autonomic responses that may be deleterious, avoid long-term consequences of nociception and physiological stress on the fetus, and decrease fetal movement to enable the safe execution of procedures	2C Weak recommendation, low-quality evidence
3	Due to maternal risk and lack of evidence supporting benefit to the fetus, we recommend against the administration of fetal analgesia at the time of pregnancy termination.	1C Strong recommendation, low-quality evidence

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The experience of pain, therefore, is dependent on an extensive developmental process. The components of the pain pathway develop at different times during gestation; the thalamocortical connections that carry stimuli (the sensory component of pain) to the cortex are present at about 25 weeks of gestation. However, although these connections are necessary, they are not sufficient for the perception of pain. Their mere presence does not indicate that a fetus at this gestational age is able to perceive tissue injury or other stimuli as painful.

Although neuroscientists have long sought a pain center in the brain, no such specific center has been identified. Many regions of the brain respond to painful stimuli, but these regions all respond to other types of salient stimuli, and noxious stimuli evoke a pattern of activity in many areas of the brain [2]. The current view is that pain arises from a distributed network of brain activity, none of which is unique to pain. However, when this network is coordinated or synchronized, it results in the sensory, emotional, motivational, and cognitive experience of pain [3]. This has been described as a pain “connectome” –rather than an anatomic center—that arises from dynamic changes in a distributed network of brain activity [4].

Given this complexity in the sensation of pain, it has long been debated if –and when– a fetus can begin to experience pain. This document reviews the literature on what is known about the potential for fetal awareness of pain and discusses the indications for the use of fetal anesthesia and analgesia.

2. What is the definition of pain?

The International Association for the Study of Pain (IASP) defines pain as “[a]n unpleasant sensory and emotional experience associated with, or resembling that associated with, actual or potential tissue damage.” This multidisciplinary association of experts goes on to elaborate that pain and nociception are different phenomena and that pain cannot be inferred solely from activity in sensory neurons [5]. Rather, awareness of pain is dependent upon the intact functioning of multiple neurologic and cognitive systems, and suffering in response to a noxious sensation requires a connectivity between these systems.

The peripheral sensory receptors responsive to noxious mechanical or thermal stimuli are known as nociceptors. When a noxious stimulus occurs, a signal travels from the peripheral sensory receptor (nociceptor) to the spinal cord dorsal horn. Sensory information that reaches the dorsal horn impinges on neural circuits that send the information to the brain and/or drive activation of the motor neurons in the spinal cord that are responsible for reflex muscle contractions to effect withdrawal away from the noxious stimulus (flexor withdrawal reflex) that is intended to protect the body from potentially damaging stimuli. Whether or not the sensory information sent to the brain results in pain depends on the development of the necessary cortical structures and a sufficient connection between these structures. The reflex withdrawal from the stimulus and the complex motor and autonomic responses to noxious stimuli are not equivalent to pain and do not require the perception of pain. This process is referred to as nociception [6,7].

The sensory signals that arise from the spinal cord and are ultimately perceived as pain travel in parallel pathways. The sensory-discriminative information (intensity and location) travels to the sensory cortex, and the emotional information associated with the noxious stimulus, for example, suffering, travels through the brain-stem nuclei to the limbic structures such as the insula. Importantly, the experience of pain not only requires the development of these structures but also the connections between them. This requirement was most clearly demonstrated by experience with lobotomy, originally used by Egas Moniz to treat pain: disconnecting the pre-frontal cortex from the rest of the brain allowed patients to describe the location and intensity of the noxious stimuli but eliminated all associated suffering [8]. It is also possible to experience pain in the absence of sensory input, as with phantom limb pain [9]. However, perceiving noxious stimuli as painful requires intact sensory and interconnected cortical systems. Although nociception involves nociceptors and reflexive movements, the pathways from the periphery to the brain must be intact for an individual to experience a noxious stimulus as painful; cortical processing of sensory signals must also be intact and connected to provide the perception of pain [10–13].

3. When do the anatomic structures and physiological processes involved in pain develop?

Histologic studies describe the development of the neural structures that are necessary to experience pain. In the first trimester, the cortex is disorganized and not yet connected to the peripheral nervous system. Toward the end of the first trimester, grooves that later become gyri and sulci begin to form, although mature gyri and sulci of the brain do not emerge until after 34 weeks of gestation. The transient subplate zone appears around 10 to 13 weeks of gestation. This structure, comprised of new neurons and extracellular material, is thought to be the primary synaptic relay area of the developing brain. Neuronal projections from the thalamus to the subplate zone appear between 12 and 18 weeks of gestation and extend to the cortex between 24 and 32 weeks of gestation. The subplate recedes after about 32 to 34 weeks of gestation, at which point numerous complex thalamocortical connections exist [11, 13–15].

The sensory receptors and spinal cord synapses required for nociception develop earlier than the pathways required for the sensory-discriminative aspects of pain. Peripheral cutaneous sensory receptors develop between 7 and 15 weeks of gestation, and fetuses display a spinal reflex arc, that is, a reflex motor response as early as 8 weeks of gestation. The neurons involved in nociception appear in the dorsal root ganglion by 19 weeks of gestation, while thalamic afferent neurons reach the subplate zone between 20 and 22 weeks of gestation. The thalamic afferent neurons reach the cortical plate between 23 and 24 weeks of gestation [11]. The immaturity of the thalamocortical connections is unlikely to support the cortical processing of external stimuli at this stage of development. Sensory stimuli, including nociceptive stimuli, can reach the cortical level at approximately 24 to 25 weeks of gestation [14, 16]. Although these pathways are necessary, they are unlikely to generate a pain experience due to the lack of functional connections between cortical structures at this stage of development [13].

4. How is pain assessed?

There are currently no objective measures of pain, and as fetuses and neonates cannot report or communicate pain, indirect measures such as physiological responses are often interpreted to represent distress. Investigators have attempted to use methods such as an electroencephalogram (EEG) and magnetic resonance imaging to investigate pain perception, although none of the methods have been demonstrated to be valid, objective measures. The IASP specifies that pain and nociception are different phenomena and that the perception of pain cannot be inferred solely from activity in the sensory neurons or from reflex motor and autonomic responses to stimuli, as these responses can be evoked in the absence of any perception of pain [5]. In other words, fetal movement in response to touch does not indicate pain. Because the autonomic responses associated with noxious stimulation are also reflexive, these may serve as indirect measures of nociception but not as a measure of pain.

Some indirect measures used to assess potential pain in neonates have been extrapolated to the fetus, but none have been validated. In addition, the fetal environment and fetal experiences are far different than those of a neonate, even at the same developmental age, so extrapolation is not appropriate. Studies of stereotyped facial expressions of preterm neonates experiencing noxious and nonnoxious stimuli beginning at the equivalent of 28 to 32 weeks of gestation have reported that more premature neonates have fewer facial and body movements compared with term neonates [12, 17–19]. Fetal facial expressions can be observed in utero using 4-dimensional ultrasound in the late second and

third trimesters, with the complexity of facial expressions increasing with gestational age [20, 21]. However, because the facial nucleus and the circuitry required for facial expression arise from the brainstem and not the cortex, these indirect measures do not reflect any experience of pain or suffering [22].

Studies have also reported hemodynamic and hormonal changes in fetuses undergoing intrauterine procedures and have compared the responses to venipuncture of innervated vs noninnervated tissue. Fetuses undergoing hepatic venipuncture through the innervated abdominal wall at 23 to 34 weeks of gestation exhibit increased cerebral blood flow and increased plasma catecholamine and cortisol concentrations compared with fetuses at the same gestational age undergoing venipuncture of the umbilical cord, which is not innervated [23–25]. However, although these physiological responses to sensory stimulation can be used to quantify nociception, they do not reflect an experience of pain. It has also been noted that physiological responses to noxious stimuli can be exhibited by anencephalic neonates and adults in vegetative states, neither of whom has the capacity for cortical activity and thus cannot be aware of pain [26, 27].

Neonatal EEG has been used to investigate the development of cortical function and infer the ability to experience pain, although pain itself does not have a particular EEG pattern. EEG studies of normal preterm infants show substantial evolution in the synchrony of brain activity between the equivalent of 24 and 30 weeks of gestation ex utero, suggesting a process of considerable cortical maturation during this time [28]. These patterns vary greatly from adult EEG patterns and change with each subsequent week of gestational age. EEG changes in response to tactile and auditory stimuli are not present until the equivalent of 28 to 30 weeks of gestation ex utero [29], and differences in EEG responses to noxious (eg, heel stick) and nonnoxious stimuli (touch) are present at 35 weeks of gestation ex utero [30]. However, although such studies provide some information on the development of brain activity in the newborn, these reported findings are specific to the neonate and cannot be extrapolated to the fetus.

5. What are the goals of analgesia and anesthesia in the setting of maternal-fetal surgery?

Considerable advances in intrauterine diagnosis and therapeutic treatments for fetal disorders have been made in recent years, and a wide range of interventions are now available. They range from percutaneous, ultrasound-guided, needle-based procedures and fetoscopic interventions to open fetal surgery and ex-utero intra-partum treatment (EXIT) procedures. The anesthetic techniques for these maternal-fetal interventions have also evolved over the years to support optimal procedural outcomes.

Diagnostic procedures in early pregnancy include chorionic villus sampling and amniocentesis. Although local maternal anesthesia may occasionally be used, these procedures do not involve any fetal structures with sensory innervation. Similarly, fetal cordocentesis and intrauterine fetal blood transfusions do not involve innervated fetal structures. However, fetal immobilization may be required to decrease the likelihood of fetal movement that could potentially dislodge the needle or tear the umbilical vein. With intrauterine transfusion, a muscle relaxant may be administered to the fetus via the intramuscular route or directly into the umbilical vein [31]. We suggest that fetal paralytic agents be considered in the setting of intrauterine transfusion, if needed, for the purpose of decreasing fetal movement (GRADE 2C).

Multiple agents and approaches have been studied for use during more invasive maternal-fetal procedures [23, 25, 32–40]. A comprehensive review of anesthesia for maternal-fetal surgery is beyond the scope of this document. Overall, optimizing the safety and efficacy of maternal-fetal surgery requires a team with experi-

Society for Maternal-Fetal Medicine Grading System: Grading of Recommendations Assessment, Development, and Evaluation (GRADE) recommendations^{49,a}

Grade of recommendation	Clarity of risk and benefit	Quality of supporting evidence	Implications
1A. Strong recommendation, high-quality evidence	Benefits clearly outweigh risks and burdens, or vice versa.	Consistent evidence from well-performed randomized controlled trials, or overwhelming evidence of some other form. Further research is unlikely to change confidence in the estimate of benefit and risk.	Strong recommendation that can apply to most patients in most circumstances without reservation. Clinicians should follow a strong recommendation unless a clear and compelling rationale for an alternative approach is present.
1B. Strong recommendation, moderate-quality evidence	Benefits clearly outweigh risks and burdens, or vice versa.	Evidence from randomized controlled trials with important limitations (inconsistent results, methodologic flaws, indirect or imprecise), or very strong evidence of some other research design. Further research (if performed) is likely to have an impact on the confidence in the estimate of benefit and risk and may change the estimate.	Strong recommendation that applies to most patients. Clinicians should follow a strong recommendation unless a clear and compelling rationale for an alternative approach is present.
1C. Strong recommendation, low-quality evidence	Benefits seem to outweigh risks and burdens, or vice versa.	Evidence from observational studies, unsystematic clinical experience, or randomized controlled trials with serious flaws. Any estimate of effect is uncertain.	Strong recommendation that applies to most patients. Some of the evidence base supporting the recommendation is, however, of low quality.
2A. Weak recommendation, high-quality evidence	Benefits closely balanced with risks and burdens.	Consistent evidence from well-performed randomized controlled trials or overwhelming evidence of some other form. Further research is unlikely to change confidence in the estimate of benefit and risk.	Weak recommendation; best action may differ depending on the circumstances or patients or societal values.
2B. Weak recommendation, moderate-quality evidence	Benefits closely balanced with risks and burdens; some uncertainty in the estimates of benefits, risks, and burdens.	Evidence from randomized controlled trials with important limitations (inconsistent results, methodologic flaws, indirect or imprecise), or very strong evidence of some other research design. Further research (if performed) is likely to have an effect on confidence in the estimate of benefit and risk and may change the estimate.	Weak recommendation; alternative approaches likely to be better for some patients under some circumstances.
2C. Weak recommendation, low-quality evidence	Uncertainty in the estimates of benefits, risks, and burdens; benefits may be closely balanced with risks and burdens.	Evidence from observational studies, unsystematic clinical experience, or randomized controlled trials with serious flaws. Any estimate of effect is uncertain.	Very weak recommendation, other alternatives may be equally reasonable.
Best practice	Recommendation in which either (1) there is an enormous amount of indirect evidence that clearly justifies strong recommendation (direct evidence would be challenging, and inefficient use of time and resources, to bring together and carefully summarize), or (2) recommendation to the contrary would be unethical.		

^a Adapted from Guyatt et al.⁵⁰

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ence in the complexities of the physiological impact of the surgery and the impact of anesthetic agents on the pregnant patient and the fetus. Reassuringly, a 2019 systematic review meta-analysis reported no maternal deaths because of fetal surgery in 10,596 procedures. In addition, no major complications attributable to analgesia or anesthesia were reported [41].

Open fetal surgery requires complete uterine relaxation and fetal immobilization. During maternal-fetal surgery, elevations in catecholamine and cortisol secretion cause increased placental vascular resistance and decreased blood flow to the fetus, which can result in fetal bradycardia and could prompt delivery at a viable gestational age [42]. In addition, the fetal physiological stress response increases uterine irritability and may precipitate preterm labor [43, 44]. Although most of the cortical connections necessary for pain perception do not develop until 23 to 30 weeks of gestation, noxious stimuli can elicit neuroendocrine and hemodynamic responses by 18 to 20 weeks of gestation, and fetal analgesia is used to prevent these neuroendocrine and hemodynamic alterations [36].

Fetal surgeries that involve laparotomy and hysterotomy require maternal anesthesia and postoperative analgesia. They are typically performed under general anesthesia with an epidural placed for postsurgical maternal analgesia. Although inhaled anesthetics transfer to the fetus, they do not reliably diminish the fetal autonomic response to noxious stimuli. High doses of general anesthetic agents administered to the mother for uterine relaxation can lead to fetal cardiovascular depression and can have a substantial adverse impact on fetal hemodynamics [45]. Direct administration of both opioids and paralytics to the fetus is used for some fetal surgeries to reduce the dosage of general anesthetic agents administered.

In 2021, the American Society of Anesthesiologists Committees on Obstetric and Pediatric Anesthesiology and the North American Fetal Therapy Network provided consensus guidance on the use of anesthesia for maternal-fetal interventions [31]. They note that there may be substantial short- and long-term adverse effects on the fetus and its developing central nervous system if the fetal physiological stress response is not blunted. Although the fetus is unlikely to feel pain at the earlier gestational ages when fetal surgery is performed, the physiological stress response can be blunted by opioids, which may prevent fetal compromise during these complex procedures. Although the fetus is unable to experience pain at the gestational age when procedures are typically performed, we suggest that opioid analgesia should be administered to the fetus during invasive fetal surgical procedures to attenuate acute autonomic responses that may be deleterious, avoid long-term consequences of nociception and physiological stress on the fetus, and decrease fetal movement to enable the safe execution of procedures (GRADE 2C). Given the concerns that some reflex physiological responses to noxious stimuli may have long-term consequences, additional research is needed to identify more effective and safe ways of attenuating nociception in the fetus [23].

6. In pregnant people undergoing diagnostic or therapeutic procedures, does the use of fetal analgesia or anesthesia improve fetal and maternal outcomes?

As described earlier, the use of fetal analgesia and anesthesia during maternal-fetal surgery primarily improves outcomes by inhibiting the fetal physiological stress response, providing uterine relaxation, and minimizing fetal movement. The use of appropriate agents decreases the chances of fetal bradycardia and emergent preterm delivery as well as uterine contractions leading to preterm labor and resultant preterm delivery. The management of anesthesia and analgesia should prioritize maintaining uteroplacental circulation, achieving complete uterine relaxation, optimizing surgi-

cal conditions by minimizing fetal movement, monitoring maternal and fetal hemodynamics, and minimizing maternal and fetal risk.

7. Should fetal analgesia be provided before pregnancy termination?

The vast majority (>99%) of abortions in the United States occur before 24 to 25 weeks of gestation, which is the minimum gestational age at which in utero pain awareness by the fetus is developmentally plausible [16, 46, 47]. Pregnancy termination in the second trimester is most commonly performed surgically via dilation and evacuation (D&E), whereas labor induction is also an option and may be preferred as the pregnancy advances or when a skilled surgical provider is not immediately available.

Most D&Es are performed with sedation or general anesthesia [48]. Direct administration of analgesia to the fetus percutaneously under ultrasound guidance is invasive and technically challenging. Maternal administration of additional analgesic medications for potential fetal benefit may be more feasible. However, administering dosages that exceed what is needed for maternal benefit could cause harm. This approach offers no value given our current understanding of the potential fetal awareness of pain in utero. Due to maternal risk and lack of evidence supporting benefit to the fetus, we recommend against the administration of fetal analgesia at the time of pregnancy termination (GRADE 1C).

8. Conclusion

In summary, pain is a complex phenomenon that involves more than simple physical responses to external stimuli. The experience of suffering in the context of noxious stimuli requires peripheral sensory receptors, a somatosensory cortex that is able to interpret these stimuli as painful, and intact pathways to relay these messages. Although these complex structures develop over gestation, the connections that carry the stimuli to the somatosensory cortex are not yet present prior to the late second or early third trimester, and the responses to fetal stimuli represent reflex movements to nociception. In maternal-fetal surgical procedures, the goals of fetal analgesia are to blunt fetal autonomic responses and minimize fetal movement. Due to maternal risk and the lack of evidence of fetal benefit, the administration of fetal analgesia at the time of abortion is not indicated.

Declaration of Competing Interest

All authors and committee members have filed a conflict of interest disclosure delineating personal, professional, business, or other relevant financial or nonfinancial interests in relation to this publication. Any substantial conflict of interest have been addressed through a process approved by the Society for Maternal-Fetal Medicine (SMFM) Board of Directors. The Society for Maternal-Fetal Medicine (SMFM) has neither solicited nor accepted any commercial involvement in the specific content development of this publication.

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