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*Corresponding author

Daniel M Doleys, Director, Pain and Rehabilitation Institute, 2270 Valleydale Road- S100, Hoover, Ala 35244, USA

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Review Article

The Emergence of Fetal Pain: Some Considerations

Daniel M Doleys*

Director, Pain and Rehabilitation Institute, USA

Abstract

Pain is a common human event. Yet, the point at which it can be said that a person is able to experience pain remains unclear. For example, is the human fetus capable of feeling pain? If so, is it the same kind of pain known to the more mature individual? The answer, in part, may depend upon the definition of pain, and what are considered to be the essential and necessary components of pain. The role of consciousness, memory, and the cortex, for example, appear to require consideration. This paper explores some of the controversies surrounding these topics. The discussion focuses on whether or not fetal pain can, or should, conform to the standard International Association for the Study Pain (IASP) definition. Or, might fetal pain present a different kind of pain demonstrating some, but not all, of the characteristics of the IASP definition.

Introduction

The neuroanatomical and neurophysiological aspects involved in the antenatal development of the sensory and nociceptive systems have been well characterized [1-6]. However, whether the fetus can, indeed, feel pain, and the point at which this phenomenon can be said to occur, continues to be a topic of debate. It has been suggested that the fetus is capable of feeling pain as early as 12-weeks Gestational Age (GA) [7]. However, some believe this does not occur until 30-weeks or more [8]. Others suggest the fetus does not experience pain, but displays a type of reflexive or a stress response [9]. Probing the topic of fetal pain raises many questions. What neurological structures are necessary for pain to be experienced remains unclear. For example, is a fully developed cortex a prerequisite, or are subcortical structures sufficient? In addition, processes such as consciousness, intentionality, and memory are often linked to the experience of pain. Is there evidence that the fetus is capable of such? Does the general philosophical framework within which the data are interpreted influence the understanding of pain? That is, can a conclusion be arrived at by examining individual structures and processes, or is there an advantage to considering a more systems-oriented approach?

At the heart of the debate over the existence of fetal pain, is the definition of pain. The IASP (International Association for the Study of Pain) has provided what many considered to be the most recognizable and heuristic definition. However, it has faced some challenges [10]. Is it realistic to expect fetal pain to fulfill each of the aspects of this definition? Are there other types of definitions one should be aware of which may be more applicable? Unlike the terms nociceptive, nociplastic, and neuropathic, which characterize different types of pain, might fetal pain represent a different kind of pain? The purpose of this paper is to provide a brief review of some of the controversies related to the above topics. An examination of these areas is not only relevant to the topic of fetal pain, but may have implications for the understanding of the nature of pain in general. Importantly, the topic of fetal pain is more than just an academic exercise. The answer may well have treatment, political, and policy implications.

Definitions

Any inquiry into the topic of fetal pain must first consider the definition of pain. However, at a more fundamental level is the nature of definitions. Definitions are rarely definitive. They are neither true nor false; just appropriate or inappropriate. Definitions tend to express the essential nature of something; to make something definite or distinct [11]. That is, to make a distinction where one exists. If too broad, a definition may fail to rule out those things which are extraneous, and fall short of providing a meaningful distinction. If too narrow, it will exclude that which can be meaningfully included. Definitions can be classified as nominal or real [12]. A nominal definition gives the meaning, or abstract idea, to the term to which it is applied. It is a definition in the classical sense of the term. A real definition, by contrast, expresses the nature of the object of the definition. A real definition clarifies the meaning by virtue of the thing (s) the term denotes. In short, to discover the real definition of a term X, one needs to investigate the thing (s) denoted by X; to discover the nominal definition, one needs to investigate the meaning and use of X. A real definition is a special case of a nominal definition; while a nominal definition may have no reference to reality, but may still be a definition. A distinction can also be made as to whether a definition relates to a kind or type of an event. As a nominal definition, fetal pain could be considered as a kind of pain. Taken as a real definition, it would be more difficult to reconciled fetal pain as a referent. That is, is what some refer to as fetal pain differ in kind or type compared to that of the more fully development human? Is the essence of it different in nature, or is it a rudimentary form of adult pain? When the phenomenon under study lacks a clear or unambiguous referent, ostensive definitions have been used. Ostensive definitions typically depend on context and experience. An ostensive definition conveys the meaning of a term to be defined by pointing out, and characterizing, the cases, or instances to be covered.

Operational definitions are based upon the outcome of specific instruments of assessment. Assessing pain in the fetus is complicated by the limited and overlapping repertoire of responses. For example, differentiating a reflex, stress, and pain response has proven difficult. At times these terms appear to be used interchangeably; at other times not. What differentiates the 'stress' response form a 'pain' response is not always clear. For some it seems to be a matter of degree (quantity), for others a matter of kind (quality). For example, a stress response, not unlike a pain response, may have a protective and beneficial role, but can also be detrimental. Noxious stimulation caused by needling through the abdomen during intrahepatic blood transfusions, has been associated with a stress hormonal response and observed as early as 13 weeks [13,14]. Jones, et al. [15] simultaneously measured nociceptive behavior, brain activity, and physiological stress in infants. Higher levels of stress were associated with a larger amplitude cortical nociceptive response. However, this increased cortical response was not reflected in the infants' behavior. That is, high levels of physiological stress, seemed to disrupt the usually relationship between nociceptive behavior and cortical activity. The authors concluded "…. Brain activity evoked by noxious stimulation is therefore enhanced by stress, but this cannot be deduced from observation of pain behavior." (p. 3846). Stress appears to have a similar effect on cortical activity as does pain, but is not accompanied by behavioral change. Therefore, if the presence of pain is defined by a particular cortical response, then stress and pain would seem to be more alike than different.

Being able to define the difference between a pain, stress, and reflexive response can have significant philosophical implications. The terms reflexive and stress describe conditions which are so ubiquitous that they almost seem necessary, if not desirable, in the normal course of development. They do not seem to invoke the same moral and ethical imperative for treatment as the term pain. Indeed, the term reflex, and to a lesser degree stress, all but sanitizes the observed reaction. The IASP definition of pain is often used as a standard for determining the existence of pain. The 2020 version of the IASP definition of pain closely resembles the original 1978 version and describes pain as …. An unpleasant sensory and emotional experience associated with, or resembling that associated with, actual or potential tissue damage' [16]. Pain is generally considered to be a subjective experience influenced by biological, psychological, and social factors. In addition, pain is not to be inferred from activity in the sensory system. The experience of pain is to be distinguished from noxious stimulation and the response thereto. Acute and chronic pain are typically viewed to be different clinical entities. In this context, fetal pain would generally be considered as acute pain. Therefore, should the existence of fetal pain be determined by the degree to which the observed response fulfills all the features of the IASP definition? If not, what are the alternatives?

In summary, the debate about fetal pain may rely, at least in part, on whether one considers a particular definition to reflect an instance of a nominal or real definition. As a nominal definition, it would be viewed as referring to the essence or abstract idea of pain. However, as a real definition, it would be taken more literally, and for the term pain to apply it would have to fulfill the requirements stated in the definition. In other words, does fetal pain represents a type of pain, as defined by the IASP, in the same fashion as nociceptive, neuropathic, and inflammatory are types of pain? Or, is fetal pain a different phenomenon, and as such is best considered as a different kind of pain, and better understood in the context of an ostensive definition? In the same way that acute and chronic pain are considered different, but related, entities, might fetal pain be different, but related, to pain experienced by a more mature individual? As such, fetal pain would represent a different kind of pain which may share some, but not necessarily all, the features of pain as described in the IASP definition.

Role of the cortex

The role of the cortex in fetal pain continues to be a source of controversy. The corticocentric view emphasizes the presence of TC (thalamocortical) connections as necessary for there to be a conscious appreciation of pain [3,4]. However, even before TC connections are completed, other pathways exist in the developing nervous system which demonstrate robust connections to the subplate (subcortical) neurons [17, 18]. In addition, the somatosensory region of the subplate has been noted to develop earlier than other regions of the subplate zone. Furthermore, this region is four times thicker than the developing cortex at mid-gestation, and may serve important sensory functions [4,19] including the subconscious processing of sensory stimuli [20,21]. The role of the cortex can also be questioned based on studies indicating that children born with minimal, or no, cerebral cortex appear to experience pain [22]. Lowrey, et al. [4] claim that although the evidence for conscious pain perception is indirect, evidence for the subconscious incorporation of pain into neurological development and plasticity seems incontrovertible. Regarding the developmental timing, Derbyshire and Bockmann [7] concluded that, even considering the neuroscience, "…we no longer view fetal pain (as a core, immediate, sensation) in a gestational window of 12–24 weeks as impossible…" (p. 6). They have effectively reduced the threshold for considering fetal pain to 12-weeks. A period prior to the establishment of TC connections.

The subjective nature of pain is usually associated with higher cortical function. However, in their discussion of fetal pain, Derbyshire and Bockmann [7] have chosen the phrase 'immediate and unreflective' pain (being in pain), in an effort to shift the focus form the more 'subjective reflection' (knowing that I am in pain). This would suggest that fetal pain may well be a different kind of pain when compared to that of the more mature individual. In a similar vein, Merker [21] stated that "…to see, to hear, to feel or otherwise to experience something is to be conscious, irrespective of whether in addition one is aware that one is seeing or hearing… Such additional awareness, is reflective consciousness or self-consciousness, is one of many contents of consciousness available to creatures with sophisticated cognitive capacities" (p 64). The implication is that one may be in pain without knowing (awareness); the later quality being a product of cognitive sophistication. Merker [21] also notes that the essential features necessary for the development of consciousness involves the midbrain and diencephalon, i.e., subcortical structures. And therefore, the emergence of consciousness is not contingent upon advanced cortical development, but may take place independent of it. He also asserted "…an adequate account of neural mechanisms of conscious function cannot be confined to the thalamocortical complex alone" (p. 63). Rather, one may need to consider brain functioning from a systems perspective (see section on systems theory below). Thus, the presence of the cortex may be neither necessary, nor sufficient, to the experience of pain. This position supports considering fetal pain as a neuroadaptive phenomenon that emerges even with an immature cortex [23].

Consciousness

There is no lack of theories regarding the nature of consciousness [24,25]. For example, Lagercrantz and Chanqeux [26] describe consciousness as sensory awareness of the body, the self, and the world. It is a progressive, stepwise, structural, and functional process involving the interaction of multiple intricate components. But, is consciousness required to experience pain? Is a response to a noxious stimulus a proxy for consciousness? Nociceptive reactions, such as withdrawal reflexes, can be recorded at 19-weeks. Stress responses to painful stimulation are complex, but can be detected from the 16th week on [27]. However, as the fetus in utero is almost continuously asleep and unconscious, partially due to endogenous sedation, it may not consciously experience nociceptive inputs as pain.

Burgess and Tawia [8] postulated that "…the fetus become conscious at 30 to 35 weeks after conception" (p. 1). They consider the capacity to experience pain and suffering as a minimal prerequisite to being considered sentient. Lee et.al. [3] asserted that…

a) "Pain perception requires conscious recognition or awareness of a noxious stimulus;
b) Neither withdrawal reflexes nor hormonal stress response to invasive procedures prove the existence of fetal pain, because they can be elicited by nonpainful stimuli, and occur without conscious cortical processing;
c) Fetal awareness of noxious stimuli requires functional TC connections; and
d) TC fibers begin appearing between 23 to 30 weeks' gestational age … the capacity for functional pain perception in preterm neonates probably does not exist before 29 or 30 weeks.",(p. 947).

However, Lowery, et al. (4) argue against requiring functional TC connections and activation as a criterion for pain and consciousness. They note that the stress response (activation of the Hypothalamus–Pituitary–Adrenal [HPA] axis), often interpreted as a sign of pain, has been observed prior to the maturation of TC connections, i.e., 24-weeks. Mellor, et al. [28] emphasize the importance of EEG activity in determining the presence of consciousness. They suggest that, early in the neurodevelopmental process, the cerebral cortex does not have the functional capacity to support any states resembling consciousness. The presence of REM - non-REM differentiation is felt to reflect the establishment of neural connections between subcortical and cortical structures. This level of brain maturity is thought to be necessary for conscious awareness to occur [3,9,28].

Therefore, any movements, facial expressions, etc., in response to stimulation, should be considered as subcortical reflexes. The absence of a response to potentially noxious stimulation, i.e., surgery-induced tissue damage, in the neurologically mature fetus from non-REM or REM sleep-like states to conscious wakefulness, is indicative of the inhibitory functional environment of the fetal brain. They argue that any comparisons or extrapolations from the brain of a new born to that of a similar gestational-aged fetal brain is unwarranted based upon the differences between the physiological environments of the 30-week-old fetus. The existence of consciousness often implies the presence of 'mental' activity. However, Derbyshire [29,30] cautions against assuming that the mind of a nonverbal (non-language) organism (i.e., fetus) is like that of a verbal organism. Or, that the fetus thinks or engages in some type of cognitive or 'mental' activity, as we ordinarily understand it. To know this would require the fetus to tell us. But, a brain capable of doing so could no longer be considered the brain of a fetus. Therefore, the problems encountered by trying to discern what the fetus is feeling or experiencing are not unlike those described by Nagel [31] in 'What is like to be a bat'. In essence, the only way to really know what it is like to be a bat-is to be a bat [32].

A corollary to the issue of consciousness reverts to the above discussion as to the role, and necessity, of the cortex. Penfield and Jasper [20] painstakingly probed multiple areas of the brain in awake patients. They concluded that "…the highest integrative functions of the brain are not completed at the cortical level, but in a system of highly convergent subcortical structures supplying the key mechanism of consciousness" [cited in 32, p. 2]. Likewise, Merker [21] stated "… The tacit consensus concerning the cerebral cortex as the 'organ of consciousness' …may in fact be seriously in error" (p.80). Derbyshire [33] also seems doubtful; "Although there is a general consensus that certain cortical structures are necessary for pain, legitimate arguments that cortical structures are not necessary continue to be raised." (p 654). Finally, Devor [34,35] questioned the assumption that the cortex is

a major cite for pain and conscious experience, suggesting that subcortical structures may play a major role in the pain experience. Thus, the definition of consciousness, its role in the experience of fetal pain, and the necessary neurophysiological/neuroanatomical components remain unresolved. However, the evidence strongly suggests the possibility that consciousness may be related to activity involving subcortical structures.

Memory

The possible existence of fetal memory has attracted interest for hundreds of years. One study reported that short-term memory was observed beginning at the 30-weeks GA [36]. Others noted the emergence of memory by 34-weeks GA [37]. Hepper [38] Questioned, a) Does the fetus have a memory? And if so, b) What functions(s) does it serve?

The review concluded that taking into consideration the evidence from fetal learning paradigms of classical conditioning, habituation, and exposure learning, the fetus does appear to have a memory. Possible functions included recognition of, and attachment to, the mother, promotion of breastfeeding, and language acquisition. If true, it would be improbable to assume that the fetus does not 'remember' negative as well as positive experiences.

Intentionality

Simply put, intentionality refers to the fact of being purposive or deliberate [cf. 11]. Although clearly related to consciousness, it appears to be separate from it [39]. Intentionality implies a somewhat more advanced interpretation of the environment, beyond that of a reflexive response and consciousness awareness. It may well be one aspect of consciousness which develops over time as part of ones learning and experience. Purposeful and targeted hand movements have been interpreted as indicative of action planning and learning, i.e., intentionality. Castiello et al [40] studied twins from 14-weeks GA on. Action planning, as exemplified by a purposeful movement of the fetus toward the co-twin, was observed. Variations in movement velocity between targeted and no-targeted regions were also noted, further supporting some level of intentionality. Kadic and Kurjak [41] asserted that action planning appears to begin by 13-week GA and well established by 22-weeks. This would seem partially support Derbyshire and Bockmann's [7] contention relating the possibility of fetal pain as early as 12 to 24-weeks.

Philosophical approaches

There are at least two approaches one can take to investigating a phenomenon like pain; classical physics, or general systems theory (GST). Classical (Newtonian) physics, emphasizes that which is observable and measurable (philosophical materialism). Also, that a phenomenon is best understood by dismantling (philosophical reductionism) it into its component parts. The interaction of these component parts, in accordance with a set of fixed laws/principles, produces, in a deterministic fashion, the event in question. In essence, a system can be broken down into its individual components so that each component can be analyzed as an independent entity, and the components can be added in a linear fashion to describe the totality of the system. General Systems Theory [GST] [41] views biological entities as consisting of multiple components/networks/systems, which interact in a complex and dynamic fashion; i.e., dynamical systems. For example, Merker [21] uses the term 'macrosystems' while discussing the role of cortical and subcortical structures as they relate to the existence of consciousness in the absence of a cerebral cortex. Indeed, Penfield and Jasper (20) asserted that a 'system' can be considered subcortical anatomically, but function in a supra-cortical fashion. Implicit in this assertion, is viewing the brain as containing various interacting macrosystems. As such, the presence of the individual structures, while perhaps necessary, may be less important than understanding their interconnection and communication among these structures [42-44]. Disproportionality and nonlinearity are characteristics of GST. The Sprague effect [45] is one example. In this instance, adding a small amount of damage in the brainstem, following much larger damage to the cortex, seems to 'cure' what appeared to be a behavioral effect of the large damage. Thus, small changes in the fetal sensory or nociceptive system could have a greater than expected (nonlinear) impact.

Within GST, the behavior of an organism is considered to possess the property of emergence, i.e., the phenomenon by which larger entities arise through interactions among smaller and simpler entities, and exhibit properties not in evidence in these entities. In others words, the whole is greater than the sum of its parts [46,47]. Thelen and Smith [48] argued that human cognitive and motor development should be explained in the context of a dynamical systems. That is, the development is not a pre-programmed process. Rather it emerges as a result of the interaction among the nervous system, body, and surrounding environments [49-51]. The unfortunate need to rely of animal data when investigating fetal pain may, because of their relative simplicity compared to the human organism, subliminally distracts from a GST approach especially in considering mental activity and consciousness. Classical physics may be more applicable to pursuing the 'real' definition of pain (see above), while GST to the 'nominal' definition. Regardless of the approach one takes, the use of inference is an inescapable reality. That which most closely approximates the accumulated scientific data, and emerges from a rational interpretation, is deserving of serious consideration independent of how compatible it may be to conventional thought.

Conclusion

The existence of fetal pain, its definition, means of quantification, and necessary neurophysiological apparatus continue to be explored. By 8-weeks the fetus has a sense of touch and is exploring the umbilical cord and uterine wall. By 13 weeks has a sense of taste and prefers sweet over bitter. There appears to be evidence that the fetus, as young as 12-weeks, responds, albeit in a very rudimentary fashion, to stimulation which would ordinarily be considered noxious. The reduced complexity of the response when compared to more mature individuals seems to require a reconsideration of how we view the nature of pain and whether any definition could, or should, be applicable across species, and their ontological developmental. This would, indeed, be a heavy epistemological burden. For example, Aydede [52] questioned "Are all experiences regularly categorized under the label "pain" sufficiently similar to nociceptive pains in terms of their sensory and affective qualities? Conversely, are all experiences that are sufficiently similar to nociceptive pains standardly categorized under the label "pain"? (P. 7). Likewise, Fink [53] questioned the belief in the 'unity of pain'. He concluded that pain refers not to one class, but a cluster of different phenomena. In the same fashion that Woolf [54] provided a description of different types of pain, fetal pain may represent a different kind of pain. Lowery et al. [4] commented that existing research suggests "…. the structures and mechanisms used for pain processing during fetal or neonatal life are unique and completely different from those used by adults," (p.277). Attempts to have it conform to an existing definition may divert one from uncovering the essential, and unique features of fetal pain, in particular, and pain in general. Furthermore, emphasizing the importance of higher cortical functions may inadvertently encourage discounting the meaning and potential consequences of the fetal response to noxious stimulation. It seems clear that the fetus is not simply an immature adult. And, that the underlying central nervous system structures and connectivity used in processing sensory (nociceptive) information are quite different from those used by adults [4,55]. The presence of higher cortical functions does not appear to be necessary. The fetal pain response seems to be associated with subcortical structures and may represent a different kind of pain defined in the context of neurophysiological maturity and complexity.

Taking the above discussion into consideration, the following is a proposed working nominal definition (description) of 'fetal pain': *a response containing physiological, motor, and hormonal components associated with stimuli considered to be nociceptive, i.e., associated with potential or actual tissue damage, in an individual without higher cortical function and attributes. And, wherein the processing of incoming stimuli is considered to occur primary at the subcortical level.* Thus, fetal pain becomes more of a sensory-related phenomenon as the commonly emphasized psycho-social, emotional, and cognitive factors have a limited, if any, role. This definition would be applicable to any individual lacking higher levels of functioning associated with advanced cortical development. 'Fetal pain' would represent a 'kind' of pain associated with a certain level of developmental maturity. Thus, the response of individuals with minimal or no cortical development could be described a demonstrating 'fetal pain'; dissociating the term from gestational age, and attaching it to the developmental maturity of the individual. In short, fetal pain would be viewed as an emergent phenomenon. It is unlikely that one will be able to assign a specific age at which this occurs, because of the complexity, and sensitivity, of the biological system involved. It is possible to assert an age range at which point it can be said that, based on the current neuro-anatomical and –physiological knowledge, the fundamental biological apparatus associated with the experience of pain is present and functional. In Aristotelian terms [56], we may be able to identified the 'material' and 'efficient' causes of fetal pain, but have yet to appreciate the 'final', or 'formal', causes.

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