

Compassionate Treatment of Fetal Pain.

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Abstract

There is no doubt that the neonate feels pain. There is also no doubt that the fetus feels pain but disagreement exists about when exactly during gestation does this fact have clinical and moral meaning. Those who disagree and those who agree that fetal pain is perceived in one way or another, actually look at the same data but from different perspectives. At present, there are indirect hormonal, sonographic, and Doppler evidence that fetal pain exists at 18-20 weeks' gestation and continues into the neonatal period. The debate is mainly about the presence or absence of functional thalmo-cortical axons—the probable prerequisite for nociception. When a fetus may undergo partial birth abortion, painful interventions, or termination, we believe that it is the duty of our profession to adopt a compassionate attitude to alleviate pain and suffering of the unborn child, starting at 18-20 weeks' gestation, as we do for our neonates.

Keywords: Fetal pain, Termination of pregnancy, Feticide, Fetal surgery.

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Being compassionate to our patients and to alleviate pain are the foremost duties of the medical profession. Compassion, in this sense, is a feeling which induces interventions to eliminate or minimize pain and suffering, and applies (but not limited) to every human being. There is an ongoing debate, started many years ago, if the unborn human (i.e., the fetus) feels pain as does the human neonate, and if yes, when exactly during intrauterine life the fetus acquires this characteristic, thus leading to the obligation to be compassionate to the fetus.

Fetal pain gained importance in recent years because interventions that might cause pain, such as fetal surgery, termination of pregnancy, and even feticide, became increasingly frequent. The American Congress passed in 2008 the "Unborn Child Pain Awareness Act" and in 2013 the "Pain-Capable Unborn Child Protection Act" to require that those who knowingly perform an abortion of a pain-capable unborn child (defined as a fetus of 20 weeks or more after fertilization), to provide explicit information to the mother about the pain that the fetus may suffer and how to alleviate it because there is "substantial evidence that the process of being killed in an abortion will cause the unborn child pain" [1,2]. As a result, 25 states started to discuss similar acts, and in 2010, Nebraska prohibited abortion beyond 20 weeks' gestation on the basis of potential perception of pain by the fetus. In contrast, there are many opponents to the theoretical origin of this view,

providing evidence that the fetus, at least at that stage, does not feel pain.

Definition of the problem

It is unanimously accepted that a viable fetus (i.e., one that has the potential to survive outside the womb, with or without support by contemporary medicine) feels pain, as do very preterm infants. Thus, it is clear that a viable fetus needs pain relief before painful stimuli. The problem, then, is with fetuses of 'borderline' viability (i.e., 20-24 weeks' gestation) that undergo dilatation and evacuation (D&E, partial birth abortion) or medical abortions that may cause excruciate pain. In such circumstances, it appears only logical, at least for humanitarian reasons to anesthetize the fetus before any painful intervention. It should be stressed that feticide alone might be of no avail, because producing cardiac arrest by injection of KCl is expected to be also very painful. Even those condemned to death by the 'lethal injection' initially undergo induction of unconsciousness followed by cardiac arrest through depolarization of cardiac muscle cells by KCl.

Argument: The fetus does not feel pain before the 3rd trimester.

The seminal paper which discussed this argument was published a decade ago with the intention to establish the scientific foundation for the different legislative acts

about the demand to explicitly inform the mother about fetal pain during abortion after 20 weeks' gestation, and to offer fetal anesthesia before termination of pregnancy. Lee et al. examined the English literature and stated (a) feeling of pain requires, among other things, conscious recognition of the painful stimulus; (b) fetal reflexes and fetal hormonal reactions to stress are no evidence of fetal feeling of pain because they may be provoked by unpainful stimuli and even without the fetal cortex (i.e., in anencephalic fetuses); (c) awareness of pain requires a functional thalamo-cortical neuronal axis, but this does not happen before 23 to 30 weeks' gestation; (d) electroencephalography does not demonstrate pain perception in preterm neonates before 29-30 weeks [3]. Hence, Lee et al. concluded that pain perception is unlikely before the 3rd trimester of pregnancy. Similar conclusions were reached more recently by Bellieni and Buonocore who inferred that most behavioral, endocrine, and electrophysiological data do not confirm that fetal pain perception exists before the 3rd trimester [3,4]. This conclusion appears, by itself, controversial, and this ambiguity translated into the Pain-Capable Unborn Child Protection Act discussed above [1,2].

Counterargument: The fetus feels pain before the third trimester.

The paper of Lee et al. is the reference for those who do not believe in fetal pain (but probably believe in neonatal pain perception, despite the fact that the interval between intra- and extra-uterine life lasts less than a minute [3]. However, after the publication of that paper, 3 letters to the JAMA Editor were published (JAMA 2006; 295:159-161) that criticize, each in its own way, the hypotheses and assumptions of Lee et al. Other doubts and conflicting views were published before and, certainly, after the publication [3].

Functional development of the thalamo-cortical neuronal axis

It appears that the timing of a functional development of thalamo-cortical neuronal axis is critical in establishing when the fetus can feel pain. On the one hand, histochemical staining showed the penetration of afferent fibers into the brain cortex between 26-34 weeks, thus suggesting that the fetus cannot feel pain before 26 weeks [5]. On the other hand, it was shown that the subplate zone of the cortex is rich in a mixture of neurons, including thalamo-cortical fibers that demonstrate synaptic connections with the cortex as early as the 20th week of gestation [6]. Lowery et al. examined the neurological development of pain in the fetus and point to the controversy which emerges from the inability to quantify fetal pain, and thus, as also Rokyata opined, pain is a subjective feeling and because the fetus (and the neonate) cannot describe its feelings, we are unable to use the conscious appreciation of pain as an inherent part of pain feeling [7,8]. Lowery et al. documented that sensory fibers exist abundantly as

early as 20 weeks, that a fetal spinal reflex operates as early as 19 weeks, that neural connections to the thalamus are present at 20 weeks, and that neurons are seen in the cortical subplate already at 17 weeks' gestation [7]. At the same time, pain needs both nociception (sensing pain stimuli) and emotional reaction to and processing of these stimuli. Hence, because of the absence of mature neurons in the thalamo-cortical axis there is probably no "emotional" pain experience by the fetus-neonate until 29-30 weeks. In contrast, pain has a distinct physiological manifestation (stress reaction) including an increase in catecholamines and cortisol which can be suppressed by opiates. Lowery et al. also maintained that in contrast to the indirect proofs of conscious fetal pain perception, there are direct proofs of subconscious 'imprinting' of pain in fetal neurodevelopment and of long term effects on the neonate [7,9].

Reaction to pain

Since the fetus is unable to verbally express the feeling of pain, one might question the feasibility of non-verbal signs and markers of pain expression. Proponents of this approach suggest that animals as well as patients under anesthesia cannot communicate the feeling of pain but are able to express a wide range of signs and markers that are recognized as reaction to pain [8]. The argument that the fetus and the neonate react in a similar manner to painful and painless stimuli is explained by the larger sensory surface area in the fetus-neonate than in the adult and by the unripe systems that can differentiate between a painful and any other somato-sensory stimuli. Put differently, the fact that the fetus reacts in the same manner to different stimuli is by no means proof that the fetus does not feel pain.

As previously stated, it is customary to use the activation of the hypothalamic-hypophysial-adrenal axis ("stress reaction") as an indicator of pain. However, the "stress reaction" does not necessarily represent reaction to pain (and appears in adults, for example, in intense physical exercise) and does not involve the brain cortex. Conversely, it is quite logical to assume that in the absence of a "stress reaction" there is little likelihood that the fetus feels pain. In any case, "stress reaction" in the fetus is associated with short and long-term side effects even if unrelated to pain [10].

A British group examined markers like cortisol, endorphin, and noradrenalin in fetuses that received in utero blood transfusions for various reasons and compared between umbilical cord blood sampled from near the placental insertion (less likely to cause pain) and that sampled from umbilical vessels inside the fetal abdomen (likely to cause pain) [10]. The results clearly indicated a significant increase in hormonal levels as a reaction to pain in those fetuses that required intrabdominal umbilical blood sampling—observations made even before 20 weeks' gestation.

Another measure of fetal reaction to pain is the redistribution phenomenon [10]. This refers to preferential blood flow to vital organs and intends to protect the brain and myocard against potential harm associated with the cause of pain, as is also seen as a protective reaction to intrauterine fetal growth restriction with Doppler velocimetry of the middle cerebral artery. It has been shown that puncture of umbilical vessels through the fetal abdomen, in contrast to sampling the cord near its placental insertion, provokes such a redistribution effect [10].

Fetal behavior

Not before long, it was believed that neonates do not feel pain. Research has clearly shown that neonates, even very preterm newborns, develop a significant "stress reaction" to pain. Thus adequate analgesia during surgery might reduce mortality rates [11]. Eventually, neonatal anesthesia became standard of care.

Neonatal reaction to pain (e.g., heel prick) is self-evident both by facial expression and by crying. Interestingly, neonatal reaction to pain somewhat depends on when during the sleep-wake cycle the prick was done. This suggests that an inborn behavioral conditioning might exist before the neonate had a chance to acquire this reaction in early extra-uterine life. This well-known observation was just a step away from similar observation of fetal facial expression. Indeed, Reissland et al. sought to identify intra-uterine facial expressions of pain and suffering with the advent of 4-D ultrasound [12]. The authors found increasing complexity of expressions, including those of pain and suffering, with advancing gestational age [12]. The authors suggested that the development of fetal facial expression has a role postpartum, and that facial expressions in-utero may help to differentiate between normal and abnormal fetal development [12]. Of importance is the fact that the startle response to external stimuli so vividly seen in the neonate was also observed in anencephalic fetuses, implying that this reaction is present at a sub-cortical level. Obviously, fetal crying vividly seen with 4-D ultrasound as early as 20 weeks' gestation involves not only activation of a complex motor sequence (coordinated breathing movements, jaw opening, mouthing, chin quiver, tongue extension, and swallowing) but also an association with a stimulus of negative connotation [13]. Also, the recognition of this stimulus as potentially harmful implies integration of brain sites that mediate affect with a proper motor response [13]. Together with the fact that we may hear the crying sound of extremely premature babies these observations suggest that the fetus is capable of expressing coordinated facial movements that mimic extrauterine cry [13].

Anesthesia for fetal surgery

Fetuses born by cesarean section to a mother under general anesthesia are usually born vigorous when maternal anesthesia was not deep or long enough to anesthetize the fetus as well. Research has shown that

fentanyl directly injected intramuscularly to the fetus reduces all measures of pain reaction as early as 20 week's gestation [4]. Opioids may reach the fetus via direct intramuscular, intra-umbilical or intramniotic application, and indirectly by significant dosing of the mother. Gupta et al. opined that not only is there a moral obligation to provide fetal anesthesia and analgesia, but it has also been shown that pain and stress may affect fetal survival and neurodevelopment [14]. At present, fetal anesthesia is recommended when surgical procedures on the fetus are performed (such as endoscopic surgery of the placenta, cord, and membranes, late termination of pregnancy, and direct surgery of the fetus) [14]. A recent review also reiterates the need for adequate fetal anesthesia regardless of the debate whether a fetus does or does not experience pain as a conscious-emotional feeling [15].

Ethical reasons to relieve fetal pain

It follows that since it is unquestionable that the fetus exhibits protective responses to tissue injury, one may question if we have a moral obligation to provide relief of fetal pain to the same extent that we do after birth. If the reply to this question is positive, then a secondary question would be when this obligation starts.

Hall and Boswell critically examined whether pain management is a human right. They maintained, *inter alia*, that despite the beliefs of physicians that it is, ethics and law do not provide clear support of this view [16]. Regardless of these theoretical arguments, there is little doubt that any physician is intentionally willing to provide anesthesia when pain management is required.

Brugger, on the other hand, suggested that it is unnecessary to have a clear-cut proof that the fetus experiences pain to provide pain relief [17]. It was argued that indirect evidence is sufficient to raise a reasonable doubt that pain is indeed felt by the fetus. There is a difference between a reasonable doubt and ethical uncertainty and it appears that uncertainty works as a restrictive rather than a permissive argument. For example, a reasonable doubt will not allow a hunter to shoot into the bush if unsure whether it is a deer stirring in the bush. This approach toward pain management of the fetus was adopted by the Society of Family Planning [18]. In simple words, even a reasonable doubt about fetal pain is a strong enough argument that calls for fetal pain management.

The motto of the concept of the 'fetus as a patient' maintains that "being a patient means that one is presented to the physician and there exist clinical interventions that are reliably expected to result in a greater balance of clinical benefits over harm" [19]. Whereas ethicists suggest that the 'fetus becomes a patient' at viability (roughly around 24 weeks' gestation), it appears that the medical duty to alleviate fetal pain begins at least 4 weeks earlier [19]. Because respect for autonomy and the concept of autonomy-based rights therefore do not apply to the fetus, it is unclear whether the approach to fetal pain should

lower the gestational age at which the fetus becomes a patient.

Avoiding livebirth

The purpose of Termination of Pregnancy (TOP) is that it does not end with a liveborn neonate. However, live birth might happen unintentionally following TOP around the limit of viability. There are numerous reports documenting a neonate born after medical induction of abortion, who suffers (in addition to the malformation that allegedly "indicated" the abortion) also from consequences of extreme prematurity [20]. This so-called 'unintended' birth, whereby a fetus destined to be aborted is born alive, has obvious legal implications. It follows that feticide before inducing a late abortion has an 'advantage' in avoiding such an undesirable complication of late abortion. The 'advantage' of feticide might, albeit rarely, be mitigated by complications such as infection, coagulopathy, and pain [20]. Also, a single case of maternal death was reported due to cardiac arrest following injection of KCl into the maternal instead into the fetal circulation. Feticide would, presumably, increase the psychological maternal stress already existing before abortion. Nevertheless, one study reported that 90% of women undergoing late abortion preferred that feticide would be done before the abortion procedure [20].

As noted above, even when feticide is considered to avoid fetal pain during abortion, it is possible that feticide by injecting KCl into the fetal heart might cause severe ischemic pain. Hence, to avoid this unwanted circumstance, a 2-step procedure should be done: first to induce anesthesia of the fetus, and then to accomplish feticide. Regrettably, this compassionate attitude used in every death penalty by intravenous KCl infusion is rarely, if ever, used in feticide.

At the end of the day, the implementation of this compassionate approach is mainly in the attitude of the medical profession to the fetus. In a recent study of expert family planning providers in the USA, half reported that they performed feticide regularly before second trimester abortions, albeit there were differences in the gestational ages and the methods used [19]. The reasons for feticide before abortion were based on legal, technical, and psychological arguments related to the possibility of a liveborn.

Summary

This paper does not take any side in the abortion controversy surrounding the moral and legal status of induced abortion. It follows that the ideas raised in this review may suite all parties in the debate irrespective whether the "pro-choice" view (right to decide whether to terminate a pregnancy) or the "pro-life" concept (right of the embryo/fetus to be born) are concerned.

In the absence of international guidelines, it is the duty of our profession to adopt a compassionate attitude to

alleviate pain and suffering from the unborn child. This quantum of solace may start as early as 18 weeks' gestation.

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