An evidence-based discussion of fetal pain and stress

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Plain Language Summary

The presence and timing of pain perception during fetal development (i.e., before birth) have remained controversial for many decades. Until recently, surgeons had to wait for the baby's birth to surgically correct any congenital malformations, but now such surgeries are conducted while the baby is still in the mother's womb. Other invasive procedures are also performed, like blood transfusions, before the baby's birth. These invasive procedures cause dramatic changes in the stress hormones, metabolism, and behaviors of the fetus – similar to those of premature newborns undergoing such procedures. Changes in the brain and other physiological systems also suggest that fetuses become capable of processing noxious stimuli about halfway through pregnancy, although their reactions may not meet the international definition of pain. In this article, we describe the key scientific evidence related to fetal pain, including clinical studies on fetuses and premature babies. We propose that sufficient data are available to serve as proof of fetal pain in the latter half of pregnancy and that no study to date has conclusively proven the absence of fetal pain beyond the age of viability. Based on this evidence, we propose that all fetuses receive anesthesia regardless of the invasive procedures being performed to guarantee the least possible pain and physiological, behavioral, or hormonal responses without exposing the mother or her baby to unnecessary complications.

Abstract

Background

The concept of fetal pain is results from procedures conducted without anesthesia in preterm newborns and fetuses, which indicate that it is possible to examine fetal pain based on stress hormone, metabolic, and behavioral changes. Anatomical and physiological data suggest that fetuses become capable of processing nociceptive stimuli around midgestation, although the associated changes in fetal brain development remain unclear. What constitutes fetal pain remains controversial in the light of the definition of pain adopted by the International Association for the Study of Pain (IASP), which posits pain as an "unpleasant sensory and emotional experience."

Summary

Here, we examine the notion that human fetuses cannot "experience" pain and potential implications of this claim. We highlight the key scientific evidence related to fetal pain, including clinical studies on pain in fetuses and preterm newborns. We argue that consistent patterns of stress hormones, metabolic changes, body movements, hemodynamic changes, and pain-related facial expressions in fetuses exposed to invasive procedures overcome the need for subjective proof of pain as articulated in the IASP definition. No study to date has conclusively proven the absence of fetal pain beyond the age of viability.

Key Messages

Based on the current evidence, we propose that all fetuses receive anesthesia regardless of the invasive procedures being performed to guarantee the least possible pain and physiological, behavioral, or hormonal responses without exposing the mother or her baby to unnecessary complications.

INTRODUCTION

Over the last 30 years the discussion on fetal and neonatal pain has changed from performing surgical and other invasive procedures without administering anesthesia/analgesia [1] to regularly administering anesthesia/analgesia for fetal [2-4] and neonatal procedures [5-9]. Assessing pain accurately is difficult given the subjective elements in measuring pain [3, 10, 11]. Furthermore, given that "pain" expressions in fetuses can occur with [12-14] and without noxious stimulation [15], we need to assess the context of fetal behaviours in order to judge whether the fetus responds to pain or not. The current review explores the scientific evidence related to fetal pain and stress to clarify our current understanding of fetal pain.

Perspectives of Professional Organizations

The Royal College of Obstetricians and Gynaecologists published a detailed report in 2010 stating that fetal pain is structurally impossible until 24 weeks of gestation and also unlikely to be functionally possible after birth [16]. These conclusions were subsequently reviewed, adding that "the possibility of pain perception before 28 weeks of gestation is unlikely" and that "there is no basis for considering the administration of analgesia or anesthesia to a fetus before termination of pregnancy in the first or second trimester to prevent fetal perception of pain" [3]. The American College of Obstetricians & Gynecologists adds that "The science conclusively establishes that a human fetus does not have the capacity to experience pain until after at least 24–25 weeks" [17]. While the American Academy of Pediatrics does not specifically address fetal pain, their policy on *Prevention and Management of Procedural Pain in the Neonate* states that pain must be treated, minimized, and/or prevented even in the most premature neonates, "not only because it is ethical but also

because [it has] the potential for deleterious consequences" [18]. The conflicting statements from various professional organizations require a careful reconsideration of the scientific evidence used as the basis for promulgating their recommendations for practice [19].

Fetal Neurodevelopment

Research contradicting that fetuses can experience pain argues that the cortex and thalamocortical tracts must be functional for fetal pain experience [20]. The reason given is that the cortex and thalamocortical tracts develop after 24 weeks' gestation, and therefore it is only possible for a fetus to experience pain in the last trimester of pregnancy [21]. In contrast, other studies arguing that fetal pain can be experienced during the first trimester (< 14 weeks of gestation), adopt a different definition of pain, and maintain that pain can be experienced without a functioning cerebral cortex since painful stimuli can be processed through alternative pathways such as the thalamic pathway. Since these thalamic pathways develops between the 7^{th} and 8^{th} weeks of gestation and the cortical subplate develops from the 12^{th} week of gestation [22], according to this argument, fetuses can experience pain after the first trimester [23]. The subplate modulation hypothesis postulates that connection networks between the subplate, cortical, and subcortical structures are sufficient to facilitate fetal sensory perception prior to 24 weeks gestation and that, similar to the transitional phases of other organ systems (i.e., circulatory system), transitional developmental phases of fetal and neonatal pain circuitry are capable of mediating pain perception [23-26].

Although the debate in most studies on fetal pain focuses on fetal neurodevelopment, other studies suggest that the development of nociception, can be based on hormonal, physiological, and behavioral responses of the fetus in addition to

the development of peripheral nociceptive receptors, or cortical and subcortical structures processing these stimuli. Nociceptive receptors are present and functional in fetal skin from the first trimester and nociceptive axons synapse with the dorsal horn at 6 weeks of gestation, reaching the skin between 11 and 15 weeks, and the mucosa at 20 weeks of gestation. Most of these axons are myelinated between 12 and 14 weeks gestation [26].

The argument that the cortex is necessary for pain perception is in contrast to studies indicating that subcortical structures (brainstem, basal ganglia, amygdala and hypothalamic-pituitary-adrenal axis) processing nociceptive stimuli before thalamocortical development have been observed in babies with no cortex (anencephaly) or with minimal cortex (hydraencephaly) [21, 27]. Furthermore, depending on the definition of consciousness [28, 29], it can be measured in subcortical structures such as the thalamus and brainstem developing primarily in the first two trimesters [23, 30-32].

Fetal Responses to Noxious Stimuli

The claim that fetal pain develops during the second trimester onward can be supported by fetal production of substance P and enkephalins, when stimulated through intrauterine procedures [26]. Additionally, when exposed to skin-breaking or other invasive procedures, fetuses mount robust hormonal reactions through the hypothalamic pituitary-adrenal (HPA) axis and the sympathoadrenal axis, leading to increased levels of cortisol, adrenaline, and beta-endorphins, and hemodynamic instability [19, 23]. For example, Giannakoulopoulos et al.[33, 34] found increased plasma cortisol, noradrenaline, and beta-endorphin levels in fetuses ranging in age between 23 and 34

weeks gestation [33} and 18- 37 weeks gestation [34} when undergoing abdominal needling to access the intra-hepatic umbilical vein, which occurred within 10 minutes of needling (from activation of nociceptors in abdominal skin, peritoneum, and hepatic capsule), whereas fetuses subjected to umbilical vein needling at the non-innervated placental cord insertion site showed no hormonal responses [33, 34].

In addition to hormonal responses, these fetuses showed hemodynamic stress responses during invasive procedures that activated nociceptive receptors [35, 36]. Changes in heart rate and cerebral blood flow (CBF, assessed using doppler ultrasound) showed that both fetal bradycardia and tachycardia are observed with painful stimulation. CBF increased with pain, as evidenced by increases in the pulsatility index of middle cerebral arteries [35, 36], likely signaling a defense mechanism to protect the brain during a threat to bodily integrity, not unlike the responses of viable preterm neonates [37, 38].

Behavioural observations further indicated that these fetuses responded to noxious stimulation with withdrawal reflexes, vigorous breathing and body movements away from the noxious stimulus [25, 39], as well as facial expressions characteristic of pain [12-14, 40]. Fisk et al. anesthetized fetuses with fentanyl while performing the same procedures and found neither a hormonal stress responses nor fetal hemodynamic changes during the procedure [41, 42]. Fentanyl also eliminated the nociception-induced vigorous breathing and body movements resulting in a fetus that was “still and appears quiescent and calm” [21]. A more complete list of studies investigating fetal responses to nociceptive stimuli are summarized by Thill (Table 1, p.05) [23].

Neuroinhibitory mediators including adenosine, progesterone, pregnenolone, allopregnenolone, and prostaglandin may produce fetal sedation but cannot lead to fetal

anesthesia, and therefore, are incapable of preventing fetal pain [26]. Mellor and colleagues claimed that the fetus remains in a continuous state of sleep, or that it was continuously sedated by placental neuromodulators [43], but subsequent research invalidated these claims [26]. Other authors have documented considerable periods of time that the fetus spends awake [44, 45], that it can be awakened from sleep [46], and that neuroinhibitory mediators may cause fetal sedation but not anesthesia [47-50].

Fetal Neuroimaging

Additionally, neuroimaging studies such as electroencephalography (EEG), functional magnetic resonance imaging (fMRI), magnetoencephalography (MEG), and near infrared spectroscopy (NIRS) were used with the aim of determining fetal brain activity at rest and during nociceptive and non-nociceptive stimulation and to corroborate that nociceptive activity in fetuses is similar to that of premature infants of corresponding gestational age [32, 38, 51-54]. Conclusions regarding pain perception based on the functional activity of particular brain regions are tentative at best [55] and, despite the progress in this area [56-58], it is questionable whether functional brain activity or neuroimaging can sufficiently represent the totality of dynamic painful experiences [55, 59].

Defining Pain

In 2020, IASP revised the definition of pain, defining it as “an unpleasant emotional and sensory “experience” associated with or similar to actual or potential tissue damage” [60]. Given the IASP definition of pain which “requires conscious

recognition of a painful stimulus" and others defining pain based on physiological, behavioural or hormonal repsonses, it is evident that the debate is around the definition of pain. Thus, arguments between researchers claiming that fetal pain is not possible and others claiming that pain reactions in the fetus signify they are in pain hinge on the reaching a common definition of pain [61, 62]. A revision of the definition of pain is called for not only in relation to fetal pain but also for the wider constituency of patients who cannot describe their pain, because of age and/or mental disabilities [63].

Implications for Clinical Practice

Since intrauterine surgical procedures are increasingly used in prenatal treatment plans, it is vital to investigate the type of anesthetics necessary to reduce or eliminate fetal pain. Current evidence indicates that maternal anesthesia is inadequate for fetal pain management due to insufficient transplacental passage of the commonly used analgesics and anesthetics [64-67]. Many invasive fetal procedures are also performed under maternal spinal or epidural anesthesia, which does not provide fetal anesthesia [4, 68-70]. Although some drugs can pass to the fetus, due to glomerular filtration and hepatic metabolism, their half-life is reduced, in addition to the fact that the placenta filters many drugs, making them inadequate for fetal anesthesia. Therefore, direct administration of analgesia to the fetus is necessary [71, 72].

Among the direct fetal anesthetic modalities, none are considered to be superior to the others, and in most cases, direct fetal analgesic was administered intramuscularly, using opioids and a muscle relaxant [73]. In relation to studies involving fetal anesthesia, a distinct preference was found for fentanyl, atropine, and vecuronium for

administration of direct fetal anesthesia [73]. Given that the doses used and their timing are heterogeneous in the different studies , this approach does not lend itself to produce a protocol. The Food Drug Association (FDA) recommends that midazolam and propofol should be avoided in procedures that only require sedation [71]. It is important to highlight that no anesthetic agent has been considered teratogenic in humans, and clinical studies in children have shown that a short period of general anesthesia is not associated with neurocognitive changes [74, 75]. Furthermore, there have been rare reports of adverse effects on fetuses and/or their mothers due to fetal analgesia [71]. Adequate anesthesia is administered directly and routinely to the fetus undergoing fetal surgery, as mandated by published studies and professional guidelines[69, 76, 77]. These guidelines are based on the universally held notion that human fetuses experience pain and stress during invasive procedures. Indeed, approval to develop a fetal surgery program requires explicit description of the protocols, procedures, and policies that will guarantee the least possible pain and physiological, behavioral or hormonal responses in the fetuses that require invasive procedures likely to cause tissue injury[78]. The American Society for Anesthesiologists and the North American Fetal Therapy Network (NAFTNet) recommends fetal anesthesia in all invasive procedures to inhibit humoral stress responses, decrease fetal movements, and provide sedation [69, 76, 77]. Despite concerns about short-term adverse effects and long-term development of the central nervous system (CNS), extensive scientific and clinical data support the use of fetal anesthesia during invasive procedures in the fetus [42, 69, 71, 73, 76, 79, 80].

CONCLUSIONS

In conclusion, fetal anesthesia should be employed not only to suppress hormonal and physiological responses but also to avoid the short- and long-term sequelae of fetal surgery. Multiples studies have shown that premature babies previously exposed to painful stimulation show greater degrees of stress when the same procedure was repeated, compared to those of the same gestational age who had not yet been exposed [71]. We suggest that direct fetal anesthesia would be preferable to only maternal anesthesia during fetal procedures. The drawbacks of fetal anesthesia include significant increase in costs related to the hospitalization of patients, the use of anesthetics, as well as professional training needs. The development of a new definition of pain that includes fetal pain would play a vital role in identifying ethical issues surrounding painful procedures involving fetuses, such as fetal surgery, abortion, and feticide [23].

2411 words

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Dr. Mohamed and Dr. Reissland declare no conflict of interest.

Dr. Anand serves as a grant reviewer for National Institutes of Health in USA, as the Editor of ***Awareness*** (an open access journal), and as a Scientific Advisory Board Member of *Sadhguru Center for a Conscious Planet* at Harvard Medical School.

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SM wrote the initial draft of this manuscript, and contributed to multiple revisions of the ms as well as replying to the comments to reviewers and approving the final version submitted for publication.

SA added extensively to multiple revisions of the draft, reviewed and added to and revised comments to the reviewers and approved the final version submitted for publication.

NR contributed and added text to multiple revisions of the ms, reviewed and contributed to comments to reviewers, approved the final version submitted for publication and submitted the paper.

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