



Direct evidence of fetal responses to noxious stimulations: A systematic review of physiological and behavioral reactions

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ABSTRACT

Fetal pain is usually debated using data extrapolated from physiology and anatomy; whereas direct observation of fetal pain reactions is only marginally used. We present the first systematic review to carefully analyse this direct evidence.

Our objective was to summarize the scientific literature based on the direct observation of fetal responses to noxious stimulation.

We retrieved 17 clinical studies focused on the direct observation of fetal responses to noxious stimulation. This systematic review suggests that direct trials of fetal responses to acute pain/stress caused by tissue injury are scarce, but nonetheless informative for therapeutic interventions using fetal surgery or fetal invasive procedures. The current evidence indicates that responses to fetal pain develop from mid-gestation onward, but further high-quality research is needed to confirm these findings and guide clinical practice.

1. Introduction

Pain management has improved greatly in the recent decades. Scientific investigations have focused on understanding the mechanisms of painful conditions in adults, identifying a pain matrix in the central nervous system (CNS), measuring the pain of non-verbal humans, identifying new analgesics and other pain therapies [1–3]. Scientific evidence has also overcome many prejudices in this area [4,5]. One area remains difficult to address and that is fetal pain, with ongoing debates about the temporal appearance of pain and sentience during fetal development. Physiological, neurologic, and anatomical observations have informed many conclusions on this area, but only a few resulted from the direct observation of fetal responses to pain. We are the first to focus on the direct observation of fetal responses to pain. Until now, all the reviews on this theme have mixed up conclusions drawn from both direct and indirect observations, with the risk of overshadowing direct by indirect observations, because indirect observations are usually descriptive and easier to get, and therefore more abundant. Yet, direct observations are those usually more informative, because they describe a direct response to noxious stimuli and are not speculative.

2. Methods

Our literature search was designed to look for clinical studies that directly assessed the fetal responses to noxious tissue-damaging stimuli. We used the PubMed and Scopus search engines, with the following search terms: “fetal pain”, “fetal stress”, and “fetal analgesia or anesthesia”. All literature searches were performed in April 2024. We retrieved the papers using the PRISMA method, including RCTs and case reports, and excluding reviews, RCTs with no pain scale, and commentaries. We did not exclude the studies based on fetuses' gestational age, but we reported it in the Results section. The same was done with the different types of stimuli that provoked pain response or with the method to assess its intensity. We also used the MINORS tool (a methodological index for non-randomized studies, ranging from 0 to 24) to assess the strength of the single studies [6].

3. Results

Using the PRISMA model of analysis, our search strategy revealed 879 reports, 757 were removed before screening, 127 reports were screened, and 110 were excluded for various reasons as listed in Fig. 1. We reviewed 17 reports, which dealt with the direct assessment of fetal

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responses to painful stimuli. Four studies [7–10] were excluded for not fulfilling the inclusion criteria.

Eleven reports [11–21] described case-control trials on groups of fetuses undergoing in utero blood sampling or intra-uterine transfusions. Fetal transfusions are performed by inserting a needle through the innervated abdominal wall, peritoneum, and hepatic capsule into the intrahepatic vein (painful stimulus) or into the non-innervated placental insertion of the umbilical vein (non-painful stimulus). Some studies compared the hormonal and hemodynamic differences between these two groups. Some studies assessed fetal cerebral flow responses provoked by an injection in the umbilical vein vs. the intrahepatic vein [11,13,17,18]. One study assessed fetal ACTH (adrenocorticotropic hormone) and cortisol responses to different types of delivery [22], whereas another study assessed reactive C-reactive protein to measure the stress induced to the fetus by different types of delivery [23]. One was a case report, that compared the pain response before and soon after a needle puncture into the fetal intrahepatic vein [21], and was not sufficiently accurate, so it was excluded from the database.

Most of the studies reviewed reported robust physiological responses when fetuses were exposed to noxious stimuli and noted that these responses were absent in fetuses exposed to non-noxious stimuli. Only one research group found no differences between the fetal responses to noxious vs. non-noxious stimuli [2,3] (Table 1).

4. Discussion

Most studies we retrieved show that noxious stimuli associated with pain and/or stress provoke fetal responses not unlike those reported in newborns and older infants (Fig. 2). Robust increases in several stress hormones and the brain-sparing increases in cerebral blood flow (due to reduced impedance in the middle cerebral artery) have been described

as a consequence of painful stimulation. Of course, there are exceptions, such as the trials by Adama van Scheltema et al. [17,18], that reported no differences between noxious vs. non-noxious stimulation. Most importantly, our systematic review highlights the scarcity of studies in this field. Thus, usually the evidence from direct fetal observations is interpreted with the help of indirect evidence. We want to assess these direct observations and what they tell us.

4.1. Are these outcomes a sign of fetal pain?

The brain-sparing effect of increases in cerebral blood flow is an index of acute stress in babies, [24–26]. The release of stress hormones is widely accepted as a sign of pain-related stress in adults [27]. Some clinical studies have tried to assess fetal pain through validated pain scales based on grimaces [21,28], and similar assessments are used routinely in infants and children, but they are still initial attempts. Some trials examined fetal hormonal changes induced by the type of delivery on the fetus, through endpoints of stress, such as corticotrophin releasing hormone (CRH), ACTH, cortisol, testosterone, or C-reactive protein [22,23] similar to adults stress responses.

What unifies these approaches is that fetal responses were activated by stimuli that we can call “critical”. Critical stimuli occur when parts of the body innervated with nociceptors signal a breach in bodily integrity, and provoke a reaction. This might be an actual sign of pain, because sudden reactions immediately after nociceptor-rich body parts are invaded forms the basis for pain signalling. Of course, this can also be just a nociceptive response, i.e. a bodily response due to nerve activation without reaching conscious perception. And this is the limitation of direct observations we retrieved. In this case, however, indirect observations can give a substantial hand.

Some weak points are to be pointed out in our study. Some may

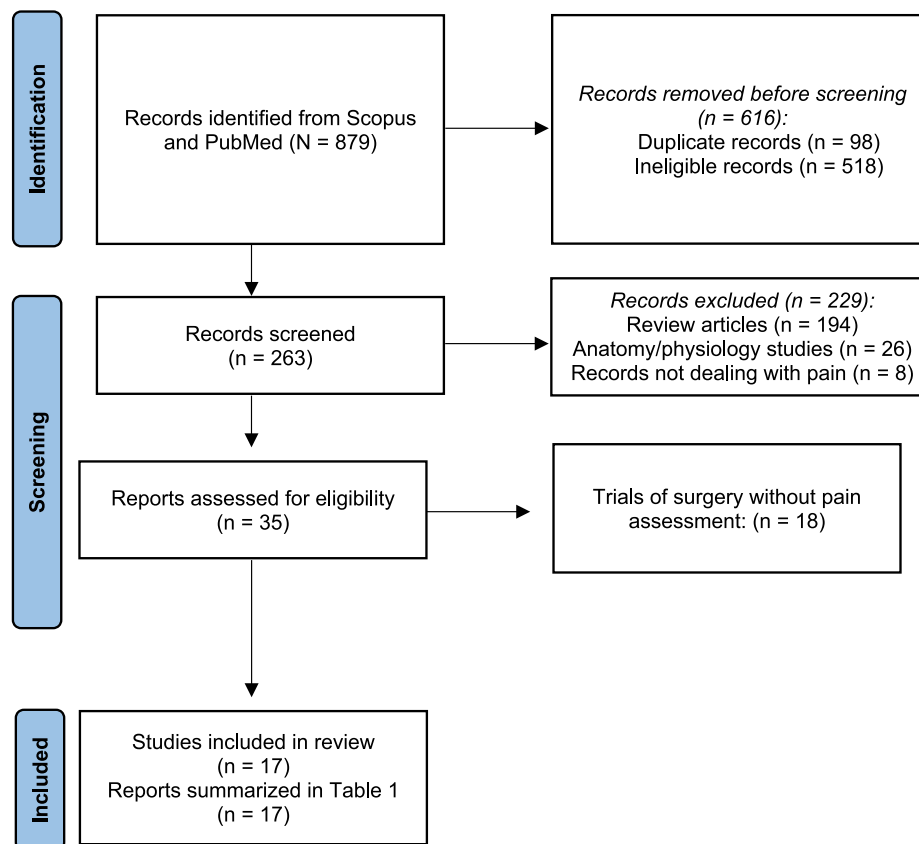


Fig. 1. PRISMA flow diagram.

Source: Page MJ, et al. BMJ 2021;372: 71. <https://doi.org/10.1136/bmj.n71>.

Table 1
Studies included in the Systematic Review.

#	Author and Year	Number of fetuses	Gestational age wks	Type of stimulus	Key fetal responses	Results	Quality	MINORS
1	Giannakoulopoulos et al., 1994 [13]	31	23–34	P-UC vs P-IHV	SH	SH increased after P- IHV but not in P- UC	2	22
2	Teixeira et al., 1996 [19]	28	18–36	P- UC vs different innervated body sites (P-DIBS).	MCAPI	MCAPI decreased following P-DIBS unlike P-UC.	2	20
3	Teixeira et al., 1999 [20]	136	23–32	P- UC vs P-DIBS.	MCAPI	MCAPI decreased following P-DIBS unlike P-UC.	2	20
4	Giannakoulopoulos et al., 1999 [14]	64	18–37	P- UC vs P-DIBS	SH (Noradrenaline)	Noradrenaline increased after P- IHV but not in P- UC	2	22
5	Fisk et al., 2001 [12]	45	20–35	P-UC vs P-IHV both with or without fentanyl administration	Stress hormones and MCAPI	Fentanyl reduced the beta-endorphin and MCA pulsatility index responses, but not the cortisol response ($p = 0.11$) in fetuses with paired IHV transfusions with and without fentanyl.	2	24
6	Gitau et al., 2001 [17]	51	17–35	P- UC vs P-IVH	Stress hormones in both mother and fetus	SH increased after P- IHV but not in P- UC Fetal stress responses were independent of the mother,	2	24
7	Gitau et al., 2004 [16]	46	17–38	P- UC vs P-IVH	Stress hormones (CRH and cortisol) in both mother and fetus	Stress hormones increased after P- IHV but not after P- UC Fetal stress responses were independent of the mother,	2	24
8	Ochedalski & Lachowicz, 2004 [22]	32	39–42	oxytocin-induced labour, vs elective cesarean section.	Maternal and fetal plasma changes in CRH, ACTH, cortisol, and dehydroepiandrosterone	ACTH increases during labour were higher in the oxytocin-induction group vs. cesarean section, but CRH and cortisol after birth were higher in the cesarean section vs. oxytocin-induction group.	4	24
9	Gitau et al., 2005 [15]	44	15–38	P- UC vs P-IVH	Testosterone in both mother and fetus	Fetal testosterone is not quantitatively different in PUC and PIVH	3	22
10	Adama van Scheltema et al., 2009 [10]	57	17–35	P- UC vs P-IVH	MCAPI	No difference between the two groups	2	24
11	Adama van Scheltema et al., 2011 [11]	25	20–35	P- UC vs P-IVH	MCAPI and stress hormones	No difference between the two groups	3	20
12	Kosinska-Kaczynska et al., 2012 [18]	81	19–36	P- UC vs P-IVH	ACTH and cortisol in both fetus and mother	ACTH and cortisol were significantly higher in PIVH group	2	22
13	Bellieni et al., 2014 [23]	1012	38–42	vaginal delivery, emergency C-section, elective C-section	CRP	CRP in babies born after vaginal delivery was statistically higher than in those born after C-section. Higher CRP values were present in emergency vs. elective C-section.	3	18
14	Bernardes et al., 2018 [21]	1	32	anesthetic injection (for the removal of a tracheal balloon)	NFCS	Pain scores were significantly higher after the injection.	5	6
15	Mayorga-Buiza et al., 2018 [9]	12	24	meningomyelocele repaired via open fetal surgery (no gestational age reported in the paper) compared with a sentinel case at 24 weeks GA.	HR	Bradycardia was present only in the fetus who did not receive analgesic treatment	5	6
16	Bernardes et al., 2021 [26]	13	31.1 ± 2.8	Intramuscular injection vs acoustic stimulus	NFCS	Higher scores for Intramuscular injections.	4	18
17	Bernardes et al., 2022 [28]	1	23	in utero cardiac surgery before and after an intramuscular injection of anesthetics	modified NFCS scale	Higher pain score after starting surgery	4	6

Legend to **Table 1**: P-UC (Puncture in the umbilical cord), P-IHV (puncture in the intrahepatic vein, SH (stress hormones), HR (Heart rate), CRP (C reactive protein). MINORS: “Methodological Index for Non-Randomized Studies”.

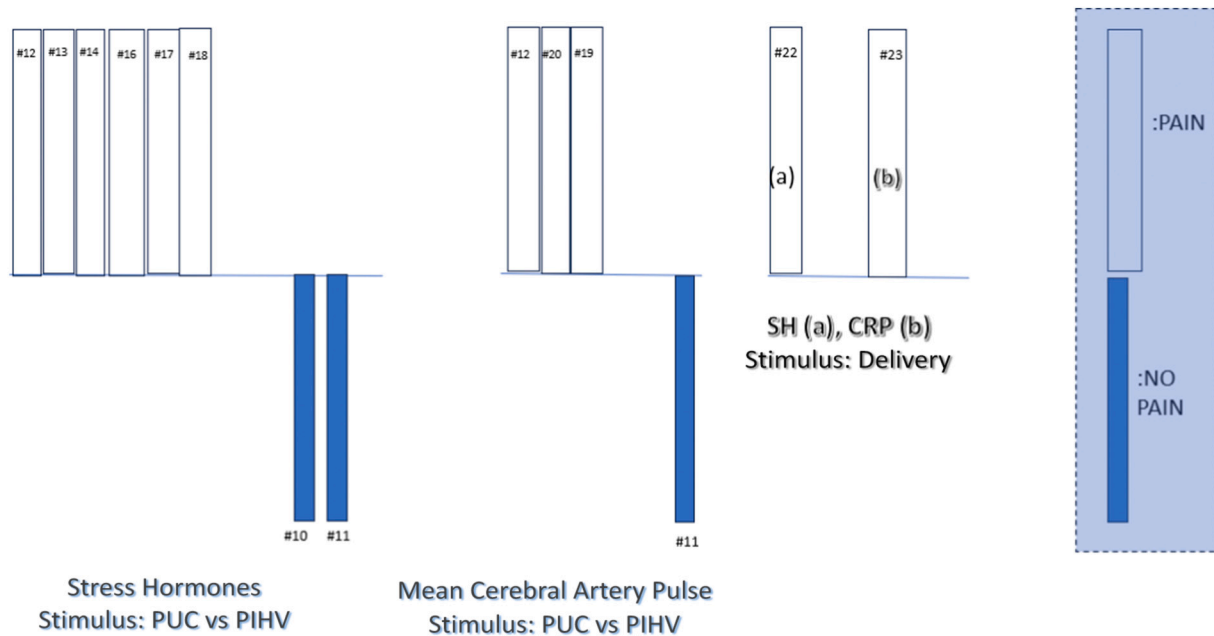


Fig. 2. number of trials indicative (blank) or non-indicative (full) for pain response
 Numbers in the histograms are correspondent to bibliography numbers.
 SH: (Stress hormones), CRP: C-reactive protein.
 Stimuli: PUC: Puncture of the umbilical cord; PIHV: Puncture of the intra-hepatic vein.

object that changes in blood flow are not such a robust sign of fetal stress (though this cannot be ruled out). Moreover, the two studies we report about the effects of delivery on fetal stress might be ignored, because this kind of stress is not a tissue-breaking pain.

4.2. What do indirect studies add?

The main issue is whether a mature cerebral cortex is required to perceive pain, though the cerebral cortex does not mature until several years after birth. Current evidence shows that pain is perceived not only in the cerebral cortex but also in other brain structures [29–32], and that established connections to the cerebral cortex are not essential for conscious pain perception [33–35]. This is further supported by the evidence for neuroanatomical maturity of the fetal pain pathways [36], correlations between fetal brain activity patterns and fetal behavior [37], and the accumulating evidence for pain in preterm infants [38].

Previous claims that the fetus was in a continuous state of sleep [39] or that it was sedated by placental neuromodulators [40] were disproved by accumulating evidence over time [41]. While most direct observation corroborate the hypothesis that fetuses can feel pain, indirect studies hesitate to find out the “core” of pain sentience: some insist to argue it is the thalamus, others say it is the mature cortex. Several scientists expect neural circuitry responsible for pain drive to be in phylogenetically older regions of the brain, which appear earlier in development [42]. Such regions include the subplate and subcortical structures such as the thalamus and brainstem. Cortical regions, which are phylogenetically newer, may be involved in the processing and regulation of pain, rather than pain perception itself [43–46].

4.3. The risks of provoking pain to the fetus

Now that we can perform prenatal surgery, it is important to know whether maternal anesthesia is sufficient to anesthetize the fetus, whether anesthesia administered directly to the fetus is necessary, and which drugs to use in these cases [47–50]. Various studies and guidelines have already been published for administering anesthesia directly to the fetus [51,52]. The routine use of anesthetics for fetal surgery and

invasive fetal procedures is based on the widely held view that human fetuses can feel pain.

Moreover, preterm babies are born earlier than when some researchers, with the scarce direct data available, say that a fetus (and consequently a newborn baby of the same gestational age) cannot feel pain. If widely accepted, this viewpoint would jeopardize the pain treatment of preterm newborns receiving intensive care at the same neurological age of fetuses or that of fetuses who should undergo pre-natal surgery.

Several limitations are evident in the retrieved studies. Few direct studies have been performed, making researchers rely on indirect evidence to interpret the presence/absence of fetal pain. The trials we retrieved reported different outcomes, with changes in cerebral blood flow, stress hormones, or vital signs. They also used different stimuli to provoke these physiological responses (intravenous transfusions, intramuscular injections, fetal surgery, vaginal delivery). No randomized controlled trials were reported and the overall quality of evidence was low, with ratings of 3–5 in eight studies and ratings of 2 in nine studies (Table 1). Moreover, several studies use small sample.

5. Conclusions

The importance of this study is to focus on direct observations, that risk being overshadowed by indirect, though useful, studies. Direct observation should be the base and the main point to draw conclusions on fetal pain. This direct evidence points toward pain perception developing in the second trimester of pregnancy, possibly around 20 weeks of gestation. We need more direct evidence to assess when this sensation has a start. We do not know what kind of pain it is [53,54], or what it means to the fetus, but the risk of causing suffering is very likely and it should be managed. The progresses in fetal surgery impose to be more and more sure of the time fetal pain appears, and this review is an important milestone.

Remaining unknowns may include: (a) what are the developmental epochs, degrees of tissue injury, and fetal behavioral states associated with fetal pain perception?; (b) what are the precise roles and physiological mechanisms in the subplate zone and subcortical structures

associated with pain perception?; (c) when do the developmental onset and states of fetal consciousness, memory and learning occur?; does consciousness emerge at 24 weeks of gestational age [55], is it correlated with the rise of memorable prenatal experiences [55], or does it appear after birth? [56]; (d) what are the critical windows and effective approaches for treating or preventing fetal pain?; (e) how can we describe the long-term effects of fetal pain exposure(s) on subsequent brain development, cognition, and behavior? Other scientific questions will arise in this investigative journey, which first starts with acknowledging, at least the possibility, of fetal pain perception.

Appendix. to Table 1: Levels of evidence from individual studies were rated according to the Quality Rating Scheme below (modified from Oxford Centre for Evidence-Based Medicine):

Level of Evidence	Study Design
1	Properly powered and conducted randomized clinical trial; systematic review with meta-analysis
2	Well-designed controlled trial without randomization; prospective comparative cohort trial
3	Case-control studies; retrospective cohort study
4	Case series with or without intervention; cross-sectional study
5	Opinion of respected authorities; case reports

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